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Impact of Platelet Reactivity After Clopidogrel Administration on Drug-Eluting Stent Thrombosis

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Objectives We sought to determine whether nonresponsiveness to clopidogrel as revealed by high in vitro post-treatment platelet reactivity is predictive of drug-eluting stent (DES) thrombosis.

Background No data exist about the impact of nonresponsiveness to clopidogrel on the risk of DES thrombosis.

Methods We conducted a prospective observational cohort study from July 2005 to August 2006 in an academic hospital. A total of 804 patients who had successful sirolimus- or paclitaxel-eluting stent implantation were assessed for post-treatment platelet reactivity after a loading dose of 600 mg of clopidogrel. Patients with platelet aggregation by 10 μmol adenosine 5′-diphosphate $\geq$70% were defined as nonresponders. All patients received chronic dual antiplatelet treatment (aspirin 325 mg and clopidogrel 75 mg daily) for 6 months. The primary end point was the incidence of definite/probable early, subacute, and late stent thrombosis at 6-month follow-up.

Results The incidence of 6-month definite/probable stent thrombosis was 3.1%. All stent thromboses were subacute or late. Of 804 patients, 105 (13%) were not responsive to clopidogrel. The incidence of stent thrombosis was 8.6% in nonresponders and 2.3% in responders ($p < 0.001$). By multivariate analysis, the predictors of stent thrombosis were as follows: nonresponsiveness to clopidogrel (hazard ratio [HR] 3.08, 95% confidence interval [CI] 1.32 to 7.16; $p = 0.009$), left ventricular ejection fraction (HR 0.95, 95% CI 0.92 to 0.98; $p = 0.001$), total stent length (HR 1.01, 95% CI 1.00 to 1.02; $p = 0.010$), and ST-segment elevation acute myocardial infarction (HR 2.41, 95% CI 1.04 to 5.63; $p = 0.041$).

Conclusions Nonresponsiveness to clopidogrel is a strong independent predictor of stent thrombosis in patients receiving sirolimus- or paclitaxel-eluting stents. (J Am Coll Cardiol 2007;49:2312–7) © 2007 by the American College of Cardiology Foundation

A dual antiplatelet regimen of aspirin and clopidogrel is the standard treatment for the prevention of stent thrombosis (1–3), and retrospective studies have shown that the discontinuation of clopidogrel, even after 6 months or later after stent implantation, is associated with an increased risk of thrombotic events in patients with drug-eluting stents (DES) (4–7). However, stent thrombosis also can occur in patients taking clopidogrel and aspirin, and it has been shown that patients who suffer stent thrombosis have a high in vitro post-treatment platelet reactivity despite the dual antiplatelet treatment, suggesting that platelet aggregation nonresponsiveness to clopidogrel is the main cause of the thrombotic event (8–12). The definite demonstration of the association between low in vitro responsiveness to clopidogrel and thrombotic events is still lacking because the large majority of previous studies were retrospective or underpowered. Moreover, post-treatment platelet reactivity may interact with 1 or more established clinical and procedural predictors of stent thrombosis, making it difficult to define its role in precipitating thrombosis. In addition, studies have used different platelet reactivity assessments and definitions for determining the platelet responsiveness to clopidogrel. This prospective study sought to determine the impact of low responsiveness to clopidogrel on the clinical outcome of patients receiving DES.

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Methods

Patients. This study is based on a cohort of 804 consecutive patients who received successful sirolimus- or paclitaxel-eluting stent implantation and for whom platelet reactivity after clopidogrel treatment was prospectively as-

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sessed. All patients were considered eligible for the study irrespective of clinical presentation or coronary anatomy. Thus, patients with acute coronary syndromes and ST-segment elevation acute myocardial infarction (AMI) were included, as well as patients with left main disease, chronic total occlusions, bifurcation lesions, or diffuse disease. The only exclusion criteria were: 1) in-hospital death that was not due to stent thrombosis; 2) anticipated noncompliance to dual antiplatelet treatment for at least 6 months; and 3) premature discontinuation of clopidogrel therapy. All patients gave informed consent. The study was approved by the local ethical committee.

Percutaneous coronary intervention and antiplatelet management. All interventions were performed according to current standard guidelines, and the type of stent implanted and the use of IIb/IIIa inhibitors were at discretion of the operator. All patients received aspirin (325 mg) and a loading dose of 600 mg of clopidogrel followed by a maintenance dose of 75 mg daily. Patients on a maintenance dose of ticlopidine or clopidogrel at the time of admission received a loading dose of clopidogrel (600 mg).

Platelet reactivity assessment. Blood samples anticoagulated with 0.129 mol/l sodium citrate (ratio 9:1) for platelet reactivity assessment was obtained 12 to 18 h from clopidogrel loading. For patients receiving in the cath lab both the loading dose of clopidogrel and a IIb/IIIa inhibitor, blood samples were obtained after 6 days while the patient was on the 75-mg maintenance dose of clopidogrel. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 200 *g*, was stimulated with 10 μmol/l adenosine 5′-diphosphate (ADP) (Mascia Brunelli, Milan, Italy) and residual aggregation was assessed using a APACT 4 light transmittance aggregometer (Helena Laboratories, Milan, Italy). The 100% line was set using platelet-poor plasma and the 0 baseline established with platelet-rich plasma (adjusted from 18×10^9/l up to 30×10^9/l). Platelet aggregation (according to the Born's method) was evaluated considering the maximal percentage of platelet aggregation in response to stimulus. Control samples from 100 healthy volunteers were run to determine the normal reference laboratory aggregation value that was 68% (range 55% to 99%). Patients with platelet aggregation by 10-μmol ADP ≥90th percentile of controls (70%) were defined as nonresponders.

End points. The primary end point of the study was definite or probable stent thrombosis during a 6-month follow-up. Definite stent thrombosis was defined as acute coronary syndrome and either angiographic confirmation of thrombosis or pathological confirmation of thrombosis. Probable stent thrombosis was defined as unexplained death or myocardial infarction in the territory supplied by a stented vessel without angiographic confirmation. The diagnosis of myocardial infarction was based on either the development of new Q waves on 2 or more electrocardiographic leads or an increase of creatine kinase-myocardial band isoenzyme or troponin T >3 times the upper limit of normal. Event time was categorized as acute (within 24 h from stent implantation), subacute (from 1 day to 30 days), and late (30 days to 6 months). The secondary end point was the composite of cardiac mortality and definite or probable stent thrombosis. All events were adjudicated by 3 observers (A.M., D.A., G.M.) who were blinded to patient responsiveness to clopidogrel and not involved in the follow-up process.

Abbreviations and Acronyms

ADP = adenosine 5′-diphosphate
AMI = acute myocardial infarction
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LVEF = left ventricular ejection fraction

Follow-up. All patients had scheduled clinical and electrocadiographic examinations at 1, 3, and 6 months. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the database.

Statistical analysis. The sample size was calculated assuming the incidence of the primary end point to be 2%, and we hypothesized a 3.5-fold increase in the incidence of stent thrombosis in nonresponders to clopidogrel. With these assumptions, to have a power of 0.80 to detect the hypotesized effect size with a 1-sided p value <0.05, a sample size of at least 800 was needed. Discrete data are summarized as frequencies, whereas continuous data as mean ± SD. The chi-square test was used for comparison of categorical variables. A 2-tailed Student *t* test was used to test differences among continuous variables. Forward stepwise Cox proportional hazards regression analysis was performed to identify independent correlates of the primary and secondary end point. The variables entered in the proportional hazards regression model were selected using stepwise regression analysis with an entry criterion of $p < 0.10$. Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. Survival curves were generated using the Kaplan-Meier method, and the difference between curves was assessed by log-rank test. A p value <0.05 was considered significant. Analyses were performed using the software package SPSS 8.0 (SPSS Inc., Chicago, Illinois).

Results

Patient and procedural characteristics. The study cohort comprised 804 patients who were treated from July 2005 to February 2006 with sirolimus- (Cypher, Cordis Corp., Miami Lakes, Florida) or paclitaxel- (Taxus, Boston Scientific Corp., Natick, Massachusetts) eluting stents. There were 105 patients who were not responsive to clopidogrel (13%). Table 1 summarizes the clinical and procedural characteristics of the patients. Nonresponsive patients were older as compared with responders; had a greater incidence of diabetes mellitus, unstable angina, and multivessel disease; and had a lower incidence of smoking and ST-segment elevation myocardial infarction. Left ven-

Table 1 Baseline Clinical and Procedural Characteristics According to Responsiveness to Clopidogrel

	Overall (n = 804)	Responders (n = 699)	Nonresponders (n = 105)	p Value
Variable	69 ± 11	68 ± 11	71 ± 10	0.021
Male gender, n (%)	602 (75)	528 (76)	74 (70)	0.265
Current smokers, n (%)	179 (22)	164 (24)	15 (14)	0.034
Arterial hypertension, n (%)	501 (62)	434 (62)	67 (64)	0.748
Diabetes mellitus, n (%)	169 (21)	131 (19)	38 (36)	<0.001
Hypercholesterolemia, n (%)	405 (50)	347 (50)	58 (55)	0.291
Previous myocardial infarction, n (%)	206 (26)	173 (25)	33 (31)	0.146
Previous PCI, n (%)	186 (23)	160 (23)	26 (25)	0.841
Previous coronary artery surgery, n (%)	58 (7)	50 (7)	8 (8)	0.866
Stable angina, n (%)	275 (34)	242 (35)	33 (31)	0.520
Unstable angina, n (%)	312 (39)	258 (37)	54 (51)	0.004
Acute myocardial infarction, n (%)*	217 (27)	199 (28)	18 (17)	0.015
Renal failure, n (%)	87 (11)	73 (10)	14 (14)	0.374
Multivessel disease, n (%)	457 (57)	386 (55)	71 (68)	0.017
2-vessel disease	226 (28)	190 (27)	36 (34)	
3-vessel disease	231 (29)	196 (28)	35 (33)	
LVEF (%)	47 ± 12	47 ± 12	44 ± 14	0.008
Multivessel PCI, n (%)	327 (41)	273 (39)	54 (51)	0.016
Vessel treated, n	1,220	1,044	176	
Lesion treated, n	1,369	1,171	198	
Thrombus-containing lesion, n (%)	177 (13)	166 (24)	11 (10)	<.001
Bifurcation lesion, n (%)	371 (27)	318 (27)	53 (27)	0.909
Chronic total occlusion, n (%)	106 (8)	86 (7)	20 (10)	0.180
Lesion length >20 mm, n (%)	359 (26)	294 (25)	65 (33)	0.022
Total stent length (mm)	38 ± 29	37 ± 29	44 ± 32	0.015
Sirolimus-eluting stent, n (%)	447 (56)	391 (56)	56 (53)	0.617
Paclitaxel-eluting stent, n (%)	303 (38)	264 (38)	39 (37)	0.902
Both stent types, n (%)	54 (7)	44 (6)	10 (10)	0.218
Post-PCI MLD (mm)	2.81 (0.54)	2.81 (0.54)	2.80 (0.54)	0.832
Glycoprotein IIb/IIIa, n (%)	349 (43)	311 (44)	38 (36)	0.110

*ST-segment elevation acute myocardial infarction.
LVEF = left ventricular ejection fraction; MLD = minimum lumen diameter; PCI = percutaneous coronary intervention.

tricular ejection fraction (LVEF) was significantly lower in the nonresponder group. Multivessel intervention was performed more frequently in nonresponders as compared with responders. Again, lesions at high risk of stent thrombosis, such as long lesions and the total chronic occlusions, were treated more frequently in nonresponder patient group. As a consequence, the mean stent length per patient of the nonresponder group was superior to the one of the responder group.

Clinical outcome. The follow-up rate was 100%. Table 2 shows the clinical outcome at 6 months. The overall primary

Table 2 Clinical Outcome

	Overall (n = 804)	Responders (n = 699)	Nonresponders (n = 105)	p Value
Definite/probable stent thrombosis, n (%)	25 (3.1)	16 (2.3)	9 (8.6)	<0.001
Definite	11 (1.4)	9 (1.3)	2 (1.9)	0.612
Probable	14 (1.7)	7 (1.0)	7 (6.7)	<0.001
Timing of stent thrombosis, n (%)				
Early	0	0	0	
Subacute	16 (2.0)	12 (1.7)	4 (3.8)	0.152
Late	9 (1.1)	4 (0.6)	5 (4.8)	<0.001
Cardiac mortality, n (%)	19 (2.4)	10 (1.4)	9 (8.6)	<0.001
Composite of cardiac death and stent thrombosis, n (%)	30 (3.5)	19 (2.7)	11 (10.5)	<0.001
ST-segment elevation AMI, n	217	199	18	
Stent thrombosis, n (%)	11 (5.1)	7 (3.5)	4 (22)	<0.001

AMI = acute myocardial infarction.

end point rate was 3.1%. Patients with ST-segment elevation AMI had a greater thrombosis rate as compared with non-AMI patients (5.1% and 2.3%, respectively, p = 0.052). There were no differences in the stent thrombosis rate among patients receving sirolimus- or paclitaxel-eluting stents or both types of stents (3.4%, 2.3%, and 5.6%, respectively, p = 0.406). Most of stent thromboses (64%) were subacute and occurred at a mean time of 54 ± 62 days from stent implantation (range 4 to 180 days), whereas no patient had acute stent thrombosis.

Definite or probable stent thrombosis occurred in 9 of 105 (8.6%) nonresponders and in 16 of 699 (2.3%) responders (p < 0.001). In both groups, patients who developed stent thrombosis had multiple high-risk features. Among the 16 responder patients with stent thrombosis, there were 7 patients with AMI, 10 with bifurcation lesions, 10 with multivessel percutaneous coronary interventions, 8 with a total stent length >30 mm, and 8 with an LVEF <30%. Similarly, among the 9 nonresponders with stent thrombosis, 3 had AMI, 5 multivessel intervention, 5 bifurcation stenting, 8 had a total stent length >30 mm, and 5 had a LVEF <30%. The event-free survival curves are shown in Figure 1. The event-free survival rate from the primary end point was 91.3% in the nonresponders and 98.1% in the responders (p < 0.001). The cardiac mortality rate was 8.6% in the nonresponders and 1.4% in responders (p < 0.001). The incidence of the composite of cardiac death and definite or probable stent thrombosis was 10.5% in the nonresponders and 2.7% in the responders (p < 0.001). Table 3 shows the results of univariate and multivariate analyses. By multivariate analysis, the predictors of the primary end point were as follows: nonresponsiveness to clopidogrel (HR 3.08, 95% CI 1.32 to 7.16; p = 0.009), ST-segment elevation AMI (HR 2.41, 95% CI 1.04 to 5.63; p = 0.041), total stent length (HR 1.01, 95% CI 1.00 to 1.02; p = 0.010), and LVEF (HR 0.95, 95% CI 0.92 to 0.98; p = 0.001). The same variables also were independently related to the risk of the secondary end point: nonresponsiveness to clopidogrel (HR 3.25, 95% CI 1.51 to 7.00; p = 0.003), ST-segment elevation AMI (HR 3.25, 95% CI 1.46 to 7.23; p = 0.004), total stent length (HR 1.01, 95% CI 1.00 to 1.02; p = 0.006), and LVEF (HR 0.94, 95% CI 0.91 to 0.96; p < 0.001).

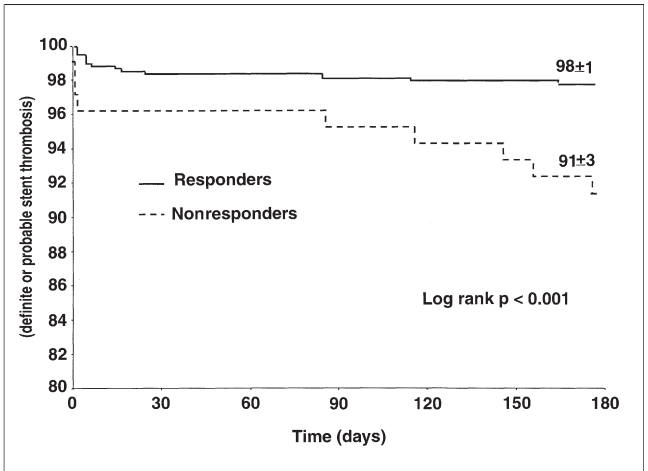

Figure 1 Kaplan-Meier Analysis of Primary End Point for Responders and Nonresponders to Clopidogrel

Table 3 Predictors of Stent Thrombosis

	Hazard Ratio (95% Confidence Interval)	p Value
Univariate analysis*		
Nonresponsiveness to clopidogrel	3.85 (1.70–8.71)	<0.001
Total chronic occlusion	2.98 (1.24–7.13)	0.014
Multivessel disease	2.43 (0.97–6.09)	0.058
Bifurcation lesion	2.27 (1.03–4.99)	0.042
Acute myocardial infarction	2.16 (0.98–4.57)	0.057
Previous myocardial infarction	1.97 (0.89–4.39)	0.096
Age, yrs	1.04 (1.00–1.08)	0.064
Total stent length, mm	1.02 (1.01–1.02)	0.001
LVEF per 1% increase	0.94 (0.91–0.96)	<0.001
Multivariate analysis		
Nonresponsiveness to clopidogrel	3.08 (1.32–7.16)	0.009
Acute myocardial infarction	2.41 (1.04–5.63)	0.041
Total stent length, mm	1.01 (1.00–1.02)	0.010
LVEF per 1% increase	0.95 (0.92–0.98)	0.001

*Variables with a p value <0.10 that were entered in the multivariate model.
LVEF = left ventricular ejection fraction.

Discussion

The definite or probable DES thrombosis rate of 3.1% in this study was greater as compared with randomized trials comparing DES with bare-metal stents and to previous observational studies that reported a thrombosis rate of 0.8% to 1.5% (6,7,13–15). Baseline and procedural characteristics of our patient cohort may explain the high stent thrombosis rate: as compared with these studies, our patients were older and had a greater incidence of unstable angina or ST-segment elevation AMI, chronic coronary occlusion, and bifurcation lesion.

This prospective study showed that post-treatment platelet aggregation after a 600-mg dose of clopidogrel is a strong marker of the risk of DES thrombosis. Patients with in vitro >70% post-treatment platelet aggregation had nearly 4-fold increase in definite or probable stent thrombosis as compared with clopidogrel responders.

Platelet reactivity assessment to address clinical outcome was based on the results of previous studies (10,16,17). In vitro platelet reactivity after clopidogrel loading may be quite variable, and low or nonresponsiveness may be the result of inadequate generation of the active drug metabolite required to inhibit the $P2Y_{12}$ receptors. The mechanisms of this variability may lie in the hepatic CYP3A4 pathway, in the polymorphisms of CYP3A4 or $P2Y_{12}$ receptor, or differences in the rate of intestinal absorption of clopidogrel (18,19). Again, responsiveness, as assessed by in vitro tests, also depends on the baseline platelet reactivity, which is higher in acute coronary syndromes as compared with stable

coronary artery disease (20,21). Furthermore, clopidogrel responsiveness is also dose dependent, and it has been shown that the incidence of low or nonresponders decreases dramatically after a 600-mg loading dose of the drug as compared with the original 300-mg dose (22–26).

Despite these variables in the single patient that may affect his or her responsiveness to clopidogrel over time, our study, based on a large unrestricted cohort of patients receiving drug-eluting stents, shows that a single assessment of the in vitro responsiveness to clopidogrel is strongly related to the risk of drug-eluting stent thrombosis.

The clinical relevance of low or nonresponsiveness to clopidogrel in patients receiving DES has not been fully investigated. A prospective study based on a sample of 379 patients undergoing coronary stent implantation showed that low responsiveness to clopidogrel is associated with an increased risk of adverse events (HR 3.71, 95% CI 1.08 to 12.69; $p = 0.037$) at 3-month follow-up (27). This study used an arbitrary cutoff for the definition of low responsiveness (clopidogrel-dependent platelet inhibition <30%), had a very short follow-up, did not focus on DES thrombosis, and also included in the primary end point nonfatal ischemic stroke and any cardiovascular death.

Another study, based on a sample of 802 patients who received elective coronary stent implantation, showed that post-treatment platelet aggregation above the median value carried a 6.7-fold increase in major adverse cardiac events (death, myocardial infarction, and target vessel revascularization) at 1-month follow-up (17). This study enrolled mainly low-risk patients with stable coronary artery disease who received, in the large majority of cases, elective bare-metal stent implantation. Again, this study focused more on periprocedural events, whose rate was very low (1.9%) and mostly driven by target lesion revascularization and non–Q-wave myocardial infarction, than on acute or subacute stent thrombosis. Another small study, based on 60 consecutive patients with ST-segment elevation myocardial infarction who underwent angioplasty and stenting, showed that those patients in the lowest quartile in terms of responsiveness to clopidogrel were at an increased risk for a recurrent cardiovascular event during a 6-month follow-up (8).

Similarly, in a prospective study of 105 patients undergoing percutaneous coronary stenting, Muller et al. (28) found that the 2 patients who developed stent thrombosis were nonresponders to clopidogrel. The Platelet Reactivity in Patients and Recurrent Events Post-Stenting study, based on a sample of 192 patients, showed that post-treatment ADP-induced aggregation in patients with adverse events was higher as compared with patients without events. Also this study did not explore specifically the issue of DES thrombosis, and did not stratify patients before clinical events to different degrees of platelet reactivity (10).

The strong predictive value of stent thrombosis provided by a single platelet aggregation assessment, as revealed by our study, has important clinical implications since a unique bedside examination may have an impact on revascularization strategies in the DES era. Alternative revascularization strategies (coronary surgery or bare-metal stents), or pharmacologic strategies with the aim of a more complete $P2Y_{12}$ receptor inhibition using increasing doses of clopidogrel or other antiplatelet agents should be considered to reduce the risk of ischemic events (29,30).

Study limitations. Our study is a a clinical trial whose primary end point is definite or probable stent thrombosis. Probable stent thrombosis is a clinical end point and may overestimate the true incidence of stent thrombosis. Conversely, definite stent thrombosis is an angiographic or pathological end point that surely underestimates the true incidence of stent thrombosis. However, we tried to overcome the intrinsic limitation in probable stent thrombosis definition assessing also the cardiac mortality not attributable to stent thrombosis. We did not report the relation between responsiveness to aspirin associated or unassociated with nonresponsiveness to clopidogrel that could be a variable related to definite or probable stent thrombosis.

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REFERENCES

1. Metha SR, Yusuf S, Peters RJG, et al. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
2. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
3. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparison of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol 2002;39:9–14.
4. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
5. Kaiser C, Brunner-La Rocca HP, Buser PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third generation bare-metal stents in a real-world setting: Randomised Basel Stent Kosten Effektivitats Trial (BASKET). Lancet 2005;366:921–9.
6. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
7. Park D-W, Park S-W, Park K-H, et al. Frequency and risk factors for stent thrombosis after drug-eluting stent omplantation during long-term follow-up. Am J Cardiol 2006;98:352–6.
8. 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;109:3171–5.
9. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis. J Am Coll Cardiol 2005;46:1827–32.
10. Gurbel PA, Bliden KP, Guyer BS, et al. Platelet reactivity in patients and recurrent events post-stenting. J Am Coll Cardiol 2005;46:1820–6.
11. Ajzenberg G, Aubry P, Huisse MG, et al. Enhanced shear-induced platelet aggregation in patients who experienced stent thrombosis. J Am Coll Cardiol 2005;45:1653–6.
12. Cuisset T, Frere C, Quilici J, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. J Thromb Haemost 2006;4:542–9.

13. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9.
14. Ong ATL, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol 2005; 45:947–53.
15. Kuchulakanti PK, Chu WW, Torquson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113: 1108–13.
16. Samara WM, Bliden KP, Tantry US, Gurbel PA. The difference between clopidogrel responsiveness and post-treatment platelet reactivity. Thromb Res 2005;115:89–94.
17. Hochholzer W, Trenk D, Bestehorn H-P, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006;48:1742–50.
18. Wiviott SD, Antman EM. Clopidogrel resistance: A new chapter in a fast-moving story. Circulation 2004;109:3064–7.
19. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation 2004;109:166–71.
20. Gawaz M, Neumann FJ, Ott I, Schiesler A, Schomig A. Platelet function in acute myocardial infarction treated with direct angioplasty. Circulation 1996;93:229–37.
21. Soffer D, Moussa I, Harjai KJ, et al. Impact of angina class on inhibition of platelet aggregation following clopidogrel loading in patients undergoing coronary intervention: do we need more aggressive dosing regimens in unstable angina? Catheter Cardiovasc Interv 2003;59:21–5.
22. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. Eur Heart J 2004;25:1903–10.
23. Kandzari DE, Berger PB, Kastrati A, et al. Influence of treatment duration with a 600 mg dose of clopidogrel before percutaneous coronary revascularization. J Am Coll Cardiol 2004;44:2133–6.
24. Gurbel PA, Bliden BS, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–6.
25. Von Beckerath N, Taubert D, Pogatsa-Murray G, Schomig E, Kastrati A, Schomig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading dose of clopidogrel. Circulation 2005;112;2946–50.
26. Cuisset T, Frere C, Quilici J, et al. Benefit of a 600-mg dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. J Am Coll Cardiol 2006;48:1339–45.
27. Geisler T, Langer H, Wydymus M, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. Eur Heart J 2006;27:2420–5.
28. Muller I, Besta F, Schulz C, Masberg S, Schonig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective stent placement. Thromb Haemost 2003;89:783–7.
29. Lee S-W, Park S-W, Homg M-K, et al. Triple versus dual antiplatelet therapy after coronary artery stenting. J Am Coll Cardiol 2005;46: 1833–7.
30. Wiviott SD, Antman EM, Winters KJ, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine $P2Y_{12}$ antagonist, with clopidogrel in percutaneous coronary intervention. Circulation 2005;111:3366–73.