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Clinical Article

Significance of Clopidogrel Resistance Related to the Stent-Assisted Angioplasty in Patients with Atherosclerotic Cerebrovascular Disease

Gyoung-Jun Rho, M.D.,[1] Woo-Ram Shin, M.D.,[1] Tae-Sik Kong, M.D.,[1] Min-Sun Kim, M.D.,[2] Chang-Ju Lee, M.D.,[2] Byung-Hee Lee M.D.[2]

Department of Neurosurgery,[1] Presbyterian Medical Center, Jeonju, Korea
Department of Radiology,[2] Eulji University Hospital, Daejeon, Korea

Objective : To evaluate the prevalence and risk factors of clopidogrel resistance, and association between thromboembolic complications and clopidogrel resistance in patient with stent-assisted angioplasty for atherosclerotic cerebrovascular disease.
Methods : Between September 2006 and June 2008, clopidogrel resistance test was performed on 41 patients who underwent stent-assisted angioplasty for atherosclerotic cerebrovascular disease. It was performed before drug administration and about 12 hours after drug administration (loading dose : 300 mg, maintain dose : 75 mg). Two patients were excluded, and 41 patients were included (mean : 67.59±7.10 years, age range : 41-79). Among 41 patients, 18 patients had intracranial lesions, and 23 had extracranial lesions. We evaluated the prevalence, risk factors and complications related to clopidogrel resistance.
Results : Twenty-one patients (51.2%) showed clopidogrel resistance [intracranial : 10 patients (55.6%), extracranial : 11 patients (47.8%)] and no clopidogrel resistance was seen in 20 patients. Hypercholesterolemia was an indepedent risk factor of clopidogrel resistance. Stent-assisted angioplasty was technically successful in all patients, but acute in-stent thrombosis occurred in 5 patients with intracranial lesions (4 patients with clopidogrel resistance and 1 without clopidogrel resistance). Acute thrombi were completely lysed after intra-arterial infusion of abciximab.
Conclusion : There was relatively high prevalence of clopidogrel resistance in patients with atherosclerotic cerebrovascular disease. Hypercholesterolemia was an independent predictive factor of clopidogrel resistance. Acute in-stent thrombosis was more frequently seen in the clopidogrel resistant group. Therefore, clopidogrel resistance test should be performed to avoid thromboembolic complications related to stent-assisted angioplasty for atherosclerotic cerebrovascular disease, especially patients with hypercholeterolemia and intracranial lesion.

Key Words : Clopidogrel · Resistance · Neurointervention · Stent.

INTRODUCTION

Peri-procedural administration of asprin and clopidogrel are considered as "standard of care" to prevent perioperative thromboembolic complications. Clopidogrel is an ADP-receptor antagonist. After oxidased by hepatic cytochrome P450, selectively and irreversibly blocking the P2Y12 receptor and then causes an irreversible blockade of ADP binding[4,5,30]. But, recently, approximately 15% to 30% of patients have been reported to be resistant to clopidogrel[6,9,10,16]. Also, prevalence of clopidogrel resistance has been reported from 42.9% to 62.3% those patients who underwent cerebrovascular stent placement procedure[20,27,29]. Furthermore, clopidogrel resistance were thought to enhance major cardiovascular events and death may in patients with acute myocardial infarction and patients who treated with coronary stent[7,22]. Therefore, we evaluated the prevalence and risk factors of clopidogrel resistance, and association between thromboembolic complications and clopidogrel resistance in patient with stent-assisted angioplasty for atherosclerotic cerebrovascular disease.

MATERIALS AND METHODS

Between September 2006 and June 2008, clopidogrel resistance test was performed on 43 patients who underwent stent-assisted angioplasty for atherosclerotic cerebrovascular disease. Two patients were excluded. We did not check clopidogrel resistance test in 2 patients. Clopidogrel resistance test was performed before drug administration and about 12 hours after drug administration (loading dose : 300 mg, maintain dose : 75 mg).

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• Address for reprints : Byung-Hee Lee, M.D.
Departement of Radiology, Eulji University Hospital, Seo-gu,
1306 Dunsan 2-dong, Daejeon 302-799, Korea
Tel : +82-42-611-3551, Fax : +82-42-611-3590
E-mail : mdbhlee@eulji.ac.kr

Among 41 patients, 18 patients had intracranial lesions, and 23 patients had extracranial lesions. We used the VerifyNow-p2y12 rapid analyzer (Accumetrics, San Diego, CA, USA) to measure platelet inhibition rate. We defined clopidogrel resistance as percentage platelet inhibition <20%.

We analysed our data by using commercial software (SPSS version 14.0, SPSS Inc., Chicago, IL, USA). We used independent t-test, uni-variate (Fisher's exact test) and multi-variate (binary logistic regression) analysis to evaluate associations between variable predictive factors and clofidogrel resistance. We used Mann-Whitney U test to evaulate the relationship between thromboembolic event and clopidogrel resistance. $p<0.05$ was considered statistically significant.

Endovascular procedures

Endovascular procedures were perfomed under local anesthesia. Arterial access was achieved via the femoral artery. A guiding catheter was placed in the internal carotid artery. We used 6F, 7F, 8F guiding catheter system (Envoy; Cordis, Bridgewater, NJ, USA), through the femoral artery via the vascular sheath. Cerebral angiography was done by using these guiding catheters with heparin infusion (heparin 5,000 IU mix normal saline 1,000 mL) during intervention. Then, a microcatheter (Echelon-10; ev3, Irvine, CA, USA) was advanced and placed into the stenotic lesion using (x-pedion 0.014-inch microwires, ev3, Irvine, CA, USA) via conventional technique.

Stent insertion was carried out using the following stents : Wallstent (Boston Scientific, Natick, MA, USA), and Cypher (Cordis, Bridgewater, NJ, USA)

RESULTS

Among 41 patients, 25 patients were male and 16 patients were female. Mean age was 67.59±7.10 years (range : 41-79). Intracranial lesions were 18 (43.9%) cases, and extracranial lesions were 23 cases (56.1%). Overall clopidogrel resistance was 27.37±28.60 (range : 0-96). Twenty-two patients showed clopidogrel resistance (4.86±5.83%). Prevalence of the clopidogrel resistance in patients who underwent stent-assited angioplasty was 53.7%.

Clinical comparrion between clopidogrel resistant group (CRG) and clopidogrel sensitive group (CSG) was demonstrated in Table 1. Base, P2Y12 reaction unit before drug administration, was 267.82±62.53 in CRG and 249±72.56 in CSG (p=0.378). PRU, P2Y12 reaction unit after drug administration, was 279.05±54.42 in CRG and 120.74±65.29 in CSG (p=0.00001). Platelet aggregation inhibition was markedly decreased in CRG. PRU showed decreased platelet aggregation inhibition in CRG. Platelet inhibition rate was 4.86±5.83 in CRG and 53.42±21.05 in CRG (p=0.00001).

In this study, we found hypercholeterolemia was a statistically significant risk factor associated with clopidogrel resistance by using univariate and multivariate analysis (p=0.036 and p=0.037, respectively) (Table 2).

We analysed association between the incidence of intra-procedural in-stent thrombosis and clopidogrel resistance. Stent-assisted angioplasty was technically successful in all patients, but acute in-stent thrombosis occurred in 5 patients with intracranial lesions (four patients with clopidogrel resistance and one patient without clopidogrel resistance). Acute thrombi were completely lysed after intra-arterial infusion of abciximab. In-stent thrombosis occurred more frequently in CRG than CSG (Table 3).

Table 1. Comparrion of clopidogrel resistant group and clopidogrel sensitive group

Characteristics (mean±standard deviation)	Clopidogrel resistant group (n=22)	Clopidogrel sensitive group (n=19)	*p*-value
Age	67.59±6.00	67.58±8.37	0.996
Base*	267.82±62.53	249±72.56	0.378
PRU†	279.05±54.42	120.74±65.29	0.00001
Platelet inhibition rate	4.86±5.83	53.42±21.05	0.00001
WBC (1,000/μL)	7.89±2.24	7.67±2.82	0.776
Platelet (1,000/μL)	263.15±113.07	278.05±81.83	0.636
CRP (mg/dL)	1.3427±1.83	0.55±0.63	0.067

*P2Y12 reaction unit before drug administraion, †P2Y12 reaction unit after drug administration.

Table 2. Analysis of the associations between variable factors and clopidogrel resistance

Characteristics		Clopidogrel resistant group	Clopidogrel sensitive group	Univariate *p*-value	Multivariate *p*-value
Age	Age<55	1 (4.5%)	1 (5.3%)	0.718	0.427
	Age≥55	21 (95.5%)	18 (94.7%)		
Sex	Male	12 (54.5%)	13 (68.4%)	0.522	0.585
	Female	10 (45.5%)	6 (31.6%)		
Hypertension	+	18 (81.8%)	13 (68.4%)	0.469	0.921
	-	4 (18.2%)	6 (31.6%)		
Diabetes	+	12 (54.5%)	7 (36.8%)	0.35	0.455
	-	10 (45.5%)	12 (62.2%)		
Smoking	+	7 (31.8%)	11 (57.8%)	0.122	0.168
	-	15 (68.2%)	8 (42.2%)		
Hypercholesterolemia	+	21 (95.5%)	13 (68.4%)	0.036	0.037
	-	1 (4.5%)	6 (31.6%)		
Coronary artery disease history	+	5 (22.7%)	4 (21.0%)	1	0.531
	-	17 (77.3%)	15 (79.0%)		
Stroke history	+	11 (50.0%)	8 (42.1%)	0.756	0.552
	-	11 (50.0%)	11 (57.9%)		

There were no statistically significant differences in level of WBC, initial platelet count, and CRP (Table 1). Hypertension, diabetes, smoking, previous coronary artery disease history, and previous stroke history showed no significant correlation with clopidogrel resistance (Table 2).

DISCUSSION

Recently, older than 55 years-old, diabetes, hypercholesterolemia and greater body weight were reported as predictive factors of clopidogrel resistance in patients who underwent stent-assited algioplasty[20,27,29]. Hypertension and diabetes were more frequent in CRG than CSG (p=0.921, p=0.455, respectively, multi-variate analysis). Older than 55 years-old was not independently significant in this study (p=0.718 and p=0.427, respectively, uni- and multi-variate analysis).

In our study, only hypercholesterolemia was an independent risk factor of clopidogrel resistace (p=0.036 and p=0.037, respectively, uni- and multi- variate analysis). Influence of hypercholeteroloemia on clopidogrel resistance is unclear. In a report, the lipophilic statin atorvastatin significantly reduced clopidogrel-induced inhibition of platelet aggregation in a dose-dependant manner at 24h[18]. Both lipophlic statins and clopidogrel are metabolized by hepatic cytochrome P450 isoenzyme[17]. Since Lau et al.[18], many investigators have studied the relationship, but the interaction between statins and clopidogrel is still controversial[3,6].

We observed a relation between clopidogrel resistance and intraprocedural complication. In our study, within 41 patients, 5 patients suffered from in-stent thrombosis (12.2%). Platelet inhibition rate of the four patients were under cutoff value (<20%). After intra-arterial infusion of abciximab 20 mg, thrombi were completely resolved, and there were no neurologic complications (Fig. 1). A comparative photographs of one patient without in-stent thromosis were demonstrated in Fig. 2. Remarkably, all the 5 patients who suffered from in-stent thrombosis had intracranial lesions. In intracranial lesion group, rate of in-stent thrombosis occurrence was 27.8% in this study. In details, complication rate of intracranial lesion was 40% (4/10) in CRG and 12.5% (1/8) in CSG. It seemed to have a relationship between intracranial lesions and in-stent thrombosis in patients with clopidogrel resistance. Vascular diameter and blood flow might be concerned. But, too small sample size to verify the relation in this study. Lee et al.[20], re-

Table 3. Analysys of the accocitation between complication occurrence and clopidogrel resistance

		Clopidogrel resistant level mean±SD	Mann-Whitney U test p-value
Complication	+	16.2±15.55	0.802
	-	28.92±28.02	

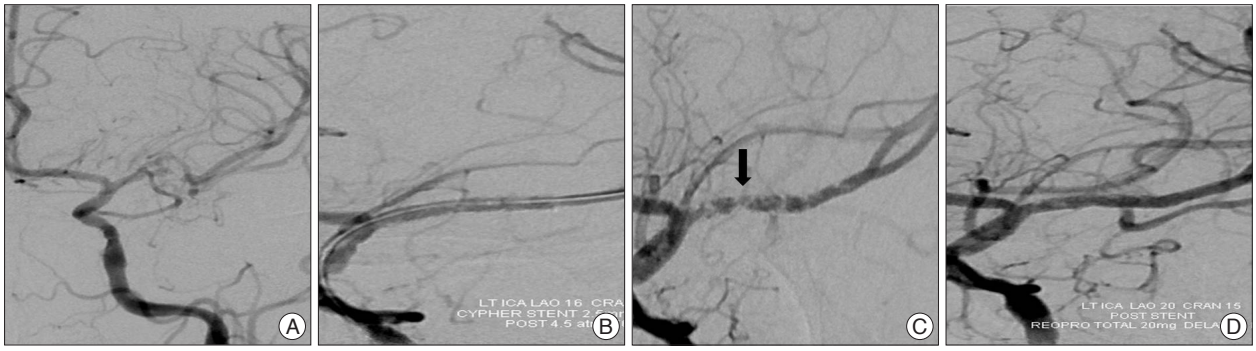

Fig. 1. Angiograms of 59-year-old female. Left M1 distal segment 95% stenosis. Intra-procedural thrombosis is observed. Inhibition rate was 9%. A : Lt M1 stenosis. B : Post-stent insertion. C : Fifteen minutes after stent insertion. D : After Reopro 20 mg Intra-arterial injection. Arrow : Acute thrombus.

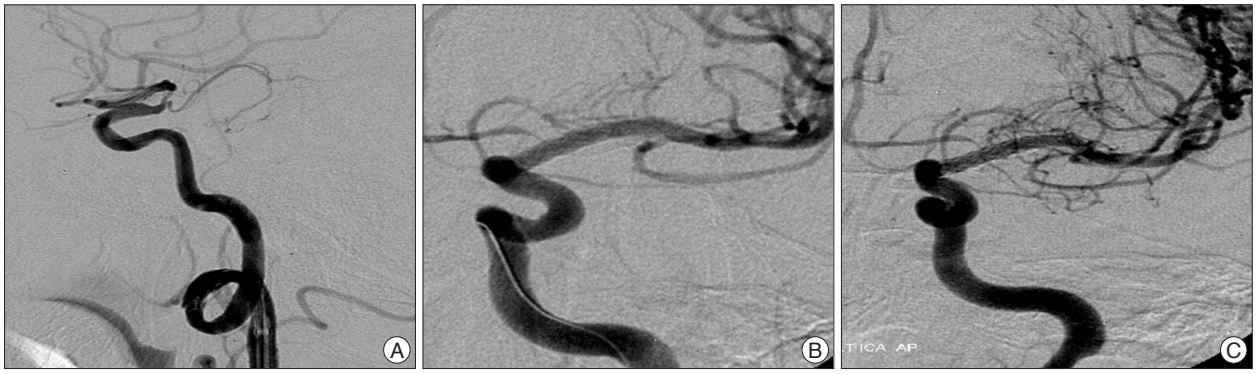

Fig. 2. Angiograms of 70-year-old female. Left internal carotid artery (ICA) bifurcation shows severe (99%) stenosis. No intra-procedural thrombosis is observed. Inhibition rate was 38%. A : Lt ICA bifurcation stenosis. B : Post-stent insertion. C : Fifteen minutes after stent insertion.

ported 3 cases of intraprocedural complication. Overall complication rate was 3.1%. All complicated patients belonged to CRG. In clopidogrel reponse group, rate of intraprocedural complication was 7.1%. They reported there were no clinical consequences after prompt administration of parenteral abciximab. Ryu et al.[27], reported 5 cases of thromboembolic complication after neurointerventional procedures. These cases showed resistance to both aspirin and clopidogrel. Total thromboembolic complication rate was 9.4%. In their study, 10 patients displayed resistance to both aspirin and clopidogrel. In both resistance groups, thromboembolic complication rate was 50%. This complication rate was relatively high. Platelet inhibition rate of one patient who suffered from in-stent thrombosis in clopidogrel sensitive group in our study was 43%. Lee et al.[20] and Ryu et al.[27] defined clopidogrel resistance as percentage platelet inhibition less than 40%. Although no statistical significance was found in our study, these data suggested that patients who had low platelet inhibition rate were more likely to suffer from periprocedural thromboembolic complications.

To overcome clopidogrel resistance, several methods are suggested. First, increasing the loading dose and maintenance dose of clopidogrel[12,33]. Second, use of the new drugs, whole replacement or addition, such as Prasugrel (CS-747), a novel thienopyridine that inhibits adenosine diphosphate-induced platelet aggregation more rapidly with less intraindividual variability and to a greater magnitude than do standard and higher doses of clopidogrel[24,35,36], Ticagrelor (AZD6140), the first reversibly binding oral, direct-acting P2Y12 receptor antagonist[11,26,31,32], Cangrelor (AR-C69931) short-acting, IV, reversible inhibitor of P2Y12 receptor[2,8], and Cilostazol, a phosphodiesterase 3 inhibitor[1,13,21,23]. St. John's Wort, a potent CYP2C19 and CYP3A4 inducer, and a popular herbal remedy used for the treatment of depression, anxiety, and insomnia[19]. We have to oberve the clinical results of these drugs to find "standard of care" for the pateints shows clopidogrel resistance.

Smoking was not an independent factor influencing clopidogrel resistance in this study, although more frequently seen in PSG (31.8% in PRG, 57.8% in PSG. p=0.122 and p=0.168, respectively, uni- and multi-variate analysis). Some reports suggested a strong relationship between smoking and clopidogrel resistance, known as "Smokre's Paradox"[15,25,28,34]. Recently, Motovska et al.[25], reported cigarette smoking as an independently associated factor with a prompt antiplatelet response to clopidogrel in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention. Schedel et al.[28], found clear evidence that agonist binding to platelet nAChRα7 receptors elicits Ca^{2+} influx and enhanced fibrinogen receptor activation. Nicotine is a major constituent of cigarette smoke and also a selective cholinergic agonist. Contrastively, in a recent randomised perspective study[14], current smokers significantly showed higher rates of procedure-ralated thromboembolism (p<0.001), and clopidogrel premedication failed to modify the risk of them in patients with unruptured intracranial aneurysms treated with coil embolization. Can we recommand smoking to enhance clopidogrel efficacy?

Our study had some limitations including small sample size, no randomized design, which could lead to some unexpected bias and lack of aspirin resistance. Most of all, clopidogrel resistance was not definitely defined yet and there was no standardized laboratory method to measure platelet inhibition rate. Further studies are needed to define clopidogrel resistance for Asian, especially for Korean and to find relationshiops between clopidogrel resistance and clinical outcome.

CONCLUSION

There was relatively high prevalence of clopidogrel resistance in patients with atherosclerotic cerebrovascular disease. Hypercholesterolemia was an independent predictive factor of clopidogrel resistance. Acute in-stent thrombosis was more frequently seen in the clopidogrel resistant group. Therefore, clopidogrel resistance test should be done to avoid thromboembolic complications related to stent-assisted angioplasty for atherosclerotic cerebrovascular disease, especially in patients with hypercholeterolemia and intracranial lesion.

References

1. Angiolillo DJ, Capranzano P, Goto S, Aslam M, Desai B, Charlton RK, et al. : A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy : results of the OPTIMUS-2 study. **Eur Heart J 29** : 2202-2211, 2008
2. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, et al. : Intravenous platelet blockade with cangrelor during PCI. **N Engl J Med 361** : 2330-2341, 2009
3. Bhindi R, Ormerod O, Newton J, Banning AP, Testa L : Interaction between statins and clopidogrel : is there anything clinically relevant? **QJM 101** : 915-925, 2008
4. Ding Z, Kim S, Dorsam RT, Jin J, Kunapuli SP : Inactivation of the human P2Y12 receptor by thiol reagents requires interaction with both extracellular cystein residues, Cys17 and Cys270. **Blood 101** : 3908-3914, 2003
5. Feher G, Feher A, Pusch G, Lupkovics G, Szapary L, Papp E : The genetics of antiplatelet drug resistance. **Clin Genet 75** : 1-18, 2009
6. Feher G, Feher A, Pusch G, Koltai K, Tibold A, Gasztonyi B, et al. : Clinical importance of aspirin and clopidogrel resistance. **World J Cardiol 2** : 171-186, 2010
7. Geisler T, Langer H, Wydymus M, Göhring K, Zürn C, Bigalke B, et al. : Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. **Eur Heart J 27** : 2420-2425, 2006
8. Greenbaum AB, Ohman EM, Gibson CM, Borzak S, Stebbins AL, Lu M, et al. : Preliminary experience with intravenous P2Y12 platelet receptor inhibition as an adjunct to reduced-dose alteplase during acute myocardial infarction: results of the Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) angiographic trial. **Am Heart J 154** : 702-709, 2007
9. Gurbel PA, Antonino MJ, Tantry US : Recent developments in clopidogrel pharmacology and their relation to clinical outcomes. **Expert Opin Drug Metab Toxicol 5** : 989-1004, 2009
10. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. : Randomized double-blind assessment of the ONSET and OFFSET of

the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. **Circulation 120** : 2577-2585, 2009
11. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G : Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis : a double-blind comparison to clopidogrel with aspirin. **Eur Heart J 27** : 1038-1047, 2006
12. Jeong YH, Lee SW, Choi BR, Kim IS, Seo MK, Kwak CH, et al. : Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity : results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients with Clopidogrel Resistance) randomized study. **J Am Coll Cardiol 53** : 1101-1109, 2009
13. Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, et al. : Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. **Eur Heart J 27** : 1166-1173, 2006
14. Kang HS, Han MH, Kwon BJ, Jung C, Kim JE, Kwon OK, et al. : Is clopidogrel premedication useful to reduce thromboembolic events during coil embolization for unruptured intracranial aneurysms? **Neurosurgery 67** : 1371-1376; discussion 1376, 2010
15. Katayama T, Iwasaki Y, Yamamoto T, Yoshioka M, Nakashima H, Suzuki S, et al. : ["Smoker's paradox" in patients with acute myocardial infarction receiving primary coronary intervention]. **J Cardiol 48** : 193-200, 2006
16. Kuliczkowski W, Witkowski A, Polonski L, Watala C, Filipiak K, Budaj A, et al. : Interindividual variability in the response to oral antiplatelet drugs : a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. **Eur Heart J 30** : 426-435, 2009
17. Lau WC, Waskell LA, Neer CJ, Carville DGM, Bates ER : The antiplatelet activity of clopidogrel is inhibited by atorvastatin but not by pravastatin. **Circulation 102** : 2086, 2000
18. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. : Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation : a new drug-drug interaction. **Circulation 107** : 32-37, 2003
19. Lau WC, Welch TD, Shields T, Rubenfire M, Tantry US, Gurbel PA : The effect of St John's Wort on the pharmacodynamic response of clopidogrel in hyporesponsive volunteers and patients : increased platelet inhibition by enhancement of CYP3A4 metabolic activity. **J Cardiovasc Pharmacol 57** : 86-93, 2011
20. Lee DH, Arat A, Morsi H, Shaltoni H, Harris JR, Mawad ME : Dual antiplatelet therapy monitoring for neurointerventional procedures using a point-of-care platelet function test : a single-center experience. **AJNR Am J Neuroradiol 29** : 1389-1394, 2008
21. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, et al. : Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus : the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). **J Am Coll Cardiol 51** : 1181-1187, 2008
22. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, et al. : Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. **Circulation 109** : 3171-3175, 2004
23. Min PK, Jung JH, Ko YG, Choi D, Jang Y, Shim WH : Effect of cilostazol on in-stent neointimal hyperplasia after coronary artery stenting : a quantitative coronary angiography and volumetric intravascular ultrasound study. **Circ J 71** : 1685-1690, 2007
24. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, et al. : Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 : an application of the classification system from the universal definition of myocardial infarction. **Circulation 119** : 2758-2764, 2009
25. Motovska Z, Widimsky P, Petr R, Bilkova D, Marinov I, Simek S, et al. : Factors influencing clopidogrel efficacy in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention : statin's advantage and the smoking "paradox". **J Cardiovasc Pharmacol 53** : 368-372, 2009
26. Prabhakaran S, Wells KR, Lee VH, Flaherty CA, Lopes DK : Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting. **AJNR Am J Neuroradiol 29** : 281-285, 2008
27. Ryu DS, Hong CK, Sim YS, Kim CH, Jung JY, Joo JY : Anti-platelet drug resistance in the prediction of thromboembolic complications after neurointervention. **J Korean Neurosurg Soc 48** : 319-324, 2010
28. Schedel A, Thornton S, Schloss P, Klüter H, Bugert P : Human platelets express functional alpha7-nicotinic acetylcholine receptors. **Arterioscler Thromb Vasc Biol 31** : 928-934, 2011
29. Schleinitz MD, Olkin I, Heidenreich PA : Cilostazol, clopidogrel or ticlopidine to prevent sub-acute stent thrombosis : a meta-analysis of randomized trials. **Am Heart J 148** : 990-997, 2004
30. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. : Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. **J Am Coll Cardiol 50** : 1852-1856, 2007
31. Storey RF, Oldroyd KG, Wilcox RG : Open multicentre study of the P2T receptor antagonist AR-C69931MX assessing safety, tolerability and activity in patients with acute coronary syndromes. **Thromb Haemost 85** : 401-407, 2001
32. Tantry US, Bliden KP, Gurbel PA : AZD6140. **Expert Opin Investig Drugs 16** : 225-229, 2007
33. von Beckerath N, Kastrati A, Wieczorek A, Pogatsa-Murray G, Sibbing D, Graf I, et al. : A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. **Eur Heart J 28** : 1814-1819, 2007
34. Weisz G, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, et al. : Impact of smoking status on outcomes of primary coronary intervention for acute myocardial infarction--the smoker's paradox revisited. **Am Heart J 150** : 358-364, 2005
35. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. : Prasugrel versus clopidogrel in patients with acute coronary syndromes. **N Engl J Med 357** : 2001-2015, 2007
36. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. : Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention : the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. **Circulation 116** : 2923-2932, 2007