Editorial

Hyporesponsiveness to Platelet-Directed Therapy

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Myocardial infarction (MI) remains a leading cause of mortality and morbidity, while percutaneous coronary intervention (PCI) has become the most commonly performed invasive therapeutic procedure among patients with cardiovascular disease[1]. Aspirin, a non-selective cycloxegenase inhibitor, and clopidogrel, a platelet P2Y12 receptor inhibitor, are universally administered to patients undergoing a percutaneous revascularization because of their proven efficacy in reducing major adverse cardiovascular events, making them one of the most frequently prescribed drugs worldwide. Despite clear improvements in platelet-directed therapy, thrombotic events remain common, both early and late after PCI with or without a stent implantation[2,3]. The most feared thrombotic complication of PCI is stent thrombosis (ST); the incidence of ST has been reported to be between of 0.5%-2% per year. Despite being a relatively uncommon event, the overall clinical impact, owing to a high risk of myocardial infarction and death, is substantial. Mortality following stent thrombosis has been reported to be as high as 45%[4].

When early stent thrombosis occurs, the physician should suspect medication non-compliance, premature cessation of drug treatment or impaired responsiveness to platelet-directed therapy. Other factors associated with a heightened risk for stent thrombosis include: use of multiple stents, small vessel diameter, coronary dissection, geographic misplacement, slow flow, long lesions, stent malapposition, under-expansion of the stent, stent design (strut thickness and polymer type), strut fracture, and bifurcation lesions. Patients' characteristics such as diabetes, acute coronary syndromes (especially ST-elevation MI), left ventricular dysfunction, renal failure and advanced age have also been associated with increased rate of both early and late stent thrombosis[5].

If resistance to antiplatelet therapy is suspected, platelet function can be evaluated by light-transmission aggregrometry (LTA), vasodilator-stimulated phosphoprotein (VASP) phosphorylation, or one of several point-of-care (POC) devices. LTA, which is based on the stimulation of platelet-platelet aggregation in platelet-rich plasma after stimulation with various agonists, remains the historical "gold standard" test. It is quantitative test that requires careful attention to technique and reproducibility[6]. Although VASP phosphorylation has demonstrated excellent reproducibility and has the added advantage of being specific for the P2Y12 receptor-activated pathway, it is also a specialized and labor-intensive technique requiring expertise in flow cytometry.

Response variability and resistance to clopidogrel therapy were first reported in 2003[7]. Recent studies have suggested a relationship between high post-treatment platelet reactivity, clopidogrel nonresponsiviness and stent thrombosis in patients undergoing PCI. The detection of nonresponsiveness to clopidogrel has been based predominantly on LTA studies using ADP as an agonist[6]. Although several definitions of clopidogrel resistance exist, a widely-used definition is an absolute change in aggregation of $\leq$ 10% after the administration of clopidogrel[6].

Response variability to aspirin administration and its relation to adverse clinical outcomes are also topics of interest, but remain controversial in the absence of well-designed, large-scale studies. Aspirin resistance, determined by LTA using COX-1 specific measures, is infrequent among patients undergoing elective PCI who are treated with 325 mg daily[8]. There is little consistency in the measurement of aspirin responsiveness between different assays in patients receiving different doses of aspirin. Therefore, the incidence of aspirin resistance appears assay-dependent, is rare when determined by methods that directly indicate the activity of COX-1, and can be difficult to assess when treatment noncompliance is present[6,9]. Aspirin resistance might be associated with concomitant clopidogrel resistance[6,10].

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At the present time, there is no single laboratory or POC test that can be used alone to determine, with sensitivity and high predictability, drug-related response. More importantly, the available testing platforms have yet to clearly document, in a clinically-relevant manner, the relationship between platelet function, drug-resistance and clinical outcomes[11,12]. The complexity of platelet biology in ACS is seen in the numerous integrated processes that include plaque rupture or endothelial denudation, platelet adherence to von Willebrand factor and collagen, tissue factor exposure, thrombin generation, outside-in signaling following activation, and finally platelet aggregation through binding of fibrinogen and other ligands to the activated glycoprotein IIb/IIIa receptor. Thus, it is difficult for any single platelet function measurement to capture and define, in quantifiable terms, the global complexity of platelet-mediated coronary thrombosis[6].

Recently, doubling the dose of clopidogrel (300 mg load followed by 150 mg/daily in the first week following the index event) in ACS patients undergoing a PCI was shown to be associated with a significant reduction of acute stent thrombosis and cardiovascular events in analyses from the CURRENT-OASIS 7 trial presented at the European Society of Cardiology meeting in Barcelona this year. This study was not published yet; therefore, caution should be given when interpreting these results.

Ongoing studies and technology advances designed to characterize platelet response to both the disease-specific environment and drug treatment, preferably at the patient level will likely advance the level of care. Additionally, data from recently completed large clinical trials support the clinical efficacy of prasugrel and ticagrelor, both P2Y12 inhibitors with greater pharmacodynamic potency than clopidogrel, in reducing thrombotic complications during PCI[13,14]. However, the increased risk of bleeding with these newer agents further challenge the field to define thresholds for both safety and efficacy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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