AJNR

Clopidogrel Resistance Is Associated with Thromboembolic Complications in Patients Undergoing Neurovascular Stenting

J.T. Fifi, C. Brockington, J. Narang, W. Leesch, S.L. Ewing, H. Bennet, A. Berenstein and J. Chong

AJNR Am J Neuroradiol 2013, 34 (4) 716-720
doi: https://doi.org/10.3174/ajnr.A3405
http://www.ajnr.org/content/34/4/716

Clopidogrel Resistance Is Associated with Thromboembolic Complications in Patients Undergoing Neurovascular Stenting

J.T. Fifi, C. Brockington, J. Narang, W. Leesch, S.L. Ewing, H. Bennet, A. Berenstein, and J. Chong

ABSTRACT

BACKGROUND AND PURPOSE: Antiplatelet drug resistance has been associated with thromboembolic complications in patients after coronary stent placement. It has not been well-studied in patients who have neurovascular stent-placement procedures. This study aimed to analyze the relationship between antiplatelet drug resistance and neurovascular stent-placement complications.

MATERIALS AND METHODS: A prospective data base of all patients treated at our institution was used to identify patients with neurovascular stent-placement procedures. During a 4.5-year period, all patients undergoing neurovascular stent placement were evaluated for aspirin and clopidogrel resistance by using the VerifyNow assay. During an observational phase, all patients received 75 mg of clopidogrel and aspirin (group A). During the intervention phase (group B), patients were given additional clopidogrel on the basis of the clopidogrel resistance assay. We assessed the development of thromboembolic complications within 30 days of the procedure in patients who were resistant-versus-nonresistant to clopidogrel.

RESULTS: Of 96 patients who had neurovascular stent placement, 5.2% were resistant to aspirin and 36.5% were resistant to clopidogrel. Periprocedural thromboembolic complications were seen in 7 patients (7.3%). In a multivariate logistic regression model, clopidogrel resistance, higher diastolic blood pressure, and lack of statin use were significantly associated with periprocedural thromboembolic complication. There was a nonsignificant decrease in thromboembolic complications in patients whose clopidogrel dosage was tailored to the assay.

CONCLUSIONS: In our series, clopidogrel resistance was associated with increased periprocedural thromboembolic complications from neurovascular stent-placement procedures. Targeting the clopidogrel dose to platelet inhibition assays may improve clinical outcomes and requires further study.

ABBREVIATIONS: ACT = activated clotting time; ARU = aspirin reaction units; LTA = light transmittance aggregometry; PCI = percutaneous cardiovascular interventions; PRU = P2Y12 reaction units

Thromboembolic events, especially stroke, account for most serious complications following neuroendovascular stent procedures.[1,2] Mainly on the basis of the larger experience from percutaneous cardiovascular interventions,[3] the use of aspirin and clopidogrel to mitigate the risk of thromboembolic events is uniformly recommended for all currently available neuroendovascular stents.[4] Pharmacologic studies in cardiovascular patients have demonstrated the wide variability of platelet inhibition in response to clopidogrel among individual patients.[5-7] Furthermore, a significant portion of patients can be classified as having aspirin or clopidogrel resistance. Observational studies from the cardiovascular literature have demonstrated a relationship between clopidogrel resistance and the development of cardiovascular events after PCI.[8,9]

Antiplatelet drug resistance has not been well-characterized in patients undergoing neurovascular stent placement. In recent years, a few studies in patients after neurovascular stent placement revealed similar rates of resistance for aspirin and clopidogrel compared with the rates in the cardiovascular literature.[10-13] Increased doses of clopidogrel have been shown to overcome resistance and increase platelet inhibition.[14-16] The aim of this study was to analyze the relationship between antiplatelet drug resistance and periprocedural thromboembolic events in patients undergoing neurovascular stent-placement procedures at a single center. In addition, we evaluated the effect of tailored clopidogrel dosing on clinical outcomes.

Received June 7, 2012; accepted after revision September 17.

From the Center for Endovascular Surgery (J.T.F., W.L., A.B.), Hyman Newman Institute for Neurology and Neurosurgery, and Departments of Neurology (C.B., J.C.) and Anesthesia (J.N., S.L.E., H.B.), St. Luke's Roosevelt Hospital Center, New York, New York.

Please address correspondence to Johanna T. Fifi, MD, 1000 Tenth Ave, Suite 10G, New York, NY 10019; e-mail: jfifi@chpnet.org

http://dx.doi.org/10.3174/ajnr.A3405

MATERIALS AND METHODS

Study Design

Between August 2006 and January 2011, all consecutive patients undergoing stent placement in the intracranial or cervical vasculature at the Hyman Newman Institute for Neurology and Neurosurgery were tested for aspirin and clopidogrel resistance by using the VerifyNow platelet function assay (Accumetrics, San Diego, California). All test results were prospectively recorded. Indications for stent placement included extracranial stenosis, symptomatic intracranial stenosis, and coiling of wide-neck aneurysms. Procedural information and complications were entered in the institute's prospectively maintained data base. Clinical and laboratory data on all patients were collected via a retrospective chart review. Thromboembolic events, defined as in-stent thrombosis or stroke up to 30 days after the stent placement procedure, were used in the analysis. We excluded patients who did not receive antiplatelet drugs before the procedure and patients for whom complete clopidogrel testing data were not available.

The study population was divided into 2 cohorts. During the observational period from September 2006 to September 2008, platelet inhibition assays were collected and no management decisions were based on the results (group A). After this, practice was changed and from October 2008 to January 2011, patients who were resistant to clopidogrel were given additional clopidogrel and were retested with a goal inhibition of >20% (group B).

Medication Regimen and Neurovascular Stent Placement

For elective patients, we initiated daily antiplatelet therapy with aspirin, 81 mg, and clopidogrel, 75 mg, 5 days before the procedure. For urgent cases, patients were given aspirin and an oral load of 600 mg of clopidogrel. Platelet inhibition levels were checked before stent placement in all patients. Immediately prior and during neurovascular stent placement, patients were anticoagulated with heparin to maintain an ACT of approximately twice baseline. All carotid stent-placement procedures were performed with distal embolic protection. Intracranial stent placement was performed by using the Wingspan and Gateway (Boston Scientific, Natick, Massachusetts) systems for intracranial stenosis or the Neuroform (Boston Scientific) or Enterprise (Codman, Raynham, Massachusetts) stents for stent-assisted aneurysm coiling. A coronary Taxus Liberté (Boston Scientific) stent was used for vertebral artery stenosis.

Platelet Function Testing

We used the VerifyNow aspirin assay to calculate aspirin reaction units and the VerifyNow P2Y12 assay (Accumetrics) to calculate P2Y12 reaction units and the percentage inhibition of platelet function immediately before the procedures. This assay measures changes in light transmittance to evaluate fibrinogen-mediated platelet aggregation in whole blood in the presence of arachidonic acid (aspirin) or P2Y12 receptor agonists (clopidogrel).[17] The degree of aggregation is expressed as ARU for aspirin, and PRU and percentage inhibition for clopidogrel. Aspirin resistance was defined as ARU $\geq$ 550. Clopidogrel resistance was defined as percentage platelet inhibition $\leq$20%, consistent with that in previous studies.[18,19] Patients were classified as resistant if testing showed the above-defined levels after 5 days of treatment or a loading dose was given.

Statistical Analysis

For all continuous variables, means and SDs were calculated. Associations between clinical variables and aspirin- and clopidogrel-related platelet inhibition and resistance were tested by using univariate ANOVA. Possible clinical indicators of periprocedural thromboembolic complications ($P \leq .25$) were then entered into a multivariate model. These were analyzed by using a stepwise multivariate regression model. Significance was defined as $P < .05$. The association of clinical variables, whether continuous, ordinal, or categoric, with the presence of thromboembolic complications was modeled by using logistic regression. Comparisons between groups were evaluated by using the χ^2 test.

RESULTS

During the study period, 101 neurovascular stent-placement procedures were performed. For 5 procedures, there were incomplete platelet inhibition assay results or the patient was not loaded with oral antiplatelets before the procedure. Ninety-six procedures were included in the analysis. Indications for stent placement were as follows: 48 for carotid artery atherosclerotic stenosis and 4 for carotid artery dissection. Twenty-seven patients underwent stent placement for intracranial aneurysm, and 16 patients had symptomatic intracranial stenosis. One patient underwent extracranial vertebral artery stent placement for symptomatic stenosis. The mean age was 63.9 $\pm$ 13.6 years with 58% being men. Further demographic and clinical characteristics are shown in Table 1. There were no significant differences between groups A and B.

Resistance to Aspirin and Clopidogrel

We report aspirin and clopidogrel resistance as determined by analyzing the initial assay results from the entire study population (groups A and B). There was 1 patient for whom aspirin-resistance results were not available. In the 95 patients in whom ARU was measured, 5.3% ($n = 5$) of patients were aspirin-resistant. The mean ARU was 442. In all 96 patients, clopidogrel testing results were available. Mean platelet inhibition was 34.5% $\pm$ 26.7%, with 36.5% ($n = 36$) of patients being clopidogrel-resistant with inhibition of <20%. The mean PRU was 205.3 $\pm$ 90.7.

In the univariate ANOVA analysis (Table 2), platelet inhibition was found to be lower in patients with diabetes ($P = .029$), hyperlipidemia ($P = .067$), and lack of statin use ($P = .012$).

Thromboembolic Events

Seven (7.3%) patients developed thromboembolic events within 30 days of stent placement (Table 3). All events were at the stent or in the territory of the stented vessel. Six of 7 were clopidogrel-resistant. The non-clopidogrel-resistant patient developed a lacunar stroke 3 weeks after intracranial stent placement. In univariate analysis, clopidogrel resistance was associated with development of a thromboembolic event, with 6/36 (16.7%) resistant patients developing an event and 1/60 (1.6%) nonresistant patients developing an event ($P < .01$). In the logistic regression prediction

Table 1: Demographics of complete study sample including before (group A) and after (group B) initiation of tailored clopidogrel dosing

	All	Group A (49)	Group B (47)	*P* Value
Male sex	58%	55%	62%	.51
Age (yr)	63.9 ± 13.6	61.7 ± 14.4	66.1 ± 12.5	.12
Weight (kgs)	81.8 ± 20.2	78.6 ± 17.4	85.2 ± 22.4	.11
Hypertension	65 (68%)	30 (61%)	35 (74%)	.17
Diabetes mellitus	32 (33%)	16 (33%)	16 (34%)	.88
History of stroke	28 (29%)	18 (37%)	10 (21%)	.09
Statin use	53 (55%)	27 (55%)	26 (55%)	.92
Smoker	38 (40%)	16 (33%)	22 (47%)	.16
Alcohol intake	23 (24%)	9 (18%)	14 (30%)	.19
Platelet count ($10^3/\mu L$)	237 ± 79	239 ± 85	234 ± 72	.75

Table 2: Univariate ANOVA of potential clinical predictors of platelet inhibition

Demographics	Mean Platelet Inhibition (%)	*P* Value
Age (yr)		
<55 years ($n = 22$)	38.6	.752
>55 years ($n = 74$)	36.7	
Sex (No.)		
Women ($n = 40$)	39.1	.509
Men ($n = 56$)	35.7	
Medical history		
Hypertension (No.)		
No ($n = 31$)	40.4	.355
Yes ($n = 65$)	35.5	
Diabetes (No.)		
No ($n = 64$)	40.9	.029
Yes ($n = 32$)	29.4	
Hyperlipidemia (No.)		
No ($n = 50$)	33.1	.067
Yes ($n = 46$)	42.2	
Coronary artery disease (No.)		
No ($n = 75$)	37.7	.652
Yes ($n = 21$)	35.0	
Prior stroke (No.)		
No ($n = 68$)	39.0	.254
Yes ($n = 28$)	32.7	
Statin use (n = No.)		
No ($n = 38$)	30.0	.012
Yes ($n = 54$)	42.7	
Aspirin use (No.)		
No ($n = 19$)	34.0	.491
Yes ($n = 73$)	38.3	

model for periprocedural thrombosis ($P = .001$), clopidogrel resistance ($P = .015$) and lack of statin use ($P = .006$) predicted development of thromboembolic complication.

Comparison between Cohorts

During the initial period (group A), 49 stents were placed without modification of the antiplatelet regimen. Thirty-three percent of the patients had clopidogrel resistance with platelet inhibition levels <20%. In group A, the mean PRU was 222.5 ± 87.8 and the mean platelet inhibition was 33.9%. In group B, 47 stents were placed. Forty percent of patients had clopidogrel resistance on initial testing. Among patients after the practice change, the mean PRU was 182.4 ± 90.4, and the mean inhibition was 37.2%. Most patients required additional clopidogrel between 150 and 600 mg to achieve levels of >20%. After these increased doses, 94% of patients were able to achieve platelet inhibition of >20% on follow-up testing ($P < .01$).

Thromboembolic events occurred with 5/49 (10.3%) stent-placement procedures that were performed in group A. After the change to the clopidogrel dosing protocol (group B), 2/47 (4.5%) patients had thromboembolic complications. This decreasing thromboembolic complication rate between the 2 cohorts was not statistically significant ($P = .38$).

DISCUSSION

Several clinical reports have focused on examining patient variation in the level of responsiveness to taking solo or dual antiplatelet therapy with acetylsalicylic acid and clopidogrel.[6,20] There is growing literature from cardiology intervention patients that shows an association between clopidogrel resistance and clinical events.[8,9,21,22] While antiplatelet drug resistance has been described in neurovascular patients, an effect on clinical events has not been previously reported.[10-13] Our study demonstrates that clopidogrel resistance is clinically relevant and can lead to complications during neurovascular stent-placement procedures.

The reason for patient variation in the level of responsiveness to clopidogrel is multifactorial and not completely understood. Almost certainly, several factors play a role, including drug compliance, bioavailability, genetic polymorphisms, and drug interactions. The presence of a gene polymorphism resulting in loss of function of the drug-metabolizing enzyme CYP2C19 was found to be an important factor.[23,24] A recent study from the Thrombolysis in Myocardial Infarction (TIMI) study group confirmed that heterozygote and homozygote carriers of the allele retain high platelet function on clopidogrel treatment.[25] This study demonstrated that increasing daily doses of clopidogrel can produce levels similar to those in noncarriers in heterozygotes. However, this was not achievable in homozygotes, even with daily doses of up to 300 mg of clopidogrel. While we did not perform genetic testing in our patients, the production of acceptable platelet inhibition with increased doses in 94% of the patients is consistent with these data. The remaining 6% who could not reach therapeutic levels may be homozygous carriers.

There are various clinical tests used for measurement of platelet function. Light transmittance aggregometry is the classic method, but it has major disadvantages, including poor reproducibility, large sample volume, slow assay time, and the need for sample preparation and a skilled technician. Recently, 2 point-of-care devices that evaluate platelet function have become available: the PFA-100 Analyzer (Dade-Behring, Marburg, Germany) and the VerifyNow system. The VerifyNow assay is a simple rapid method that has become widely used in daily practice instead of LTA. Breet et al found that a high score on treatment platelet reactivity measured by the VerifyNow system (P2Y12 and aspirin) ($n = 422$) in patients on dual antiplatelet therapy undergoing elective stent implantation predicted atherothrombotic events.[26]

Table 3: Details for patients who experienced thrombotic complications

Group	Diagnosis	Sex	Age (yr)	Clopidogrel Resistance	PRU	% Inhibition	Thromboembolic Event	30-Day Follow-Up
A	Bilateral carotid artery dissection	Female	53	Yes	298	3%	Post-op in-stent thrombosis with TIA, required 1 ECA-ICA bypass	Normal
A	Right internal carotid artery occlusion, secondary to right carotid artery dissection	Male	42	Yes	291	0%	Perioperative R frontal stroke	Normal (recovered)
A	Basilar apex aneurysm	Female	48	Yes	289	0%	R cerebellar stroke POD 1	Dizziness (resolved)
A	Right MCA stenosis	Female	77	Yes	235	0%	Intra-op in-stent thrombus formation treated with IA abciximab; right basal ganglia stroke	Nonfocal; psychomotor retardation
A	Left hemisphere subcortical subacute infarct, left MCA severe stenosis	Male	68	Yes	360	0%	Periprocedural in-stent thrombosis, required ECA-ICA bypass	Dysarthria and R hemiparesis
B	Giant left MCA aneurysm	Male	75	Yes	243	0%	Stroke after being decreased from double clopidogrel dose	Right-handed weakness (resolved)
B	MCA stenosis	Male	79	No	30	80%	L MCA small vessel stroke in the MCA stent distribution	Mild word-finding difficulty (resolved)

Note:—ECA indicates external carotid artery; R, right; POD, post-operative day; intra-op, intraoperative; L, left; PcomA, posterior communicating artery; IA, intra-arterial; PCA, posterior cerebral artery; Post-op, postoperative; periop, perioperative.

Because there is no standard definition for clopidogrel resistance, neurovascular specialists have relied on data from cardiovascular patients. In the first period of our study, all thromboembolic complications were noted to occur in patients with clopidogrel platelet inhibition of <20%. This finding is consistent with those in previous reports.[18,19] More recent reports from the cardiovascular literature suggest using a threshold based on PRU.[27] It is important to distinguish between a cardiovascular and neurovascular patient population for 1 major reason: risk of hemorrhage. Patients in our population are more likely to have a history of stroke, especially those undergoing stent placement for atherosclerotic disease. Several studies have shown increased risk of hemorrhage on more potent antiplatelet therapy in patients with stroke.[28,29] Our data appear to support using a higher threshold for clopidogrel resistance in neurovascular patients.

Because of the observations of achieving higher inhibition with targeted dosing of clopidogrel, many practitioners have begun to use higher daily maintenance doses in resistant patients, especially in patients undergoing stent placement. However, this practice has not been definitively shown to decrease thrombotic complications. Several studies have evaluated this, including the recently published Gauging Responsiveness with a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) trial,[27] in which resistant patients were randomized to receive either standard or double-dose clopidogrel after PCI. This study did not demonstrate any difference in death, myocardial infarction, or stent thrombosis between the 2 groups. However, patients were given double-dose clopidogrel and were not targeted to a specific inhibition level. In the recent TIMI group study referenced above,[25] patients often required a triple standard dose to achieve acceptable levels. In fact, in the GRAVITAS study, patients achieved just a moderate pharmacologic response with baseline mean PRU of 283 reduced to 211 with a double dose. In contrast, patients without resistance had a mean PRU of 151. Our patients achieved a mean PRU of 182 with targeted dosing, which may explain the reduction in thromboembolic events with this type of dosing.

There are several limitations to this study. As with any retrospective study, there are potential confounding effects and bias. Practitioners were not blinded, and all complications of the procedures were documented by the operators and additional retrospective chart review. Most important, thrombotic events during the procedure may not be wholly attributable to clopidogrel resistance and may be related to technique. Furthermore, the decrease in complication rates between the 2 cohorts may also be related to more operator experience with the techniques. Additionally, this is not a uniform patient population, with varying indications from atherosclerotic disease to aneurysm placement in nonstenosed vessels. Larger studies analyzing clopidogrel resistance in these diseases separately are necessary.

CONCLUSIONS

Our study demonstrates an association between clopidogrel resistance based on platelet aggregometry testing and clinical thromboembolic events in patients after neurovascular stent placement. In addition, we confirm the high incidence of clopidogrel resistance seen in prior studies in a population of patients undergoing neurovascular stent placement. This study also demonstrates that increased platelet inhibition can be achieved with additional doses of clopidogrel in most poor responders. The hypothesis that thromboembolic events may be decreased by titrating the clopidogrel dose to platelet aggregometry testing and the use of alternative antiplatelet agents needs further testing.

ACKNOWLEDGMENTS

The authors thank Mindi Nahoum, RN, for help with data collection and maintenance.

Disclosures: Alejandro Berenstein—*RELATED*: *Consulting Fee or Honorarium*: MicroVention, Sequent Medical, Scientia Vascular, Rapid Medical. Ji Chong—*UNRELATED*: *Grants/Grants Pending*: National Institutes of Health,* *Other*: Janssen Pharmaceuticals advisory board. **Money paid to the institution.*

REFERENCES

1. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. **Stenting versus aggressive medical therapy for intracranial arterial stenosis.** *N Engl J Med* 2011;365:993–1003
2. Oxley TJ, Mitchell PJ, Yan B. **Antiplatelet resistance and thromboembolic complications in neurointerventional procedures.** *Front Neurol* 2011;2:83
3. Leon MB, Baim DS, Popma JJ, et al. **A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting: stent anticoagulation restenosis study investigators.** *N Engl J Med* 1998;339:1665–71
4. Fiorella D. **Anti-thrombotic medications for the neurointerventionist: aspirin and clopidogrel.** *J Neurointerv Surg* 2010;2:44–49
5. Gurbel PA, Bliden KP, Hiatt BL, et al. **Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity.** *Circulation* 2003;107:2908–13
6. Järemo P, Lindahl TL, Fransson SG, et al. **Individual variations of platelet inhibition after loading doses of clopidogrel.** *J Intern Med* 2002;252:233–38
7. Price MJ, Coleman JL, Steinhubl SR, et al. **Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers.** *Am J Cardiol* 2006;98:681–84
8. Bonello L, Tantry US, Marcucci R, et al. **Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate.** *J Am Coll Cardiol* 2010;56:919–33
9. Pinto Slottow TL, Bonello L, Gavini R, et al. **Prevalence of aspirin and clopidogrel resistance among patients with and without drug-eluting stent thrombosis.** *Am J Cardiol* 2009;104:525–30
10. Lee DH AA, Morsi H, Shaltoni H, et al. **Dual antiplatelet therapy monitoring for neurointerventional procedures using a point-of-care platelet function test: a single-center experience.** *AJNR Am J Neuroradiol* 2008;29:1389–94
11. Müller-Schunk SL, Peters N, Spannagl M, et al. **Monitoring of clopidogrel-related platelet inhibition: correlation of nonresponse with clinical outcome in supra-aortic stenting.** *AJNR Am J Neuroradiol* 2008;29:786–91
12. Prabhakaran S, Wells KR, Lee VH, et al. **Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting.** *AJNR Am J Neuroradiol* 2008;29:281–85
13. Drazin D, Choulakian A, Nuno M, et al. **Body weight: A risk factor for subtherapeutic antithrombotic therapy in neurovascular stenting.** *J Neurointerv Surg* 2011;3:177–81
14. Bonello L, Camoin-Jau L, Arques S, et al. **Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study.** *J Am Coll Cardiol* 2008;51:1404–11
15. Ari H, Ozkan H, Karacinar A, et al. **The effect of high-dose clopidogrel treatment in patients with clopidogrel resistance (the EFFICIENT trial).** *Int J Cardiol* 2012;157:374–80
16. Aradi D, Rideg O, Vorobcsuk A, et al. **Justification of 150 mg clopidogrel in patients with high on-clopidogrel platelet reactivity.** *Eur J Clin Invest* 2012;42:384–92
17. van Werkum JW, Hackeng CM, Smit JJ, et al. **Monitoring antiplatelet therapy with point-of-care platelet function assays: a review of the evidence.** *Future Cardiol* 2007;49;1505–16
18. Maruyama TH, Dembo T, Nagoya H, et al. **Clopidogrel resistance and the effect of combination cilostazol in patients with ischemic stroke or carotid artery stenting using the VerifyNow P2Y12 assay.** *Int Med* 2011;50:695–98
19. Shim CY, Yoon SJ, Park S, et al. **The clopidogrel resistance can be attenuated with triple antiplatelet therapy in patients undergoing drug-eluting stents implantation.** *Int J Cardiol* 2009;134:351–55
20. 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
21. Matetzky S, Shenkman B, Guetta V, et al. **Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction.** *Circulation* 2004;109:3171–75
22. Lev EI, Patel RT, Maresh KJ, et al. **Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance.** *J Am Coll Cardiol* 2006;47:27–33
23. Shuldiner AR, O'Connell JR, Bliden KP, et al. **Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy.** *JAMA* 2009;302:849–57
24. Hochholzer W, Trenk D, Fromm MF, et al. **Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement.** *J Am Coll Cardiol* 2010;55:2427–34
25. Mega JL, Hochholzer W, Frelinger AL, et al. **Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease.** *JAMA* 2011;306:2221–28
26. Breet NJ, van Werkum JW, Bouman HJ, et al. **High on-treatment platelet reactivity to both aspirin and clopidogrel is associated with the highest risk of adverse events following percutaneous coronary intervention.** *Heart* 2011;97;983–90
27. Price MJ, Berger PB, Teirstein PS, et al for the GRAVITAS Investigators. **Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial.** *JAMA* 2011;305:1097–105
28. Diener HC, Bogousslavsky J, Brass LM, et al. **Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial.** *Lancet* 2004;364:331–37
29. Wiviott SD, Braunwald E, McCabe CH, et al. **Prasugrel versus clopidogrel in patients with acute coronary syndromes.** *N Engl J Med* 2007;357:2001–15