Stent thrombosis associated with first-generation drug-eluting stents: issues with antiplatelet therapy

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Notice of the rare but catastrophic occurrence of stent thrombosis in association with deployment of drug-eluting stents has focused attention on the adequacy of the current dual antiplatelet regimen of aspirin and clopidogrel. Some patients will not respond to clopidogrel and a glycoprotein (GP) IIb/IIIa inhibitor may be strongly considered during stenting procedures, especially in high-risk patients or those not receiving pretreatment with clopidogrel. Insisting upon and confirming adherence to antiplatelet therapy are complicated tasks, especially because the reasons for premature discontinuation are myriad, from cost to bleeding complications to the need for minor surgery. Nevertheless, the concern about adherence to antiplatelet therapy represents a new and significant clinical reality in our stenting era, one previously less appreciated with the deployment of bare metal stents. (*Neth Heart J* 2007;15:148-50.)

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Notice of the rare but catastrophic occurrence of stent thrombosis – in particular ‘late’ stent thrombosis – in association with deployment of drug-eluting stents has focused attention on the adequacy of the current dual antiplatelet regimen of aspirin and clopidogrel. Stent thrombosis is very likely a multifactorial event, due to specific stent features (delayed

healing or polymer hypersensitivity), procedural factors (stent length and stent malapposition), and clinical risk factors such as nonresponsiveness to or premature discontinuation of antiplatelet treatment.

Responsiveness to clopidogrel is variable, and in some patients the antiplatelet effect is dose-dependent. In one study, in which 96 patients undergoing elective coronary stenting received a 300 mg loading dose of clopidogrel, the incidence of nonresponsiveness to the drug was 31% when measured at five days post-procedure.¹ In another study, when a 600 mg loading dose of clopidogrel was compared with a 300 mg loading dose of clopidogrel in 192 patients undergoing elective coronary stenting, the incidence of nonresponsiveness significantly declined from 32% with the 300 mg loading dose to 8% with the 600 mg loading dose.² Nonresponsiveness to clopidogrel thus appears to be dose-dependent. In the first and second Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) trials, the 600 mg loading dose of clopidogrel was well tolerated,^{3,4} but this loading dose still requires further investigation as the new standard for antiplatelet therapy. In the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (AMMYDA-2) study, 255 patients were randomised to a preprocedural loading dose of 300 mg or 600 mg of clopidogrel.⁵ In this trial, treatment with the higher loading dose was associated with a significant reduction in the 30-day composite endpoint of death, myocardial infarction (MI), and target-vessel revascularisation. In particular, a 600 mg loading dose of clopidogrel resulted in a relative reduction of approximately 50% in the occurrence of early MI (odds ratio 0.48, $p=0.044$). As yet, however, there has been no large-scale randomised study powered to determine the clinical efficacy of the 300 mg loading dose compared with that of the 600 mg loading dose.

Nonresponsiveness to clopidogrel appears to be due to inadequate generation of the active drug metabolite required to inhibit the P2Y₁₂ receptors. The primary mechanism of this variability lies in the hepatic CYP3A4

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pathway; the variability of response to clopidogrel may be caused by polymorphisms of CYP3A4, drug-to-drug interactions (for example, with statins),⁶ or differences in the rate of intestinal absorption of clopidogrel.⁷ Whether newer generation P2Y₁₂ platelet receptor antagonists that are metabolised differently to clopidogrel are as clinically safe and effective as clopidogrel in patients undergoing percutaneous coronary revascularisation is an issue being examined in ongoing clinical trials.

Preliminary data link nonresponsiveness to clopidogrel with a higher risk for thrombotic events. However, only a few small trials have explored the clinical relevance of an inadequate platelet response to clopidogrel.⁸ In the Clopidogrel Effect on Platelet Reactivity in Patients with Stent Thrombosis (CREST) study, post-treatment platelet reactivity was higher in patients who suffered from subacute stent thrombosis than in patients without subacute stent thrombosis, despite the use of clopidogrel therapy in both groups.⁹ The results strongly suggested that the P2Y₁₂ receptor was not adequately inhibited by clopidogrel in a large percentage of patients who had experienced subacute stent thrombosis. In a prospective study of 60 consecutive patients with ST-segment elevation MI who underwent angioplasty and stenting, Matetzky and colleagues found 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 six-month follow-up.¹⁰ Similarly, in a prospective study of 105 patients undergoing percutaneous stenting, Muller and colleagues found that the two patients who developed stent thrombosis were nonresponders to clopidogrel.¹¹

Currently, testing for nonresponsiveness to clopidogrel is impractical. There is no single and validated platelet function assay to measure the antiplatelet effect of clopidogrel, and significant prospective data are lacking to recommend routine screening on all patients undergoing stenting. Further, there are no current therapeutic alternatives to clopidogrel. Nonresponsiveness to aspirin has most likely been overestimated. This overestimation is due either to the basing of laboratory measurements on nonspecific methods that do not isolate the response of platelet cyclooxygenase-1 (COX-1) to aspirin or to aspirin dosing that is inadequate to fully inhibit COX-1 in selected patients. In a recent study, by means of arachidonic-acid-induced light-transmittance platelet aggregation and thrombelastography platelet mapping, resistance to aspirin was investigated in 223 patients reporting compliance with the therapy before undergoing percutaneous intervention. Twenty of these patients had a history of stent thrombosis. Of the 223 patients, only one (approximately 0.4%) was identified as resistant to aspirin treatment, although seven patients were found to be noncompliant.¹²

Premature discontinuation of clopidogrel after implantation of a drug-eluting stent is associated with risk of late stent thrombosis. A prospective study by Iakovou and colleagues of 2229 consecutive real-world patients who received sirolimus- or paclitaxel-eluting stents found an overall nine-month incidence of stent thrombosis of 1.3%; the fatality rate for patients experiencing stent thrombosis was 45%.¹³ In this study, the single strongest independent predictor of stent thrombosis was premature discontinuation of antiplatelet therapy (hazard ratio 89.78, $p < 0.001$), confirming the observations of several case reports.^{14,15} Similarly, in a retrospective analysis of 2974 consecutive patients who received a drug-eluting stent, of whom 38 (1.27%) had angiographic evidence of stent thrombosis, Kuchlakanti and colleagues found that the rate of premature discontinuation of clopidogrel was higher in patients who suffered stent thrombosis than in those who did not (36.8 vs. 10.7%, $p < 0.0001$).¹⁶ In the recent multicentre PREMIER registry study of premature thienopyridine discontinuation after deployment of drug-eluting stents, nearly one in seven MI patients discontinued use of the medication by 30 days post-procedure.¹⁷ During the next 11 months of follow-up, patients who had discontinued thienopyridine therapy by 30 days postprocedure were significantly more likely to experience death (7.5 vs. 0.7%, $p < 0.0001$) or rehospitalisation (23.0 vs. 14.0%, $p = 0.08$).

What to do? Given that some patients will be non-responders to clopidogrel, a glycoprotein (GP) IIb/IIIa inhibitor may be strongly considered during stenting procedures, especially in high-risk patients or those not receiving pretreatment with clopidogrel. In a series of 670 patients that examined intraprocedural stent thrombosis occurring during percutaneous coronary intervention, there were no thrombotic complications in 235 patients pretreated intravenously with GP IIb/IIIa inhibitors.¹⁸ The second ISAR-REACT study found that in patients with non-ST-segment-elevation acute coronary syndrome undergoing percutaneous intervention, abciximab reduced the risk of adverse events after pretreatment with 600 mg of clopidogrel.⁴ In a meta-analysis of trials involving patients with non-ST-elevation acute coronary syndromes, treatment with GP IIb/IIIa inhibitors in diabetic patients may also be associated with a significant reduction in 30-day mortality (6.2 vs. 4.6% reduction, $p = 0.007$).¹⁹ In a systematic overview of trials evaluating treatment with abciximab in ST-elevation MI, treatment with GP IIb/IIIa inhibition was associated with significant reductions in 30-day death and recurrent infarction.²⁰

Because premature discontinuation of clopidogrel is associated with stent thrombosis with the first generation of drug-eluting stents, the need for vigilance about patient adherence to antiplatelet therapy cannot be overemphasised. This fact highlights the importance of

knowing in detail a patient's medical history before implanting a drug-eluting stent. It is critical to determine beforehand whether a patient is a suitable candidate for prolonged dual antiplatelet therapy. Certain comorbid issues may entail a high likelihood of discontinuation of antiplatelet therapy, thereby enhancing the risk of stent thrombosis. In the PREMIER registry study, for example, relevant predictors of premature discontinuation included advanced age, lower socioeconomic status, pre-existing cardiovascular disease, and the absence of counselling about medication use at discharge.¹⁷

After implantation of a drug-eluting stent, dual antiplatelet therapy is generally prescribed for at least three to six months depending on the type of stent, and many physicians prefer to extend the regimen to 12 months (or even longer) for patients with acute coronary syndromes or severe lesion complexity (e.g. bifurcation lesions, long lesions, chronic total occlusions). The optimal term for dual antiplatelet therapy for different types of drug-eluting stents, however, remains unknown and practices have largely been determined empirically.

Insisting upon and confirming adherence to antiplatelet therapy are complicated tasks, especially because the reasons for premature discontinuation are myriad, from cost to bleeding complications to the need for minor surgery. Nevertheless, the concern about adherence to antiplatelet therapy represents a new and significant clinical reality in our stenting era, one previously less appreciated with the deployment of bare metal stents. As drug-eluting-stent thrombosis is almost uniformly associated with MI and mortality rates have ranged from 15 to 45% in recent studies,²¹ these issues inform the need for more detailed study to identify predictors of stent thrombosis and clarify the appropriate duration of antiplatelet therapy. ■

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