Thrombogenicity in patients with percutaneous coronary artery intervention and dual antiplatelet treatment

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This editorial refers to “Determinants of thrombin generation, fibrinolytic activity, and endothelial dysfunction in patients on dual antiplatelet therapy: involvement of factors other than platelet aggregability in Virchow’s triad” by Y. Yano et al., on page 1729

Antiplatelet drugs are very effective and widely used for both the initial management of acute coronary syndrome and the long-term prevention of myocardial infarction, stroke, and peripheral artery disease. Dual antiplatelet therapy with clopidogrel and aspirin is more effective than aspirin monotherapy in most patients with cardiovascular disease. In addition, in patients with percutaneous coronary artery intervention (PCI), the addition of cilostazol on top of the dual antiplatelet treatment further increases clinical efficacy, as was shown in the CREST (Cilostazol for RESTenosis) trial. Finally, in a large randomized trial in 13 608 patients who were scheduled for PCI, prasugrel, a more potent and rapidly acting thienopyridine compound than clopidogrel, was more effective in reducing death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke. So, the degree of platelet function inhibition directly relates to clinical outcome in patients with PCI.

Despite the use of more potent antiplatelet drugs, a considerable number of vascular patients have recurrent thrombotic events after PCI. It is thought that an ineffective response to these drugs contributes to the occurrence of these events, although the prevalence of aspirin resistance using aggregometry is only between 5.2 and 8%. The current literature is, however, skewed by the use of less sensitive platelet aggregation tests, such as the PFA-100, that detect aspirin resistance in 22% of the patients. Nevertheless, there are some well-designed prospective studies that suggest a relationship between the degree of thromboxane A2 inhibition in aspirin users and the occurrence of adverse cardiovascular events. Therefore, undoubtedly, there will be patients in whom aggressive antiplatelet inhibition is insufficient.

PCI can induce superficial injury to the coronary artery. This will lead to expression of tissue factor, a transmembrane protein, which will activate the coagulation cascade and generate thrombin. Thrombin is the key player of both fibrin formation and platelet activation: thrombin cleaves fibrinogen to form fibrin, but can also trigger platelet activation through protease-activated receptors (PARs) 1 and 4. This may lead to the formation of thrombi and ultimately to vascular occlusion. Importantly, tissue factor and PARs are highly expressed in human atheroma and are induced in response to injury in animal models. In vitro, PAR activation induces leukocyte chemotaxis, and smooth muscle cell proliferation and migration, which may lead to arterial remodelling and stenosis of the injured artery. In addition, coagulation factors and PARs are also involved in inflammatory responses and repair after injury. These data suggest that local arterial damage, such as that due to PCI, may trigger both platelet activation and thrombin formation. It may well be that in these circumstances, dual antiplatelet treatment, which is aimed at other targets, is unable to downregulate excessive thrombin formation and, consequently, to inhibit platelet activation sufficiently.

Yano et al. have assessed residual platelet aggregability under dual antiplatelet therapy in 85 patients undergoing PCI because of symptomatic coronary artery stenosis. Antiplatelet therapy consisted of aspirin 100 mg/day, clopidogrel 75 mg/day, ticlopidine 200 mg/day, and cilostazol 200 mg/day. All patients underwent blood sampling after normalization of cardiac enzymes, ambulatory blood pressure measurement, and monitoring of ankle–brachial index and cardiorespiratory function. Platelet aggregation was carefully measured by light scattering intensities. Furthermore, the phosphorylation of vasodilator-stimulated phosphoprotein (VASP) in platelets, a marker of platelet activation, was quantified by flow cytometry. Inhibition of platelet function was assessed...
by measuring 11-dehydrothromboxane B₂ concentration, an end product of thromboxane A₂. Both serum thromboxane B₂ level and ADP-stimulated VASP dephosphorylation were greatly reduced in all patients, suggesting a sufficient inhibition of the pharmacological targets in these PCI patients treated with dual antiplatelet agents. Interestingly, upon stimulation by different agonists, platelet aggregation showed interindividual differences that were not explained by the use of different drugs. These differences under dual antiplatelet treatment seemed to be determined by individual characteristics of platelet function.

Although coagulation factors such as D-dimer, plasminogen activator inhibitor-1 (PAI-1), and soluble fibrin were not associated with platelet aggregation, soluble fibrin was significantly associated with total cholesterol, brain natriuretic peptide (BNP), and ankle-brachial index. BNP predicted D-dimer levels, while cardiorespiratory function was correlated with PAI-1. Body mass index and diabetes mellitus were inversely correlated with E-selectin, a marker of endothelial function. Fasting glucose level determined platelet aggregates. These results suggest that (i) true antiplatelet resistance under dual antiplatelet therapy is rare in PCI patients; (ii) this treatment results in interindividual variability in platelet aggregation; and (iii) thrombin generation in PCI patients with dual treatment is determined by cardiovascular risk factors, endothelial dysfunction, or impaired cardiac function.

The results of this elegant study add to the evidence that co-morbidity of PCI patients enhances platelet activation.14 From clinical practice, patients with heart failure, hypertension, inflammatory disorders, and diabetes mellitus have a decreased efficacy of aspirin, both in vitro and in vivo. These conditions are all associated with systemic inflammation and hypercoagulability.14 Although dose escalation of antiplatelet agents gives some additional protection against vascular events, it will not prevent thrombin formation and activation of the PARs. Consequently, these patient categories may benefit from antithrombotic agents that are targeted against either thrombin generation or activation of PAR.

In the near future, in PCI patients, we may expect the introduction of new antithrombotic agents that specifically inhibit the aforementioned coagulation proteins. A phase II trial with an oral PAR1 antagonist in patients undergoing PCI has been completed (see www.clinicaltrials.gov, NCT00132912), and numerous new oral direct thrombin inhibitors and oral factor Xa inhibitors are being evaluated in patients with both venous and arterial thrombosis. It will be essential to assess whether these new anticoagulants will be more effective on top of antiplatelet drugs, and whether this efficacy outweighs the risk of major bleeding.

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**References**


