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High Residual Platelet Reactivity After Clopidogrel

Extent of Coronary Atherosclerosis and Periprocedural Myocardial Infarction in Patients With Stable Angina Undergoing Percutaneous Coronary Intervention

Fabio Mangiacapra, MD,*† Bernard De Bruyne, MD, PHD,* Olivier Muller, MD, PHD,* Catalina Trana, MD,* Argyrios Ntalianis, MD, PHD,* Jozef Bartunek, MD, PHD,* Guy Heyndrickx, MD, PHD,* Germano Di Sciascio, MD,† William Wijns, MD, PHD,* Emanuele Barbato, MD, PHD*

Aalst, Belgium; and Rome, Italy

Objectives We tested the hypothesis that residual platelet reactivity after clopidogrel correlates with the extent and severity of coronary atherosclerosis in patients undergoing elective percutaneous coronary intervention (PCI).

Background Platelets are actively involved in vascular atherosclerosis.

Methods We prospectively enrolled 338 patients undergoing PCI for stable angina, loaded with 600-mg clopidogrel. Platelet reactivity was assessed 12 h later by measuring P2Y12 reactivity unit (PRU) with VerifyNow P2Y12 assay (Accumetrics, San Diego, California). High platelet reactivity (HPR) was defined as PRU value ≥240. Presence of multivessel disease (MVD) and total stent length (TSL) were used as surrogate markers of atherosclerosis severity and extension.

Results Patients with MVD showed higher PRU compared with single-vessel disease (SVD) patients (222 ± 85 vs. 191 ± 73; $p < 0.001$). The PRU increased with the number of stenotic coronaries (1-vessel disease: 191 ± 73; 2-vessel disease: 220 ± 88; 3-vessel disease: 226 ± 80; $p = 0.002$). The PRU was higher in the third TSL tertile compared with first tertile (217 ± 83 vs. 191 ± 73; $p = 0.048$). The HPR was most frequently observed among MVD patients (40.5% vs. 21.6% in patients with SVD, respectively; $p < 0.001$) and those in the third TSL tertile (35.8% vs. 22.2% first tertile; $p = 0.028$). Higher incidence of periprocedural myocardial infarction was observed in patients with HPR (41.2% vs. 26.7% in patients without HPR; $p = 0.008$) and in those in the third tertile TSL (37.7% vs. 23.1% first tertile; $p = 0.020$). By multivariate analysis, HPR was the only independent predictor of periprocedural myocardial infarction ($p = 0.034$).

Conclusions Patients with more extensive coronary atherosclerosis have a higher rate of HPR, which might partly account for higher risk of periprocedural MI. (J Am Coll Cardiol Intv 2010;3: 35–40) © 2010 by the American College of Cardiology Foundation

From the *Cardiovascular Center, OLV Hospital, Aalst, Belgium; and the †Department of Cardiovascular Sciences, Campus Bio-Medico University, Rome, Italy.

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Platelets are actively involved in the inflammatory cascade leading to vascular atherosclerosis (1,2). Platelet aggregability has been directly related with systemic atherosclerotic disease (3). In addition, the most detrimental manifestation of coronary atherosclerotic disease (i.e., myocardial infarction [MI]) is mediated by platelet activation (4). On this basis, numerous therapeutic options, targeting platelet aggregability, have been proposed.

Dual therapy with aspirin and clopidogrel is the most commonly used antiplatelet strategy in patients undergoing percutaneous coronary intervention (PCI) (5). In these patients a residual high platelet reactivity (HPR) after clopidogrel has been associated with increased cardiovascular events both periprocedural (6) and at long-term follow-up (7,8). Several mechanisms have been described for the suboptimal platelet response to clopidogrel, including genetic, cellular, and clinical factors (9). In addition, baseline platelet reactivity is a strong predictor of platelet response to clopidogrel (10). Given that baseline platelet reactivity is higher in patients with more diffuse vascular atherosclerosis, the potential relationship between residual platelet reactivity after clopidogrel and extent and severity of coronary atherosclerosis has not yet been investigated.

Abbreviations and Acronyms

ANOVA = analysis of variance
CI = confidence interval
HPR = high platelet reactivity
MI = myocardial infarction
MVD = multivessel disease
OR = odds ratio
PCI = percutaneous coronary intervention
PRU = P2Y12 reactivity unit
SVD = single-vessel disease
TSL = total stent length

In the present study, we tested the hypothesis that residual platelet reactivity after clopidogrel correlates with the extent and severity of coronary atherosclerosis in stable angina patients at the occasion of PCI. In addition, we evaluated whether higher residual platelet reactivity after clopidogrel might partly account for an unfavorable periprocedural outcome in patients with more extensive coronary atherosclerosis.

Methods

Patient population and study protocol. We prospectively enrolled 338 patients undergoing PCI for stable angina or a positive functional test and presence of an angiographic significant stenosis (diameter stenosis >50%) in at least 1 native coronary artery. Patients were excluded who had an acute coronary syndrome in the previous month, elevated myocardial necrosis markers before the procedure, thrombocytopenia (platelet count <100,000/l), left ventricular ejection fraction <30%, high bleeding risk, allergy to thienopyridines, PCI for chronic total occlusions, and lesions with extensive calcifications requiring rotational atherectomy. All patients received standardized antiplatelet therapy with clopidogrel 600 mg and aspirin 500 mg loading doses at least 12 h before PCI, irrespective of the ongoing antiplatelet therapy. Of note, there was no significant difference in chronic thienopyridine therapy among patients with single-vessel disease (SVD) and multivessel disease (MVD) (24% vs. 26%, p = 0.617). The local ethics committee approved the study, and written informed consent was obtained from all the included patients.

Technicalities of the procedure, including use of drug-eluting stents and glycoprotein IIb/IIIa inhibitors, were left to the operator's discretion. Heparin was administrated to achieve an activated clotting time of 250 to 300 s. Procedural success was defined as a reduction of stenosis to <30% residual narrowing.

Platelet reactivity after clopidogrel was assessed in the catheterization laboratory by the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) immediately before PCI (and, where appropriate, before the administration of glycoprotein IIb/IIIa inhibitors). Blood was collected from the femoral artery immediately after sheath placement. The first 5 ml of blood were discarded, then samples were collected in 2-ml tubes containing 3.2% sodium citrate. VerifyNow P2Y12 is a validated point-of-care assay specifically assessing clopidogrel effects on P2Y12 receptor by optical turbidimetry (11,12). Specific cartridges contain 20-μmol adenosine diphosphate, which activates platelets by binding P2Y1 and P2Y12 receptors, and 22-nmol prostaglandin E1 (PGE-1), which increases assay specificity by suppressing P2Y1-induced intraplatelet signaling. Activated platelets agglutinate around fibrinogen-coated polystyrene beads, therefore increasing light transmittance through the sample. Results are reported as P2Y12 reactivity units; the lower the P2Y12 reactivity unit (PRU) value, the higher the platelet aggregation inhibition by clopidogrel.

End points. The primary end point of the study was the correlation between extent of atherosclerotic coronary artery disease and residual platelet reactivity after clopidogrel. Presence of MVD (defined as coronary artery stenosis >50%, as assessed by quantitative coronary angiography, in at least 2 major epicardial coronary arteries) and total length of the implanted stents were considered as surrogate markers of atherosclerosis extension and severity, as previously described (13).

The secondary end point was to assess whether HPR, as defined by a PRU value ≥240, in the context of a more extensive atherosclerosis, might partly account for the periprocedural MI. Periprocedural MI was defined as a post-procedural Troponin-T increase more than 3 times the 99th percentile of the upper reference limit (14).

Statistics. Statistical analysis was performed with SPSS version 15.0 software (SPSS, Inc., Chicago, Illinois). The hypothesis of the study is that patients with MVD present a 15% increase in PRU as compared with patients with SVD after 600-mg clopidogrel loading dose. Assuming a 50% incidence of MVD, we calculated that at least 153 patients

should be included in each group (alpha 0.05, statistical power 0.80). Continuous variables are expressed as mean ± SD. Categorical variables are reported as frequencies and percentages. Normality of PRU distribution among the whole population was confirmed by Kolmogorov-Smirnov test. Student *t* test was used to compare continuous variables. The PRU values within total stent length (TSL) tertiles and patients with 1-, 2-, or 3-vessel disease were compared with 1-way analysis of variance (ANOVA) with Bonferroni correction for multiple testing. Comparisons between categorical variables were evaluated with 2-tailed Fisher exact test or Pearson's chi-square test, as appropriate. All clinical and procedural variables that showed a significant univariate association with periprocedural MI ($p < 0.05$) were entered in a multivariable logistic regression model. Statistical significance was defined as a p value <0.05.

Results

A total of 338 patients were enrolled in the study, 185 (55%) with SVD and 153 with MVD. Among patients with MVD, 97 (63%) presented with 2-vessel disease and 56 (37%) had 3-vessel disease. Main clinical and procedural features are shown in Table 1. Left ventricular ejection fraction was lower and previous MI more common in patients with MVD. C-reactive protein was higher in patients with MVD as compared with SVD patients. No significant differences between the 2 groups were observed with respect to other risk factors and ongoing medical therapy. Time from clopidogrel to procedure was similar in the 2 study groups (13 ± 1 in SVD patients, and 13 ± 1 in MVD patients, $p = 0.898$).

Procedural characteristics were comparable between the 2 groups, except for higher number of stents implanted and a longer TSL in the MVD group. In the latter group, 59 (39%) patients underwent multivessel PCI.

PRU and extent of atherosclerosis. Mean PRU value in the overall population was 205 ± 80. Patients with MVD showed significantly higher mean value of PRU compared with subjects with SVD (222 ± 85 vs. 191 ± 73; $p < 0.001$). The PRU values progressively increased with number of diseased coronary arteries (1-vessel disease: 191 ± 73; 2-vessel disease: 220 ± 88; 3-vessel disease: 226 ± 80; p =

Table 1. Clinical and Procedural Features

	Overall Group (n = 338)	SVD (n = 185)	MVD (n = 153)	p Value
Age, yrs	67 ± 10	66 ± 10	68 ± 10	0.068
Male sex	274 (81)	147 (79)	127 (83)	0.686
Diabetes	124 (37)	63 (34)	61 (40)	0.269
Smoking	65 (19)	34 (18)	31 (20)	0.662
Hypertension	242 (72)	132 (71)	110 (72)	0.912
Dyslipidemia	250 (74)	137 (74)	113 (74)	0.967
Body mass index, kg/m^2	28.0 ± 4.1	28.3 ± 4.1	27.7 ± 4.0	0.366
LVEF, %	60 ± 13	61 ± 13	57 ± 12	0.004
Previous MI	85 (25)	34 (18)	51 (33)	0.002
Aspirin	338 (100)	185 (100)	153 (100)	1.000
Beta-blockers	109 (32)	54 (29)	55 (36)	0.186
ACE-inhibitors/ARB	269 (80)	143 (77)	126 (82)	0.251
Statins	251 (74)	134 (72)	117 (76)	0.399
Proton pump inhibitors	88 (26)	50 (27)	38 (25)	0.648
CRP, mg/dl	0.61 ± 0.69	0.47 ± 0.49	0.75 ± 0.83	0.003
LAD	192 (48)	88 (48)	104 (48)	0.872
LCx	91 (23)	46 (25)	45 (21)	0.349
RCA	117 (29)	51 (28)	66 (31)	0.493
B2/C lesions	178 (53)	92 (50)	86 (56)	0.235
Multivessel PCI	59 (18)	—	59 (39)	—
Use of drug-eluting stent	144 (43)	82 (44)	62 (41)	0.482
Direct stenting	125 (37)	67 (36)	58 (37)	0.748
Stents implanted/patient, n	1.62 ± 0.86	1.49 ± 0.84	1.79 ± 0.85	0.002
Total stent length, mm	28 ± 17 (8–117)	26 ± 17 (8–112)	32 ± 17 (9–117)	0.002
Glycoprotein IIb/IIIa inhibitors	4 (1)	1 (1)	3 (2)	0.229

Values are mean ± SD, n (%), or mean ± SD (range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CRP = C-reactive protein; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVEF = left ventricular ejection fraction; MVD = multivessel disease; PCI = percutaneous coronary intervention; RCA = right coronary artery; SVD = single-vessel disease.

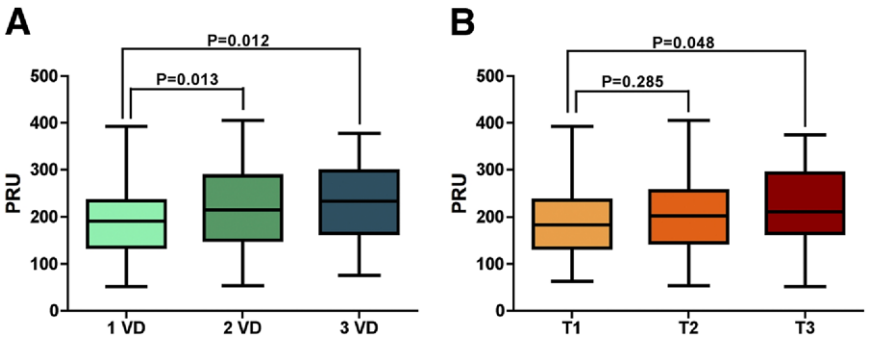

Figure 1. Correlation Between Extent of Coronary Atherosclerosis and Platelet Reactivity After Clopidogrel

Distribution of P2Y12 platelet reaction units (PRU) according to the number of diseased vessels **(A)** and total stent length tertiles **(B)**. **Boxes** extend from the 25th to the 75th percentile, with a **line** at the 50th percentile (median). **Whiskers** show the highest and the lowest value. T = tertile; VD = vessel disease.

0.002 for ANOVA; p = 0.013 for 1-vessel disease vs. 2-vessel disease; p = 0.012 for 1-vessel disease vs. 3-vessel disease) (Fig. 1A). In addition, a significantly higher PRU was also detected in patients in the third TSL tertile compared with those in the first tertile (217 ± 83 vs. 191 ± 73; p = 0.048; p = 0.048 for ANOVA) (Fig. 1B).

HPR and extent of atherosclerosis. Incidence of residual HPR in the entire population was 30%, and it was most frequently observed among patients with MVD (40.5% vs. 21.6% in patients with SVD; odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.53 to 3.98, p < 0.001). Patients with 3-vessel disease presented the highest incidence of HPR (42.9% in 3-vessel disease, 39.2% in 2-vessel disease, and 21.6% in 1-vessel disease; p for trend < 0.001) (Fig. 2A). Likewise, individuals in the third TSL tertile had significantly higher incidence of HPR compared with those in the first tertile (35.8% vs. 22.2%, respectively; OR: 1.96, 95% CI: 1.07 to 3.57, p = 0.028) (Fig. 2B).

HPR and periprocedural MI. Periprocedural MI occurred in 105 patients (31% of the overall population). Patients with HPR had periprocedural MI more frequently (41.2 vs. 26.7 in subjects without HPR; OR: 1.92, 95% CI: 1.18 to 3.13, p = 0.008) (Fig. 3A). Furthermore, periprocedural MI was significantly more frequent in patients in the third TSL tertile compared with those in the first tertile (37.7% vs. 23.1%, respectively; OR: 2.01, 95% CI: 1.11 to 3.65, p = 0.020) (Fig. 3B). By univariate analysis, presence of diabetes, HPR, MVD, and TSL values in the third tertile versus first tertile showed a significant correlation with periprocedural MI. By multivariate analysis (including only MVD as a marker of coronary atherosclerosis extent), HPR was the only independent predictor of periprocedural MI (p = 0.043) (Table 2).

Discussion

This prospective study conducted in patients with stable angina at the occasion of PCI showed a significant correlation between extent of coronary atherosclerosis and residual platelet reactivity after clopidogrel administration. In addi-

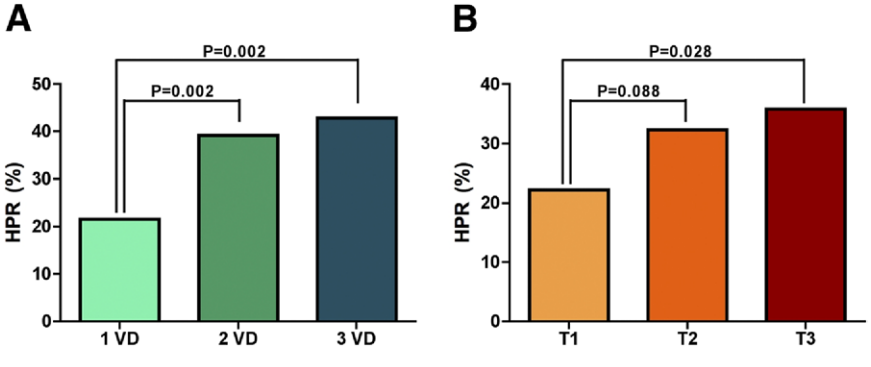

Figure 2. Correlation Between Extent of Coronary Atherosclerosis and High Residual Platelet Reactivity After Clopidogrel

Incidence of high platelet reactivity (HPR) (%) according to the number of diseased vessels **(A)** and to the tertiles (T) of total stent length **(B)**. VD = vessel disease.

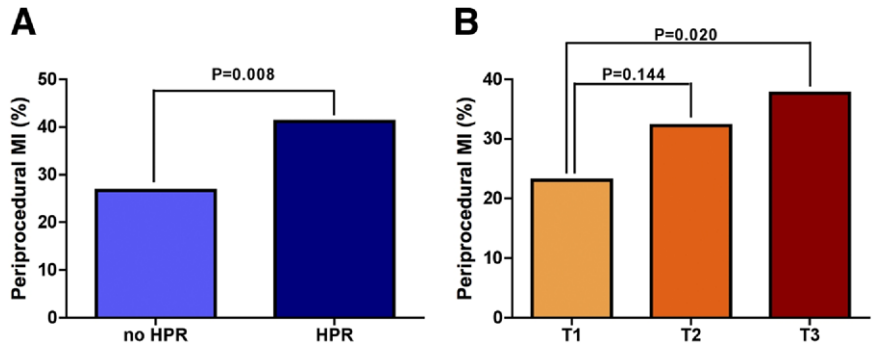

Figure 3. Periprocedural MI

Incidence of periprocedural myocardial infarction (MI) according to presence of high platelet reactivity (HPR) **(A)** and to the tertiles (T) of total stent length **(B)**.

tion, patients with MVD demonstrated an increased rate of HPR, which was confirmed also in our study as the strongest predictor of periprocedural MI.

Role of platelets in vascular atherosclerosis. Platelets are actively involved in vascular atherosclerosis (1,2,15). Patients with stable coronary artery disease have increased platelet reactivity and circulating monocyte-platelet aggregates (16), which also have been demonstrated early markers of acute MI (17). In addition, platelet reactivity is progressively increased as a function of the number of vascular districts involved by atherosclerosis (cerebral, cardiac, peripheral) (3). Our findings extend these observations, showing that the higher baseline platelet reactivity observed in patients with more diffuse coronary atherosclerosis results also in higher platelet reactivity after clopidogrel. This relationship between coronary atherosclerosis extent and platelet reactivity after clopidogrel was found significant for both parameters used to evaluate coronary atherosclerotic burden (i.e., number of diseased vessels and TSL).

Vascular atherosclerosis and variability in platelet response after clopidogrel. A large variability in platelet response to clopidogrel has been described, ranging from patients with high (so-called "low-responders") to low residual platelet reactivity (9). Optimal platelet inhibition is crucial in patients undergoing PCI, as suggested by the fact that patients with low response to clopidogrel present higher risk of recurrent ischemic events (18). Different studies have aimed at identifying low-responders to clopidogrel, supporting the use of a simple and readily available point-of-care assay, VerifyNow P2Y12. In the present study, we adopted a PRU value ≥240 at the VerifyNow assay as a threshold to define HPR patients "low responders" after clopidogrel. This value has been previously demonstrated as optimal cutoff to discriminate those patients undergoing PCI at higher risk of major adverse cardiovascular events (6). We found significant correlation between HPR and extension/severity of coronary atherosclerosis. In particular, higher incidence of HPR was observed in those patients with MVD or higher TSL. Our data are in agreement with findings of Angiolillo et al. (19), who also observed higher TSL in patients "low responder" to clopidogrel undergoing elective PCI, loaded with 300-mg clopidogrel before PCI. In contrast, Gurbel et al. (10) showed significantly higher TSL in patients who are good responders. This discrepancy in the latter study might be explained by the fact that clopidogrel was administered after PCI and by the smaller atherosclerotic burden as compared with that of our patients (e.g., shorter lesion length, lower percent of B2/C lesions, lower stent/patient ratio). TSL, as surrogate of atherosclerosis extension, is of limited use if not paralleled by angiographic estimation of coronary severity. In this situation, in fact, procedural factors (like edge dissections, operator's choice, and so forth) might be predominant in determining final TSL.

HPR and periprocedural MI. Coronary manipulation and side branch occlusion are known determinants of periprocedural MI in patients undergoing elective PCI (20). Several studies have clearly shown a direct relationship among the implantation of multiple stents, total length of stents implanted, and periprocedural outcome (21–23). Patients with MVD are expected, in view of the more extensive coronary manipulation, to present higher risk of periprocedural myonecrosis, as confirmed also in our study where a higher rate of periprocedural MI was observed in patients in the highest tertile of TSL compared with those in the lowest tertile. Yet, the higher rate of HPR found in

Table 2. Multivariate Analysis: Predictors of Periprocedural MI

	Odds Ratio	95% Confidence Interval	p Value
HPR	1.684	1.016–2.789	0.043
Diabetes	1.525	0.943–2.466	0.085
MVD	1.507	0.934–2.432	0.093

HPR = high platelet reactivity; MI = myocardial infarction; MVD = multivessel disease.

our MVD patients suggests that suboptimal platelet inhibition in this clinical setting might at least in part be responsible for the higher risk of periprocedural MI. In fact, we confirmed HPR as the strongest predictor of periprocedural MI, as also previously shown (6,24). This is further corroborated by the recent demonstration that increased risk of periprocedural MI observed in the highest TSL quartile can be largely mitigated by a more aggressive platelet inhibition with eptifibatide to the level observed in patients in the lowest TSL quartile (23).

Study limitations. By study design, only patients with stable angina were enrolled; therefore our results are not applicable to patients with acute coronary syndromes. No clinical follow-up of the patients is available.

Coronary atherosclerosis severity and extension have been evaluated by the presence of coronary artery stenosis >50% and/or total length of the implanted stents. This latter has been described as a valid surrogate of total lesion length (13). We cannot exclude that actual final stent length has been slightly overestimated by stent overlapping.

Conclusions

Patients with more extensive coronary atherosclerosis have a higher rate of HPR, which might partly account for higher risk of periprocedural MI, advocating the need for more aggressive platelet inhibition in this clinical setting.

Reprint requests and correspondence: Dr. Emanuele Barbato, Cardiovascular Center OLV, Moorselbaan 164, B-9300 Aalst, Belgium. E-mail: emanuele.barbato@olvz-aalst.be.

REFERENCES

1. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. Circulation 2001;103:1718–20.
2. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482–94.
3. Keating FK, Whitaker DA, Kabbani SS, Ricci MA, Sobel BE, Schneider DJ. Relation of augmented platelet reactivity to the magnitude of distribution of atherosclerosis. Am J Cardiol 2004;94:725–28.
4. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. N Engl J Med 1986;315:983–89.
5. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
6. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008;52:1128–33.
7. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008;29:992–1000.
8. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to adenosine diphosphate detected by a point-of-care assay: a 12-month follow-up. Circulation 2009;119:237–42.
9. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
10. 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.
11. Malinin A, Pokov A, Swaim L, Kotob M, Serebruany V. Validation of a VerifyNow-P2Y12 cartridge for monitoring platelet inhibition with clopidogrel. Methods Find Exp Clin Pharmacol 2006;28:315–22.
12. van Werkum JW, van der Stelt CA, Seesing TH, Hackeng CM, ten Berg JM. A head-to-head comparison between the VerifyNow P2Y12 assay and light transmittance aggregometry for monitoring the individual platelet response to clopidogrel in patients undergoing elective percutaneous coronary intervention. J Thromb Haemost 2006;4:2516–8.
13. Yan BP, Duffy SJ, Clark DJ, et al. Rates of stent thrombosis in bare-metal versus drug-eluting stents (from a large Australian multicenter registry). Am J Cardiol 2008;101:1716–22.
14. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.
15. Gawaz M, Stellos K, Langer HF. Platelets modulate atherogenesis and progression of atherosclerotic plaques via interaction with progenitor and dendritic cells. J Thromb Haemost 2008;6:235–42.
16. Furman MI, Benoit SE, Barnard MR, et al. Increased platelet reactivity and circulating monocyte-platelet aggregates in patients with stable coronary artery disease. J Am Coll Cardiol 1998;31:352–8.
17. Furman MI, Barnard MR, Krueger LA, et al. Circulating monocyte-platelet aggregates are an early marker of acute myocardial infarction. J Am Coll Cardiol 2001;38:1002–06.
18. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. J Am Coll Cardiol 2005;46:1820–6.
19. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Identification of low responders to a 300-mg clopidogrel loading dose in patients undergoing coronary stenting. Thromb Res 2005;115:101–8.
20. Bates ER. Ischemic complications after percutaneous transluminal coronary angioplasty. Am J Med 2000;108:309–16.
21. Kereiakes DJ, Wang H, Popma JJ, et al. Periprocedural and late consequences of overlapping Cypher sirolimus-eluting stents: pooled analysis of five clinical trials. J Am Coll Cardiol 2006;48:21–31.
22. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005;294:1215–23.
23. Tcheng JE, Lim IH, Srinivasan S, et al. Stent parameters predict adverse clinical outcomes and response to platelet glycoprotein IIb/IIIa blockade: findings of the ESPRIT trial. Circ Cardiovasc Intervent 2009;2:43–51.
24. Cuisset T, Hamilos M, Sarma J, et al. Relation of low response to clopidogrel assessed with point-of-care assay to periprocedural myonecrosis in patients undergoing elective coronary stenting for stable angina pectoris. Am J Cardiol 2008;101:1700–3.

Key Words: atherosclerosis ■ clopidogrel ■ PCI ■ platelets.