

Platelet reactivity as a risk-factor for stent thrombosis: can this be one of the currently available appropriate methods to determine platelet reactivity?

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Introduction

Stent thrombosis (ST) carries with it substantial morbidity and mortality^{1,2}. The identification of clinical, lesion, and procedural risk-factors (RF) that are associated with ST may improve individual risk stratification³. The additional role of platelet reactivity as a risk factor, although appealing, is still in an investigational phase. In the present review we discuss the currently available evidence on platelet reactivity as a risk-factor for stent thrombosis.

The vascular response to stenting

Under physiological conditions the intact endothelium plays a key role in the regulation of thrombosis and haemostasis. Paradoxically, endothelial cells secrete both multiple prothrombotic substances (such as tissue factor and von Willebrand factor) as well as antithrombotic molecules (such as nitric oxide and prostacyclin). When the endothelial barrier becomes injured (e.g., as a result of balloon angioplasty or coronary stent implantation), the modulating capacities of the endothelium disappear and the subendothelial extracellular matrix and lipid core components become exposed to the flowing blood⁴. The role of platelets in response to the iatrogenic induced endothelial injury, or to the implanted (prothrombotic) coronary stent is well recognised and can be divided in three consecutive phases (Figure 1): adhesion (A), activation (B) and aggregation (C)⁵.

Adequate anti-thrombotic therapy during and after PCI is therefore of utmost importance, and the currently recommended strategy with dual antiplatelet therapy has proven to be highly effective in the prevention of stent thrombosis until the stent struts are covered with endothelium. Despite antiplatelet therapy, however, it has become clear that a substantial number of patients still suffer from recurrent ischaemic coronary events⁶.

Evidence is mounting in recent years that besides the already recognised clinical, lesion and procedural factors, a persistent heightened (residual) platelet reactivity – despite the use of aspirin and clopidogrel – may also be an important determinant of stent thrombosis. This crucial evidence is derived from multiple sources:

- 1) Intensified antiplatelet therapy decreases the incidence of stent thrombosis⁷.
- 2) Premature discontinuation of antiplatelet therapy increases the risk for stent thrombosis^{2,8}.
- 3) Autopsy reports describe platelet deposition in the stent-area⁹.
- 4) Platelet function studies have suggested a causal relationship between the absolute magnitude of platelet reactivity and the occurrence of stent thrombosis^{10,11}.

In this review, we discuss the contribution of platelet reactivity to the phenomenon of stent thrombosis and we briefly review the available techniques to measure platelet reactivity.

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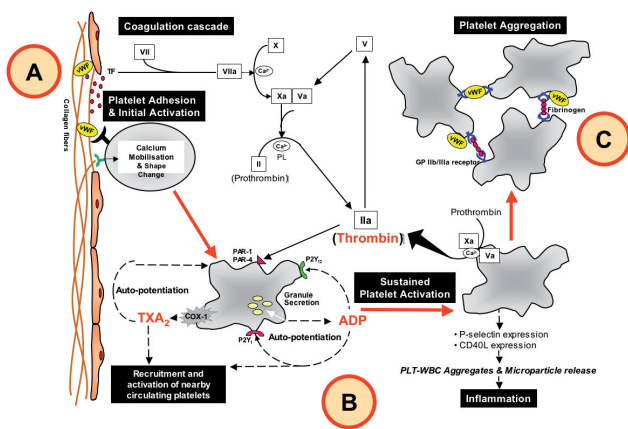


Figure 1. Coagulation cascade: Exposure of tissue factor after vascular injury (A) leads to complex formation with factor VIIa. The TF-VIIa complex cleaves factor X to factor Xa. Factor Xa in the prothrombinase complex activates prothrombin (factor II) to thrombin (factor IIa). The activation of thrombin occurs on the surface of activated platelets. Platelet phase: Upon vascular injury (A), platelets adhere to exposed proteins (such as collagen, von Willebrand factor) and are activated via several independent mediators (B). Once activated, platelet release secondary agonists (such as ADP and thromboxane A₂), that in turn recruit additional platelets to aggregate with one and another via GP IIb/IIIa mediated fibrinogen cross-linking (C). ADP: adenosine diphosphate, Ca²⁺: calcium, COX: cyclo-oxygenase activity, PL: phospholipids, PLT: platelet, TF: tissue factor, TXA₂: thromboxane A₂, vWF: von Willebrand factor, WBC: white blood cells

Wide variability in the response to antiplatelet therapy

In the last years, multiple studies have demonstrated that the response to a fixed dose of antiplatelet therapy (clopidogrel and aspirin) is highly variable and the responsiveness to clopidogrel as measured with ADP-induced aggregation follows a bell-shaped Gaussian-distribution⁶. Consequently, a substantial proportion of patients receiving combination therapy with aspirin and clopidogrel fail to obtain optimal benefit from it. This phenomenon has been termed “resistance to antiplatelet therapy” in the medical literature^{12,13}. However, the somewhat confusing term “resistance” implies that these drugs do not reach its pharmacological target at all, which is not the case in most instances. Hence, alternative definitions have been recently introduced (Figure 2)¹⁴.

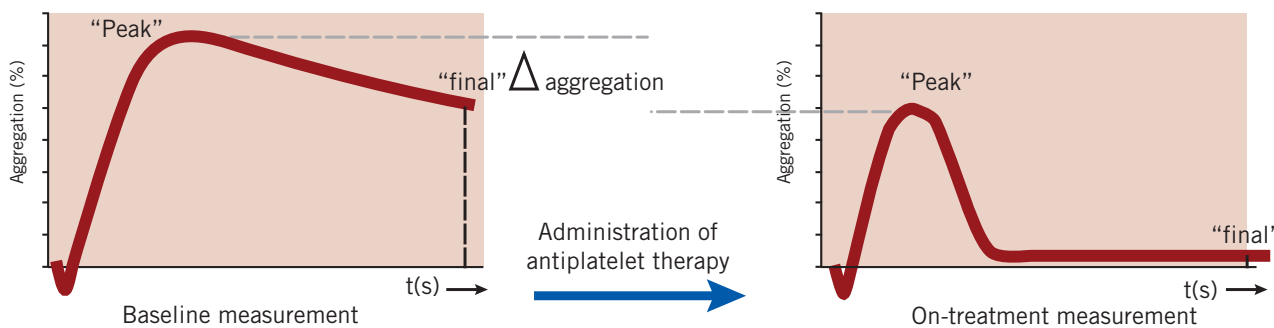
Responsiveness to antiplatelet therapy

The individual responsiveness to antiplatelet therapy can be determined when platelet function is evaluated at two time points: before the administration of the antiplatelet drug and after the antiplatelet drug has reached its maximum effect. The absolute difference in the degree of platelet reactivity before and after the administration of antiplatelet therapy is defined as responsiveness.

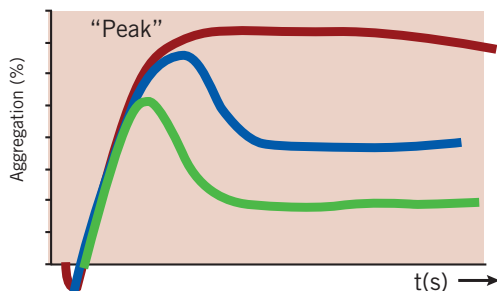
Pre-treatment platelet reactivity

Evidence strongly suggests that individuals vary in their platelet response to pro-activating stimuli (e.g., vascular injury, atherosclerosis, adenosine diphosphate, thromboxane A₂) and thus

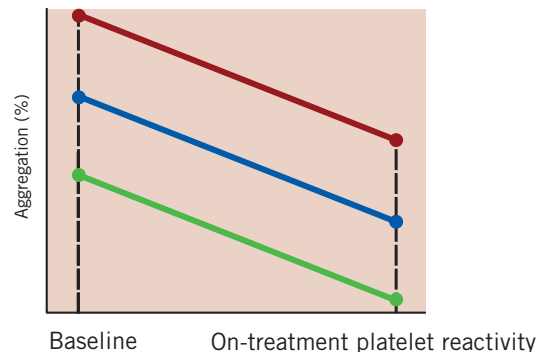
Responsiveness



Pre-treatment platelet reactivity



On-treatment platelet reactivity



Baseline (off-drug) platelet reactivity ~ On-treatment reactivity

Figure 2. Platelet aggregation curves to illustrate the essential difference between the three definitions. Upper part: responsiveness to antiplatelet therapy. Lower part: Pre- and on-treatment platelet reactivity.

in their thrombotic potential.¹⁵ Consequently, a subgroup of individuals exhibit hyper-reactivity and this increases the likelihood for the occurrence of an atherothrombotic event. The absolute magnitude of the individual's intrinsic baseline (off-drug) platelet reactivity is called: pre-treatment platelet reactivity.

On-treatment platelet reactivity

The absolute magnitude of (residual) platelet reactivity that is measured in patients receiving antiplatelet therapy is defined as on-treatment platelet reactivity (also referred to as residual platelet reactivity).¹⁴

Low responsiveness, as well as high on-treatment platelet reactivity, has been linked to adverse clinical outcome. However, it remains unclear which parameter is the most predictive. In an attempt to answer this difficult question, Samara and co-workers have recently posted the following statement: "Measuring clopidogrel responsiveness may overestimate the risk of stent thrombosis in non-responders with low pre-treatment reactivity and underestimate risk in those responders who remain with high on-treatment platelet reactivity. Therefore, high on-treatment platelet reactivity is a better measure of thrombotic risk than responsiveness to clopidogrel."¹⁶

Platelet reactivity as a determinant of stent thrombosis

Several studies have suggested that some – but not all patients who eventually develop a stent thrombosis – exhibit high on-treatment platelet reactivity. The initial evidence for this hypothesis was derived from a number of retrospective case-control studies (Table 1)¹⁷⁻²¹.

It is important to note that these studies are relatively small and yield conflicting results: some indicate significant differences in the

magnitude of ADP-induced aggregation between patients with ST and controls, whereas others report no differences at all. A likely explanation for this apparent contradiction appears to be due to differences in the timing of platelet function evaluation (in the acute phase of the ST versus later on, when platelet activation is normalised), differences in control group selection and the use of different platelet function assays.

Results from prospective observational studies also support the hypothesis that patients with high on-treatment platelet reactivity despite aspirin and clopidogrel therapy are more likely to suffer from a stent thrombosis (Table 2)^{11,22-25}. The problem with these studies is the relatively low number of events and the diversity in definitions (thresholds) to identify those patients who are at an increased risk for ST.

Methods to determine platelet reactivity

An abundant variety of techniques is currently available to monitor platelet function in patients receiving antiplatelet therapy (Table 3)²⁶⁻³⁰. However, given the very complex nature of platelet biology, there is no platelet function test that covers all aspects. Moreover, the answer to "which is the right test to measure platelet function?" varies according to the purpose of testing. Several commercial "point-of-care" platelet function assays have been designed with the specific purpose of monitoring different types of antiplatelet therapy. As a consequence, these assays can be used to answer the question: "does the aspirin or clopidogrel therapy actually work in my patient". Nonetheless, the residual magnitude of platelet reactivity can still be heightened despite an adequate effectiveness of antiplatelet drugs. Likewise, other platelet function assays have been developed to screen the general platelet reactivity status of a patient without knowing the individual effects of antiplatelet drugs.

Table 1. Currently available case-control studies.

Study	Total No. of patients	No. of patients with stent thrombosis	Platelet function test	Result	Timing between the occurrence of ST and Platelet Function Testing
Barragan et al	52	16	Flowcytometric VASP-assay	- Significant higher platelet reactivity index in patients with ST	At presentation of ST
Wenaweser et al	82	23	LTA	- Significant difference in ADP-induced aggregation between cases and controls - Significant higher prevalence of aspirin resistance in patients with ST	64±3.4 months between index PCI and pft.
Ajzenberg et al	49	10	LTA and Shear-induced platelet aggregation (SIPA)	- No significant difference in ADP-induced aggregation between cases and controls - Significant difference in SIPA between cases and controls	4.6±3.4 days after ST
Gurbel et al	120	20	LTA	- Significant difference in ADP-induced aggregation between cases and controls - Significant higher platelet reactivity index in patients with ST - Significant higher ADP-stimulated GP IIb/IIIa receptor expression	5-14 days after the procedure
Morel et al	36	12	LTA and Flowcytometric VASP-assay	- No significant difference in ADP-induced aggregation between cases and controls - Significant higher platelet reactivity index in patients with ST	At presentation of ST

ACS: acute coronary syndrome; ADP: adenosine diphosphate; LTA: light transmittance aggregometry; PCI: percutaneous coronary intervention; PFT: platelet function test; ST: stent thrombosis; VASP: vasodilator-stimulated phosphoprotein

Table 2. Prospective observational studies.

Study	Patient population	Total No. of patients	No. of patients with stent thrombosis	Platelet function test	Result
Jacopo et al	All-comers (stable angina [40%], ACS [60%])	256	6	PFA-100 Collagen/epinephrine cartridge	Patients who developed ST had lower COL/EPI closure times (<190s)
Price et al	Stable angina patients	380	6	VerifyNow P2Y12 assay	Patients who developed ST exhibited higher on-treatment platelet reactivity
Buonamici et al	All-comers (stable angina [34%], ACS [66%])	804	25	LTA with 10 µmol/L ADP as the agonist	Patients who developed ST exhibited higher residual aggregation values.
Wetzel et al	All-comers (stable angina [67%], ACS [33%])	2,847	51	LTA with 20 µmol/L ADP as the agonist	Patients who developed ST exhibited higher residual aggregation values.
Blindt et al	High-risk patients undergoing PCI	99	9	LTA and Flowcytometric VASP-assay	Patients who developed ST exhibited higher ADP-induced aggregation values as well as a higher platelet reactivity index.

ACS: acute coronary syndrome; ADP: adenosine diphosphate; COL/EPI: collagen/epinephrine; LTA: light transmittance aggregometry; PCI: percutaneous coronary intervention; ST: stent thrombosis; VASP: vasodilator-stimulated phosphoprotein

Table 3. Currently available platelet function tests to quantify the magnitude of (on-treatment) platelet reactivity.

Light transmittance aggregometry (LTA)

Whole-blood Impedance aggregometry (Multiplate® or Chronolog)

VerifyNow®

Plateletworks®

Cone-and-Plate(let) Analyzer (IMPACT)

Plateletworks®

TEG®

Flowcytometry

PFA-100®

Under development:

Platelet Reactivity test (Placor)

T-Guide (Thrombovision)

Currently available platelet function assays

The following assays are currently available for the monitoring of the individuals response to antiplatelet therapy in the catheterisation laboratory. The advantages and shortcomings of these methods as well as their potential role for possible application in the catheterisation laboratory are highlighted.

Light transmittance aggregometry

The most commonly used method to evaluate platelet function has been the optical detection of platelet aggregation in platelet-rich plasma (PRP) termed light transmittance aggregometry (LTA).³¹ A sample of citrated blood is collected and centrifuged to obtain PRP. After removing the platelets in the centrifuged tube, platelet-poor plasma (PPP) is prepared from the remaining sample to serve as the 100% aggregation reference. PRP is then pipetted in a cuvette and is warmed to 37 °C and light transmission through the PRP is detected by a photometer. Various agonists can be added to the cuvette to stimulate specific platelet activating-pathways: e.g., ADP, the agonist to evaluate the effects of clopidogrel; arachidonic acid, the agonist to evaluate the effects of aspirin, collagen and/or thrombin-receptor activating peptide (to quantify magnitude of the general platelet reactivity of an individual). Upon addition of an agonist, the platelets change from

their disc shape to a more rounded form with pseudopods, resulting in a transient, small decrease in light transmission that is followed by an increase in light transmission as the platelets aggregate. Parameters measured include the slope of aggregation, the measurement of aggregate stabilisation and the maximal amplitude or percentage of aggregation after a fixed period of time.

ADVANTAGES OF LTA

LTA is available in almost every laboratory and has been in use for more than 35 years. Additionally, multiple studies (despite arbitrarily chosen cut-offs to segregate responders from non-responders) have shown that LTA is capable of predicting the occurrence of atherothrombotic events.

SHORTCOMINGS OF LTA

LTA has several serious drawbacks that make it impossible to incorporate LTA into the routine practice. These include: poor reproducibility which makes comparison between laboratories difficult, a long sample processing time and the expertise of specialised technicians. Furthermore, many factors such as platelet activation by centrifugation, sample ageing and the presence of other substances (e.g. lipids) may affect the magnitude of platelet aggregation. Another limitation of LTA is that it is based on fibrinogen-GP IIb/IIIa mediated aggregation. However, under physiological conditions (e.g., under the high shear rates of arterial flow) the interaction between the GP IIb/IIIa receptor, vWF and subendothelial components (e.g. collagen) are at least of equal importance in the process of thrombus formation.

The VerifyNow™ system

The VerifyNow system (formerly known as the Rapid-Platelet Function Analyzer or Ultegra; Accumetrics, San Diego, USA) is based upon the principle that agonist-induced activated platelets bind to fibrinogen-coated polystyrene beads that agglutinate in whole-blood²⁶. After whole blood is added in the mixing chamber, the platelets become activated by a specific agonist if the antiplatelet drug does not adequately exert its antiplatelet effect. As a result, the platelets bind via GP IIb/IIIa receptors to the fibrinogen-coated beads and cause agglutination. Infra-red light transmittance through the chamber increases as the platelet-beads

complexes fall out of the solution. Currently, three different cartridges are available: the VerifyNow™ aspirin assay (using arachidonic acid [AA] as the agonist), the VerifyNow™ P2Y12 assay (using ADP as the agonist, antagonised by prostaglandin E₁) and the VerifyNow™ IIb/IIIa assay (using thrombin receptor-activating peptide [TRAP] as the agonist).

ADVANTAGES OF THE VERIFYNOW™ SYSTEM

It is a bedside device (really “point-of-care”) that provides simple, rapid and accurate results. Although relatively small, several studies have indicated that the results obtained from any of the three assays correlate with the (re)occurrence of cardiovascular events.

SHORTCOMINGS OF THE VERIFYNOW™ SYSTEM

In contrast to other commercial platelet function assays, the VerifyNow™ assay differs from *in vivo* conditions because it does not assess platelet function under high shear conditions. In addition, the VerifyNow™ assays are relatively expensive when compared to the other available platelet function assays.

The Platelet Function Analyzer™ (PFA-100)

The PFA-100® Analyzer (Dade Behring Marburg GmbH – A Siemens Company, Marburg, Germany) measures platelet function, in particular adhesion and aggregation, in whole blood under high shear conditions (thereby mimicking the pressure in a capillary in the human body)²⁷. Specifically, the time needed to form a platelet plug occluding the aperture cut into a collagen/epinephrine (COL/EPI) or collagen/ADP (COL/ADP) coated membrane is determined and reported as closure time (CT) in seconds. If the formed clot is too weak, the CT can not be measured and the results are presented as >300 seconds.

ADVANTAGES OF THE PFA-100™ SYSTEM

The instrument uses whole blood, the technique is easy to learn and is semi automated. The assay evaluates both shear-stress and fibrinogen-induced GP IIb/IIIa-mediated aggregation, which corresponds better with the *in vivo* process of thrombus formation. Also, the results obtained of the COL/ADP provide a general view of the individual's magnitude of platelet reactivity. As a result, there is some evidence that has linked shorter COL/ADP closure times with a higher (re)-occurrence of atherothrombotic events.

SHORTCOMINGS OF THE PFA-100™ SYSTEM

It has been estimated that the concentrations of collagen and ADP are far beyond the physiological concentrations of these substances *in vivo*. Hence, it has been suggested that clopidogrel is not able to inhibit the platelet plug formation under these high concentrations of collagen and ADP in the cartridges. A new cartridge with the specific purpose to monitor the inhibitory effects of clopidogrel is currently under development.

The Plateletworks® system

The PlateletWorks® system (Helena laboratories, Beaumont, USA) is based on a single platelet counting principle, expressed as the platelet count ratio before and after exposure to ADP, to calculate the percentage of platelet inhibition³⁰. A total reference platelet count is performed in whole blood in a Plateletworks® tube

containing K₃-EDTA as the anticoagulant on a cell counter. This process is repeated with a second sample of fresh whole blood in a Plateletworks® tube containing both D-Phe-Pro-Arg-chloromethylketone (PPACK) 50 µmol/L and ADP, AA or collagen. In the presence of a the agonist, platelets associate and aggregate. As the aggregated platelets exceed the threshold limitations for platelet size, they are no longer counted as individual platelets. The ratio of the platelet count between the agonist tube and reference tubes is expressed as percentage of inhibition of platelet aggregation (IPA).

ADVANTAGES OF THE PLATELETTWORKS®

The method is simple, inexpensive, quick to perform (5 minutes) and thus easy to incorporate into daily practice.

SHORTCOMINGS OF THE PLATELETTWORKS®

Measurements should be performed within ten minutes after the addition of 1 ml of whole blood. Thereafter, ADP-induced platelet aggregates will dissociate and the extend of platelet inhibition will be overestimated (van Werkum, unpublished data). Also, it has been shown that the Plateletworks® assay measures lower levels of IPA as compared to LTA. This has led to the hypothesis that LT aggregometry provides information regarding the platelet macro-aggregate formation only, while the platelet count ratio measures the platelet macro- and micro- aggregate formation. The relevance of micro-aggregation as predictor for clinical outcome, however, has not been established.

Conclusion

The observed wide inter-individual variability in the response to aspirin and clopidogrel therapy has increased the interest in the use of platelet function assays. Moreover, the body of evidence showing that heightened platelet reactivity and/or an impaired responsiveness to antiplatelet therapy are associated with the occurrence of stent thrombosis is growing, and this opens doors to a new era of tailoring the antiplatelet therapy itself. Although the most predictive and easy-to-use platelet function assay has not yet been identified, ongoing research will elucidate which aspects of platelet function are most involved in the pathogenesis of stent thrombosis.

References

1. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP Jr., Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967-1971.
2. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-2130.
3. Honda Y, Fitzgerald PJ. Stent thrombosis: an issue revisited in a changing world. *Circulation*, 2003;108:2-5.
4. Gross PL, Aird WC. The endothelium and thrombosis. *Semin Thromb Hemost* 2000;26:463-478.
5. Michelson AD. How platelets work: platelet function and dysfunction. *J Thromb Thrombolysis* 2003;16:7-12.

6. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol* 2005;45:246-251.
7. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De SS, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-2015.
8. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Sattler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 2006;113:1108-1113.
9. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 2007;115:2435-2441.
10. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation* 2003;108:1701-1706.
11. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Panicia R, Moschi G, Gori AM, Abbate R, Antoniucci D. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;49:2312-2317.
12. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;45:1157-1164.
13. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006;367:606-617.
14. Cattaneo M. Resistance to antiplatelet drugs: molecular mechanisms and laboratory detection. *J Thromb Haemost* 5 Suppl 2007;1:230-237.
15. Yee DL, Sun CW, Bergeron AL, Dong JF, Bray PF. Aggregometry detects platelet hyperreactivity in healthy individuals. *Blood* 2005;106:2723-2729.
16. Samara WM, Bliden KP, Tantry US, Gurbel PA. The difference between clopidogrel responsiveness and posttreatment platelet reactivity. *Thromb Res* 2005;115:89-94.
17. Barragan P, Bouvier JL, Roquebert PO, Macaluso G, Commeau P, Comet B, Lafont A, Camoin L, Walter U, Eigenthaler M. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. *Catheter Cardiovasc Interv* 2003;59:295-302.
18. Wenaweser P, Dorffler-Melly J, Imboden K, Windecker S, Togni M, Meier B, Haerberli A, Hess OM. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol* 2005;45:1748-1752.
19. Ajzenberg N, Aubry P, Huisse MG, Cachier A, El AW, Feldman LJ, Himbert D, Baruch D, Guillin MC, Steg PG. Enhanced shear-induced platelet aggregation in patients who experience subacute stent thrombosis: a case-control study. *J Am Coll Cardiol* 2005;45:1753-1756.
20. Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissaha MZ, Tantry US. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005;46:1827-1832.
21. Morel O, Faure A, Ohlmann P, Jesel L, Desprez D, Grunebaum L, Bareiss P. Impaired platelet responsiveness to clopidogrel identified by flow cytometric vasodilator-stimulated phosphoprotein (VASP) phosphorylation in patients with subacute stent thrombosis. *Thromb Haemost* 2007;98:896-899.
22. Jacopo G, Elisabetta V, Silverio S, Massimiliano M, Sergio B, Grazia AM, Philippe CJ. Identification of platelet hyper-reactivity measured with a portable device immediately after percutaneous coronary intervention predicts in stent thrombosis. *Thromb Res* 2007;121:407-412.
23. Price M, Valencia R, Gollapudi R.R, Endemann S, Stinis C, Levisay J.P, Teirstein PS. The Response To Clopidogrel Measured By A Point-of-Care Assay Following Percutaneous Coronary Intervention Is Associated With Stent Thrombosis Over 6-Month Follow-up. (Abstract). Abstract presented at the i2 Summit 2007 in New Orleans, 2007.
24. Wetzel T, Schulz M, Schulze-Waltrup N, Dedner R, Weber-Albers J, Schmitz D, Marks M, Heuer H: Clinical Relevance Of Clopidogrel-hyporesponse To Subacute Stent Thrombosis (Abstract). *Circulation* 2007; Volume 116: 16 supplement.
25. Blindt R, Stellbrink K, de TA, Muller R, Kiefer P, Yagmur E, Weber C, Kelm M, Hoffmann R. The significance of vasodilator-stimulated phosphoprotein for risk stratification of stent thrombosis. *Thromb Haemost* 2007;98:1329-1334.
26. Steinhubl SR, Kereiakes DJ. Ultegra Rapid Platelet Function Analyzer. 2006.
27. Favaloro EJ. Clinical application of the PFA-100. *Curr Opin Hematol* 2002;9:407-415.
28. Savion N, Varon D. Impact—the cone and plate(let) analyzer: testing platelet function and anti-platelet drug response. *Pathophysiol Haemost Thromb* 2006;35:83-88.
29. Mueller T, Dieplinger B, Poelz W, Calatzis A, Haltmayer M. Utility of whole blood impedance aggregometry for the assessment of clopidogrel action using the novel Multiplate® analyzer-comparison with two flow cytometric methods. *Thromb Res*, 2007.
30. White MM, Krishnan R, Kueter TJ, Jacoski MV, Jennings LK. The use of the point of care Helena ICHOR/Plateletworks and the Accumetrics Ultegra RPFA for assessment of platelet function with GPIIb-IIIa antagonists. *J Thromb Thrombolysis* 2004;18:163-169.
31. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 1962;194:927-929.