

EDITORIAL COMMENT

## Clopidogrel and Endothelial Injury After Percutaneous Coronary Interventions

### Beyond the Antiplatelet Effects\*

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Dual antiplatelet therapy with clopidogrel and aspirin is the cornerstone of treatment for patients with acute coronary syndrome and those who undergo percutaneous coronary intervention (PCI) (1). Clopidogrel is a thienopyridine that selectively and irreversibly inhibits the ADP receptor P2Y<sub>12</sub>, resulting in inhibition of platelet aggregation and concomitant reduction of risk for secondary atherothrombotic events (2). Although the clinical efficacy of clopidogrel has been proven in several large randomized clinical trials (3–5), considerable interindividual heterogeneity still exists in the response to this therapy (6). In approximately 5% to 30% of clopidogrel-treated patients, the inhibition of platelet aggregation is insufficient (7,8). As a consequence, patients with high residual on-clopidogrel platelet reactivity are at a higher risk of atherothrombotic events (6,9). Clearly, achieving an optimal level of platelet inhibition in every patient is of utmost importance. Or is there more to it?

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In this issue of the *Journal*, Bonello et al. (10) deal with an interesting topic on response variability to clopidogrel as a determinant of the magnitude of endothelial injury after PCI. Endothelial injury and loss of vascular integrity, in general, is a crucial factor for the initiation and progression of atherosclerosis, as well as a key trigger for atherothrombosis. Damage to the endothelium leads to the exposure of

thrombogenic subendothelial layers and the progression of local vascular inflammation. Circulating endothelial cells (CEC) are mature endothelial cells that have detached from a vascular lesion. As such, levels of CEC in peripheral blood can serve as a biomarker of endothelial injury, which has been suggested to have diagnostic and prognostic value in patients with acute coronary syndrome and those undergoing PCI (11). In case of PCI, stent implantation inflicts (additional) mechanical injury to the endothelium and is characterized by a sharp increase in levels of CEC, which is detectable already at the end of the procedure (12,13). Preserving the endothelial integrity in the event of stent placement and thereafter seems to be of special importance.

Bonello et al. (10) evaluated the relationship between the magnitude of P2Y<sub>12</sub> receptor blockade with clopidogrel and the amount of endothelial injury after PCI with bare metal stent implantation. For this purpose, 149 patients with stable angina or silent ischemia were included. Specific P2Y<sub>12</sub> receptor blockade, induced by a 600-mg loading dose of clopidogrel, was assessed by means of a vasodilator-stimulated phosphoprotein (VASP) assay. Levels of CEC were measured immediately before and 6 h and 24 h after PCI. The investigators report that patients with a VASP index above 50% (considered having high on-treatment platelet reactivity) have a significantly higher rise in CEC levels and concomitantly higher peak levels of CEC 6 h after PCI, compared with patients with a VASP index below 50% (considered good responders to clopidogrel). Overall, VASP index correlated positively with the magnitude of rise in CEC levels after PCI. This magnitude of endothelial injury appeared to be independently predicted by the VASP group (comprised of either “good” or “bad” responders to clopidogrel), the number of diseased vessels, and the number of stents implanted. Aspirin had no effect on the CEC levels.

Clearly, the reduction of endothelial injury after PCI is not the primary mechanism of action of clopidogrel but is rather one in a row of pleiotropic effects of clopidogrel for which scientific evidence is emerging. In addition to platelet inhibition (as well as the reduction of endothelial injury reported by Bonello et al. [10]), clopidogrel has been reported to have anti-inflammatory and vasoprotective effects. In these studies, clopidogrel treatment was associated with a reduction in plasma levels of the inflammatory marker C-reactive protein (14), whereas clopidogrel treatment was associated with improved systemic endothelial nitric oxide bioavailability in patients with coronary artery disease in another study (15). Recent studies have reported that clopidogrel withdrawal (16), or impaired response to clopidogrel (17), is associated with pro-thrombotic and pro-inflammatory effects. Together, these findings suggest that indeed the underlying mechanism of suboptimal clopidogrel-induced platelet inhibition on increased risk of adverse vascular events involves not only persistent platelet activation but also a proinflammatory state and an increased

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amount of endothelial injury. However, the clinical importance of these pleiotropic effects of clopidogrel remains unclear. Unfortunately, the prospective study by Bonello et al. (10) does not include data on clinical outcome and therefore does not provide an answer to this. Moreover, biologic evidence explaining the observed associations is lacking; therefore, the question remains: does the reduction of endothelial injury relay via platelet-mediated effects (e.g., the release of cytokines from platelet granulas) or does clopidogrel somehow exert its effects on the endothelial cells directly? Given the improved efficacy of novel P2Y<sub>12</sub> receptor antagonists, such as prasugrel and ticagrelor, that are starting to replace clopidogrel use in practice, it would be interesting to investigate whether the pleiotropic effects of clopidogrel also relate to these novel compounds and whether they are characterized by large interindividual differences.

Interestingly, an increasing number of published reports on the pleiotropic effects of clopidogrel has recently started to appear. The study by Bonello et al. (10) is one of these but is novel regarding the association between clopidogrel and endothelial injury; as such, the study adds to our understanding of the complex mechanisms underlying atherothrombosis and its modulation by antiplatelet pharmacotherapy. The results of this study further suggest the importance of the efficacy of clopidogrel therapy for the prevention of atherothrombotic events and open a path to novel studies dealing with additional markers of response to antiplatelet treatment than platelet activation and aggregation alone, which have been, and are still, studied extensively.

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