Stent Thrombosis: Role of Compliance and Nonresponsiveness to Antiplatelet Therapy

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Percutaneous coronary intervention with drug-eluting stents has revolutionized the management of patients with symptomatic coronary artery disease. Although this strategy significantly reduces the incidence of restenosis and repeat revascularization, concern has been raised about an increased frequency of late stent thrombosis with drug-eluting stents compared with bare-metal stents. The mechanism of stent thrombosis remains unclear, and various hypotheses have been described. Platelets are believed to play a pivotal role in the development of stent thrombosis, with pathological studies demonstrating an abundance of platelets within the occlusive thrombi. Premature discontinuation and nonadherence to antiplatelet therapy are considered important risk factors for late stent thrombosis. Early identification of vulnerable patients and definition of the role of antiplatelet nonresponsiveness in the development of stent thrombosis should be the focus of future diagnostic and therapeutic strategies.
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Key words: Percutaneous coronary intervention • Drug-eluting stents • Bare-metal stents • Thrombosis • Platelets • Antiplatelet therapy

Percutaneous coronary intervention (PCI) with stenting has become the primary approach to managing patients with stable and unstable coronary artery disease (CAD). Initially, catheter-based brachytherapy was used to address the problem of in-stent restenosis and repeat revascularization associated with bare-metal stents (BMS).[1] Although this approach significantly reduced in-stent restenosis rates, an increase in the occurrence of late stent

thrombosis (LST) (>30 days post-stenting) was observed.[2] Delayed re-endothelialization following radiation therapy and stenting was felt to be the cause of stent thrombosis. It was postulated that the prothrombotic environment associated with delayed re-endothelialization facilitated platelet adhesion, activation, and recruitment, and resulted in the development of thrombosis.[3] Given the concern for delayed re-endothelialization following brachytherapy, it was recommended that dual antiplatelet therapy be administered for 6 months following treatment and up to 12 months if concomitant stenting was performed.[4] The experience with brachytherapy supports the fundamental link between delayed target lesion healing and stent thrombosis risk.

Restenosis rates have markedly declined with the advent of drug-eluting stents (DES). This dramatic reduction in restenosis spurred the exponential growth in the utilization of DES, even though the majority of patients treated with BMS had excellent outcomes. There has been little apparent effort to triage patients to BMS versus DES, as is evident by the current utilization of DES in 90% or more of PCI procedures.[5] However, LST, which was initially associated with coronary brachytherapy, has now been associated with DES, which also appear to delay re-endothelialization with pharmacologic agents such as rapamycin and paclitaxel.[6,7] Recent autopsy studies have confirmed delayed arterial healing with DES as compared with BMS.[8] Moreover, recent registry data that may be more applicable to "real-world" clinical practice demonstrate a relatively higher incidence of stent thrombosis with DES compared with BMS.[9] The influence of increased patient and target lesion complexity among patients treated with DES (vs BMS) on the apparent relative increase in LST following DES deployment cannot be statistically adjusted for in these nonrandomized comparisons, which are often conducted with historical BMS "controls."

Definition and Timing of Stent Thrombosis

Acute stent thrombosis has been defined as total or subtotal occlusion of the target vessel, with angiographic visualization of filling defects within 24 hours after stenting. Subacute stent thrombosis occurs between 24 hours and 30 days after the index stenting procedure. Stent thrombosis occurring more than 30 days after stent implantation is considered LST, and very late stent thrombosis refers to those events that occur beyond 1 year.

Effect of Dual Antiplatelet Therapy Versus Other Anticoagulant Strategies

Two important early observations suggested that stent thrombosis was strongly influenced by platelet function. In a landmark study, Schomig and colleagues[10] randomly assigned patients to phenprocoumon plus aspirin versus ticlopidine plus aspirin following coronary artery stenting. Patients treated with dual antiplatelet therapy had a stent occlusion rate of 0.8% to 30 days, versus 6.2% in the aspirin plus anticoagulant group.[10] In the Stent Anticoagulation Restenosis Study (STARS), patients undergoing successful stent implantation were randomly assigned to treatment with aspirin alone, aspirin plus warfarin, or aspirin plus ticlopidine. All stent-related clinical events were included in the primary composite endpoint of death, target lesion revascularization, angiographically evident thrombus, and myocardial infarction (MI) to 30-day follow-up. The results demonstrated a superior effect of dual antiplatelet therapy, with the primary endpoint observed in 3.6% of patients with aspirin alone, 2.7% with aspirin and warfarin, and 0.5% with dual antiplatelet therapy.[11]

Importance of Drug Compliance and Discontinuation to Stent Thrombosis

Waksman and colleagues[12] demonstrated that the prevalence of stent thrombosis in patients treated with brachytherapy for in-stent restenosis correlated with the duration of antiplatelet therapy after the index procedure. LST rates in patients enrolled in the Washington Radiation for In-Stent Restenosis Plus 6 Months of Clopidogrel (WRIST PLUS) trial, in which dual antiplatelet therapy was administered for 6 months, were lower than those in patients enrolled in the WRIST and LONG WRIST (for long lesions) trials, in which dual antiplatelet therapy was administered for only 1 month.[12]

Spertus and coworkers[13] examined the prevalence of thienopyridine discontinuation 30 days after DES implantation in patients treated for MI and compared clinical outcomes between patients who continued antiplatelet therapy versus those who did not. Patients who discontinued therapy (13.6%) had a higher mortality and more frequent repeat hospitalizations. Park and colleagues[14] studied the prevalence of DES thrombosis in 1911 consecutive patients followed for a median of 19.4 months post-procedure. LST occurred in 0.6% of patients. The most powerful independent predictor of LST was premature interruption of antiplatelet therapy (hazard ratio, 24.8). The incidence of stent thrombosis was 3.3% in patients with complete interruption of antiplatelet

therapy versus 0.6% in those without. Thirty-six percent of LST and 46% of all stent thromboses occurred in patients during dual antiplatelet therapy.[14]

Ferrari and colleagues[15] investigated the role of aspirin therapy withdrawal in patients with known CAD who subsequently developed an acute coronary syndrome. Thirteen percent of patients had discontinued aspirin therapy within 1 month of presentation. Ten patients experienced LST involving BMS, which accounted for a high proportion (20%) of all coronary events occurring after aspirin withdrawal. McFadden and colleagues[16] reported 2 cases of LST following paclitaxel-eluting stent (PES) and sirolimus-eluting stent (SES) deployment 343 to 442 days post-PCI and coincident with the cessation of aspirin therapy (4 to 14 days prior to the event).[16]

In a recent prospective observational study, Iakovou and colleagues[9] evaluated the incidence and predictors of stent thrombosis after PES and SES implantation. Aspirin therapy was continued indefinitely in these patients, and a thienopyridine was continued for at least 3 months (in the SES group) or 6 months (in the PES group) following the index procedure. At 9-month follow-up, stent thrombosis had occurred in 1.3% of patients (29 out of 2229): 0.8% in the SES group and 1.7% in the PES group. Among these patients, 14 (0.6%) had subacute stent thrombosis and 15 (0.7%) had LST. Premature discontinuation of antiplatelet therapy was the main independent predictor of subacute stent thrombosis (hazard ratio, 161.17; 95% CI, 26.03-997.94; $P < .001$) and LST (hazard ratio 57.13; 95% CI, 14.84-219.96; $P < .001$).[9]

In a presentation at the 2006 Transcatheter Cardiovascular Therapeutics Meeting, Morici and colleagues[17] reported a retrospective study of 2160 consecutive patients treated with DES in whom stent thrombosis was diagnosed by autopsy, angiographic confirmation, or target vessel–related myocardial infarction. Stent thrombosis was higher in the first 6 months following the procedure in patients who discontinued antiplatelet therapy (14.3%) compared with those who remained on either aspirin alone (7.5%) or dual antiplatelet therapy (0.4%). In the Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events (BASKET-LATE) study, Pfisterer and colleagues[18] reported 1-year follow-up data on a consecutive series of 746 patients who survived 6 months without clinical events after DES or BMS procedures. Clopidogrel was discontinued 6 months after the initial stenting procedure. DES were associated with a 2-fold higher incidence of documented LST, which translated into a higher incidence of death/target vessel distribution MI for DES compared with BMS (2.6% vs 1.3%).[18] More recently, Eisenstein and colleagues[19] provided observations on consecutive patients treated with either BMS (n = 3165) or DES (n = 1501) who were followed for 2 years after stent deployment. Landmark analyses were performed among patients who were event-free (no death, MI, or revascularization) at 6-month and 12-month follow-up by stent type (BMS or DES) and patient report of clopidogrel use (yes or no). The authors concluded that patients treated with clopidogrel at 6 months and 12 months after DES deployment had significantly lower subsequent rates of death or myocardial infarction than DES-treated patients not receiving clopidogrel at these time intervals. Furthermore, as observed by Kereiakes,[20] DES-treated patients who received extended clopidogrel treatment to at least 1 year had significantly lower rates of death and death or myocardial infarction when compared with BMS-treated patients, regardless of their clopidogrel therapy status. The salutary effects of extended clopidogrel therapy were maintained to at least 2 years of follow-up. Taken together, the above studies support the central role of dual antiplatelet therapy in preventing stent thrombosis. Continuation of thienopyridine therapy even beyond 1 year following DES may continue to provide clinical benefit, and the optimal duration of therapy remains to be determined.[19,20]

Clopidogrel Response Variability: Effect of Dose and Timing

Wide interindividual variability in response, including nonresponsiveness, has been demonstrated in patients receiving clopidogrel therapy following stenting.[21] Various studies have demonstrated the importance of the measurement of aspirin and clopidogrel responsiveness in predicting post-stenting ischemic events, periprocedural MI, and stent thrombosis.[22] Prospective randomized trials have demonstrated that clopidogrel responsiveness is dependent on dose (both loading and maintenance) and time post-stenting. We have demonstrated that clopidogrel nonresponsiveness, defined as less than 10% absolute change in aggregation compared with pre-treatment, decreases over time after stenting. In a study of patients undergoing elective stenting who were treated with 300 mg of clopidogrel at the time of PCI, 53% to 63% of patients were nonresponsive to clopidogrel at 2 hours post-stenting, about 30% were resistant at day 1 and day 5 post-stenting, and 13% to 21% were resistant at day 30 post-stenting.[23] In a subsequent pharmacodynamic study comparing 300-mg and 600-mg

clopidogrel loading doses, treatment with a 600-mg loading dose during PCI reduced clopidogrel nonresponsiveness to 8%, compared with 28% to 32% following the 300-mg dose.[24] In addition, a recent study has demonstrated that a 150-mg/d maintenance dose of clopidogrel is associated with increased platelet inhibition compared with a 75-mg dose.[25]

We have examined the durability of clopidogrel-induced platelet inhibition with a maintenance dose of 75 mg/d during a 30-day period in patients undergoing elective PCI.[26] At 5 days post-stenting, 66% of patients who were nonresponsive at 24 hours continued to be nonresponsive. However, at 30 days post-stenting, approximately 50% of the patients who were nonresponsive at 5 days failed to meet the definition of nonresponsiveness. In contrast, at least 90% of patients responsive at 5 days remained responsive at 30 days. Thus, the responsive phenotype appears stable, whereas clopidogrel nonresponsiveness appears to fall over the 30-day period following stent deployment.[26]

Platelet Reactivity Contributes to Stent Thrombosis

Stent thrombosis can still occur in patients compliant with dual antiplatelet therapy. An unresolved issue is whether patients with high post-treatment platelet reactivity to adenosine diphosphate (ADP) while receiving dual antiplatelet therapy are at increased risk of adverse ischemic events, including stent thrombosis. There have been no large-scale, prospective studies that have been adequately powered to definitively link high platelet reactivity as measured by an ex vivo assay to the occurrence of stent thrombosis. Because stent thrombosis event rates are very low, the number of patients required to validate such a study would range well into the thousands. However, emerging data from small studies are accruing that suggest a mechanistic link between platelet-driven thrombotic events and insufficient platelet inhibition. In the Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) elective stenting study, we demonstrated that superior platelet inhibition obtained with a glycoprotein (GP) IIb/IIIa inhibitor at the time of PCI was associated with decreased periprocedural myonecrosis biomarker release.[27,28] Similarly, in the Platelet Reactivity in Patients and Recurrent Events Post-Stenting (PREPARE POST-STENTING) study, high periprocedural platelet reactivity was associated with an increased ischemic event rate during the 6-month period following elective stenting.[29] In a recent study in which CAD patients already maintained on long-term clopidogrel therapy underwent PCI, we observed markedly higher preprocedural platelet reactivity in the group of patients who subsequently suffered an ischemic event within 6 months following the procedure. Interestingly, treatment with a GP IIb/IIIa inhibitor resulted in fewer ischemic events during the 6-month follow-up.[30] A similar observation was made by Wenaweser and colleagues,[31] who indicated that omission of abciximab at the time of treatment for stent thrombosis was an independent predictor of recurrent thrombosis. These studies suggest that rigorous antiplatelet therapy during stenting may reduce the risk of future stent thrombosis, and that measurement of platelet function immediately after stenting may assist in the detection of patients at high risk for LST.

Barragan and coworkers[32] demonstrated that high $P2Y_{12}$ receptor reactivity may be a risk factor for stent thrombosis by measuring vasodilator-stimulated phosphoprotein (VASP) phosphorylation levels (a highly specific indicator of $P2Y_{12}$ reactivity—the target of thienopyridine drugs) in 16 patients with stent thrombosis and 30 stented patients free of stent thrombosis. All patients were on aspirin and either clopidogrel or ticlopidine therapy. Patients who suffered stent thrombosis had significantly higher $P2Y_{12}$ reactivity compared with patients who were free of stent thrombosis (63% ± 10% vs 40% ± 11%; $P < .001$).[32] Muller and colleagues[33] reported 2 cases of subacute stent thrombosis in patients who were nonresponders to clopidogrel therapy using light transmittance aggregometry.

Rigorous antiplatelet therapy during stenting may reduce the risk of future stent thrombosis, and measurement of platelet function immediately after stenting may assist in the detection of patients at high risk for late stent thrombosis.

In the recent Clopidogrel Effect on Platelet Reactivity in Patients With Stent Thrombosis (CREST) study, platelet function was evaluated retrospectively in patients with stent thrombosis (n = 20) and prospectively in patients without stent thrombosis (n = 100) using light transmittance platelet aggregation, ADP-stimulated expression of active GP IIb/IIIa expression, and the $P2Y_{12}$ reactivity ratio measured by VASP phosphorylation.[34] All patients were on a 75-mg clopidogrel maintenance dose and aspirin therapy at the time the platelet studies were conducted. Higher levels of all of

Table 1
Relation of Clopidogrel Nonresponsiveness and Stent Thrombosis

Study	Total Number of Patients	Patients With Stent Thrombosis	Results
Barragan P et al[32]	52	16	↑ $P2Y_{12}$ reactivity ratio (VASP-levels) in patients with stent thrombosis
Muller I et al[33]	105	2	Both clopidogrel non-responders by 5 and 20 μM ADP-induced aggregation
Gurbel PA et al[34] (CREST Study)	120	20	↑ $P2Y_{12}$ reactivity ratio ↑ 5 and 20 μM ADP-induced aggregation ↑ ADP-stimulated active GP IIb/IIIa in patients with stent thrombosis
Ajzenberg N et al[35]	49	10	↑ Shear-induced platelet aggregation in patients with stent thrombosis
Price JM et al[36]	264	4	3 of 4 stent thrombosis patients were clopidogrel nonresponders by VerifyNow $P2Y_{12}$ assay

VASP, vasodilator-stimulated phosphoprotein; ADP, adenosine diphosphate; GP, glycoprotein.

these measurements were observed in patients with stent thrombosis, indicating inadequate inhibition of the $P2Y_{12}$ receptor.[34]

A recent study demonstrated that patients receiving dual antiplatelet therapy who develop stent thrombosis show increased shear-induced platelet aggregation as compared with patients receiving dual antiplatelet therapy who do not develop stent thrombosis and to normal controls not receiving dual antiplatelet therapy.[35] Price and colleagues,[36] using the point-of-care VerifyNow™ $P2Y_{12}$ assay, measured clopidogrel responsiveness (platelet inhibition) and platelet reactivity (aggregation) in patients undergoing PCI followed to 30 days. Three out of 4 patients who developed stent thrombosis were in the lowest quartile of platelet inhibition and also in the highest quartile of platelet reactivity as measured by the VerifyNow $P2Y_{12}$ assay (Table 1).[36]

Evidence for a Platelet Reactivity Threshold in Predicting Stent Thrombosis

Data from our center suggest that there may be a threshold of platelet reactivity, as measured by light transmittance aggregometry after ADP stimulation of platelet-rich plasma, which predicts an increased risk of thrombotic events following PCI. The CLEAR PLATELETS study results demonstrated that more than 50% mean platelet aggregation in response to 5 μM ADP marked a threshold for periprocedural myonecrosis.[27] In the PREPARE POST-STENTING study, a threshold of about 50% periprocedural platelet aggregation in response to 20 μM ADP predicted the subsequent development of ischemic events following stenting during the 6-month follow-up.[29] Similarly, in the CREST study, about 40% platelet aggregation in response to 20 μM ADP predicted the occurrence of stent thrombosis. In a recent study by our group, a threshold of about 40% preprocedural platelet aggregation in response to 5 μM ADP in patients who were already on long-term clopidogrel and aspirin treatment prior to PCI predicted the occurrence of ischemic events to the 6-month follow-up (Figure 1).[34] Taken together, these results may provide a therapeutic threshold for future studies that will evaluate the utility of determining platelet responsiveness to dual antiplatelet therapy and allow appropriate adjustment in treatment in order to reduce the development of ischemic events, including stent thrombosis.

Conclusion

Stent thrombosis is associated with serious adverse events. There is a definite relationship between the cessation of antiplatelet therapy and the occurrence of stent thrombosis. The optimal duration of dual antiplatelet therapy after DES implantation remains unknown. Individual variability in response to clopidogrel has been well established. The occurrence of stent thrombosis in patients compliant with dual antiplatelet therapy may be related to antiplatelet nonresponsiveness or inadequate inhibition of platelet function. However, at this time, there have been no definitive, adequately powered clinical trials to prove a mechanistic link between high post-stenting platelet function and stent thrombosis. It is

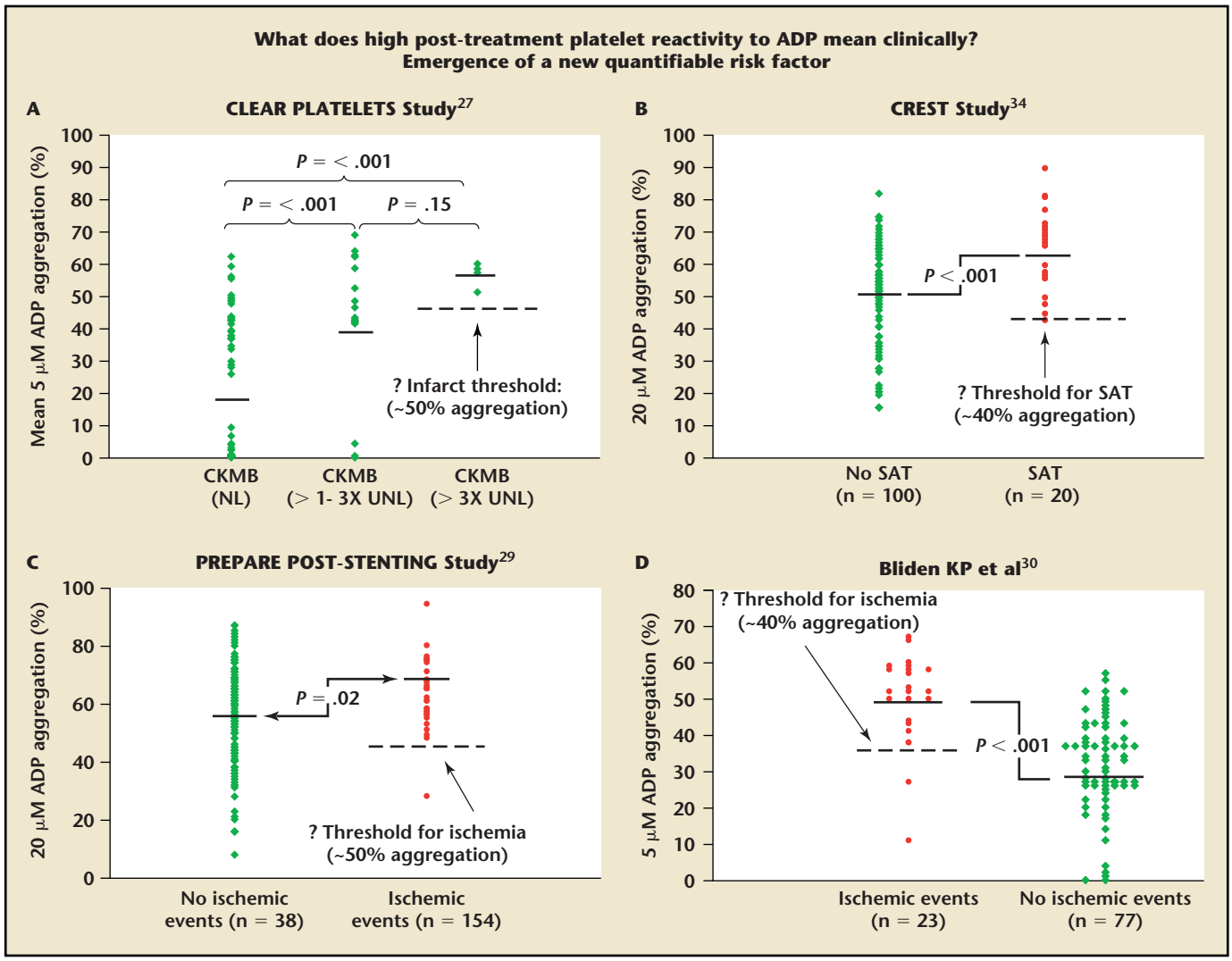

Figure 1. *There is evidence from small studies that high platelet reactivity may be a risk factor for post-stenting ischemic events. Shown are results from 4 translational research studies suggesting that there may be a platelet reactivity threshold predictive of events as measured by light transmittance aggregometry following stimulation with ADP in platelet-rich plasma. High platelet reactivity was linked in the CLEAR Platelets Study* **(A)** *to periprocedural myocardial infarction; in the CREST study* **(B)** *to SAT; and in the PREPARE POST-STENTING study* **(C)** *to 6-month ischemic events. Patients on chronic clopidogrel therapy undergoing stenting who developed ischemic events within 6 months of the procedure had higher pre-stenting platelet reactivity than patients who did not develop ischemic events* **(D)**. *ADP, adenosine diphosphate; CLEAR PLATELETS, Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets; CKMB, creatine kinase, myocardial bound; NL, normal limits; UNL, upper normal limits; CREST, Clopidogrel Effect on Platelet Reactivity in Patients With Stent Thrombosis; SAT, subacute stent thrombosis; PREPARE POST-STENTING, Platelet Reactivity in Patients and Recurrent Events Post-Stenting.* www.medreviews.com

likely that "vulnerable blood" characterized by hypercoagulability, increased inflammatory cytokines, and heightened platelet reactivity plays a role in the development of stent thrombosis. Although indefinite treatment with dual antiplatelet therapy to prevent stent thrombosis has been advocated by some, the associated bleeding risk and cost are of major concern. It also does not seem rational to indefinitely treat all DES patients with dual antiplatelet therapy to prevent the occurrence of a very low frequency adverse event. Therefore, large, adequately powered prospective studies designed to predict which patients are prone to stent thrombosis based on platelet function testing appear to be a step in the correct direction that may lead to personalized antithrombotic therapy (Figure 2). The Strategic Transcatheter Evaluation of New Therapies (STENT) Thrombosis study will enroll about 10,000 patients who will undergo testing by the VerifyNow

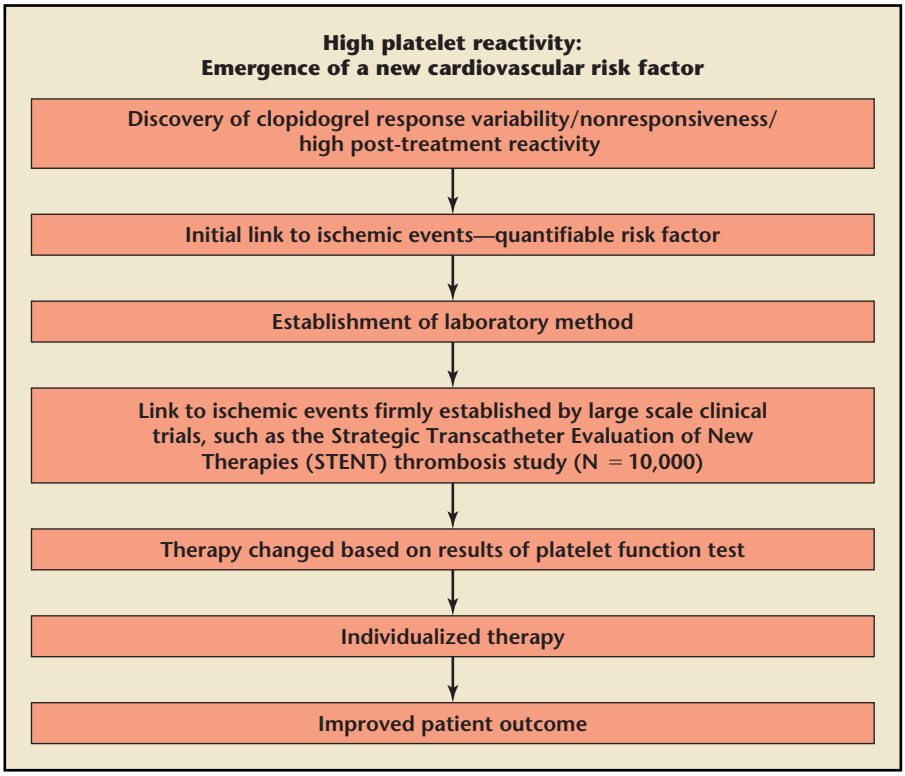

Figure 2. *High platelet reactivity to adenosine diphosphate may be established as a cardiovascular risk factor by the discovery of clopidogrel response variability/high post-treatment platelet reactivity. Figure lists the progress of events that could support personalized antithrombotic therapy in patients treated by coronary stenting.*
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$P2Y_{12}$ assay and be followed for the occurrence of stent thrombosis. Finally, laboratory assays designed to identify the patient at high risk for restenosis may facilitate the decision-making algorithm for selecting DES versus BMS in certain patient subsets.[37] ■

References

1. Teirstein P, Reilly JP. Late stent thrombosis in brachytherapy: the role of long-term antiplatelet therapy. *J Invasive Cardiol*. 2002;14:109-114.
2. Maehara A, Mintz GS, Weissman NJ, et al. Late thrombosis after gamma-brachytherapy. *Catheter Cardiovasc Interv*. 2003;58:455-458.
3. Salame MY, Verheye S, Mulkey SP, et al. The effect of endovascular irradiation on platelet recruitment at sites of balloon angioplasty in pig coronary arteries. *Circulation*. 2000;101:1087-1090.
4. Waksman R, Ajani AE, Pinnow E, et al. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS. *Circulation*. 2002;106:776-778.
5. Thanigaraj S, Wollmuth JR, Zajarias A, et al. From randomized trials to routine clinical practice: an evidence-based approach for the use of drug-eluting stents. *Coron Artery Dis*. 2006;17:673-679.
6. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation*. 2001;104:2007-2011.
7. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. *Circulation*. 2001;103:2289-2295.
8. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
9. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
10. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of

Main Points

- Clopidogrel nonresponsiveness, defined as less than 10% absolute change in aggregation compared with pretreatment, decreases over time after stenting.
- In a pharmacodynamic study comparing 300-mg and 600-mg clopidogrel loading doses, treatment with a 600-mg loading dose during percutaneous coronary intervention reduced clopidogrel nonresponsiveness to 8%, compared with 28% to 32% following the 300-mg dose.
- Emerging data from small studies are accruing that suggest a mechanistic link between platelet-driven thrombotic events and insufficient platelet inhibition.
- In a recent study in which coronary artery disease patients already maintained on long-term clopidogrel therapy underwent percutaneous coronary intervention, a markedly higher preprocedural platelet reactivity in the group of patients who subsequently suffered an ischemic event within 6 months following the procedure was observed.
- Data from our center suggest that there may be a threshold of platelet reactivity, as measured by light transmittance aggregometry after adenosine diphosphate stimulation of platelet-rich plasma, which predicts an increased risk of thrombotic events following percutaneous coronary intervention.

coronary-artery stents. *N Engl J Med*. 1996; 334:1084-1089.
11. 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;339:1665-1671.
12. Waksman R, Ajani AE, White RL, et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). *Circulation*. 2001;103:2332-2335.
13. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113: 2803-2809.
14. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol*. 2006;98:352-356.
15. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol*. 2005;45:456-459.
16. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519-1521.
17. Morici N, Airoldi F, Briguori C, et al. Relationship of occurrence of drug-eluting stent thrombosis and assumption of double antiplatelet therapy. *Am J Cardiol*. 2006;98:8M (abstract-TCT-15).
18. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48:2584-2591.
19. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel after drug-eluting stent implantation. *JAMA*. 2007;297:159-168.
20. Kereiakes DJ. Does clopidogrel each day keep thrombosis away? *JAMA*. 2007;297:209-211.
21. Gurbel PA, Tantry US. Drug insight: clopidogrel nonresponsiveness. *Nat Clin Pract Cardiovasc Med*. 2006;3:387-395.
22. Tantry US, Bliden KP, Gurbel PA. Resistance to antiplatelet drugs: current status and future research. *Expert Opin Pharmacother*. 2005;6: 2027-2045.
23. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003;107:2908-2913.
24. Gurbel PA, Bliden KP, Hayes KM, et al. 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: 1392-1396.
25. Hochholzer W, Trenk D, Mueller B, et al. Efficacy of adjusted clopidogrel dosing in patients with insufficient platelet inhibition after elective coronary stenting: the ExcelsiorACT study. Available at: http://www.escardio.org/knowledge/congresses/abol/presentation?id=41523. Accessed December 28, 2006.
26. Gurbel PA, Bliden KP. Durability of platelet inhibition by clopidogrel. *Am J Cardiol*. 2003;91: 1123-1125.
27. Gurbel PA, Bliden KP, Zaman KA, et al. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation*. 2005;111:1153-1159.
28. Stankovic G, Chieffo A, Iakovou I, et al. Creatine kinase-myocardial band isoenzyme elevation after percutaneous coronary interventions using sirolimus-eluting stents. *Am J Cardiol*. 2004;93:1397-1401.
29. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. *J Am Coll Cardiol*. 2005; 46:1820-1826.
30. Bliden KP, DiChiara J, Tantry US, et al. Increased risk in patients with high platelet aggregation on chronic clopidogrel therapy undergoing PCI: is the current antiplatelet therapy adequate? *J Am Coll Cardiol*. 2007;49: 657-666.
31. Wenaweser P, Rey C, Eberli FR, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. *Eur Heart J*. 2005;26:1180-1187.
32. Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. *Catheter Cardiovasc Interv*. 2003; 59:295-302.
33. Muller I, Besta F, Schulz C, et al. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost*. 2003;89:783-787.
34. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol*. 2005;46:1827-1832.
35. Ajzenberg N, Aubry P, Huisse MG, et al. Enhanced shear-induced platelet aggregation in patients who experience subacute stent thrombosis: a case-control study. *J Am Coll Cardiol*. 2005;45:1753-1756.
36. Price JM, Wong GB, Valenica R, et al. Measurement of clopidogrel inhibition with a point-of-care assay identifies patients at risk for stent thrombosis after percutaneous coronary intervention [abstract]. *Am J Cardiol*. 2006;98:204M.
37. Gurbel PA, Zaman K, Bliden KP, Tantry U. Maximum clot strength is a novel and highly predictive indicator of restenosis: a potential future measure to determine who needs antiproliferative therapy and how much. *J Am Coll Cardiol*. 2006;47:43B.