Aspirin Resistance

An Underestimated Risk in Patients With Drug-Eluting Stents?*

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For many years, dual antiplatelet therapy with aspirin and a thienopyridine (ticlopidine or clopidogrel) has been the mainstay of prevention of stent thrombosis after percutaneous coronary intervention (PCI) with stent placement. In the early days, the risk reduction by dual antiplatelet therapy was so impressive that the variability of the antiplatelet effect received little attention. Nowadays, with the widespread use of drug-eluting stents (DES), there is increased need for more effective and sustained antiplatelet therapy. It has become clear that high residual platelet reactivity on clopidogrel is associated with adverse events after coronary stent placement (1–6).

Evidence linking clinical outcome to the results of ex vivo assays for aspirin resistance has been sparse. The strongest evidence derives from a nested case-control study on 970 patients of the HOPE (Heart Outcomes Prevention Evaluation) study who had baseline measurements of urinary 11-dehydrothromboxane B2 excretion, AA-stimulated expression of surface receptors, optical platelet aggregometry after stimulation with AA, and various assays measuring platelet aggregation induced by other agonists. To a variable degree the results of these assays are influenced by mechanisms other than aspirin resistance. Hence, there is only partial overlap between the various tests and, in particular, with the gold standard, direct measurement of serum thromboxane B2. Depending on assay, cut-point, clinical setting, and aspirin dosage, putatively defective pharmacodynamic action of aspirin is found in <1% to 65% of the patients (7).

Apart from direct measurement of serum thromboxane B2, various assays have been developed for ex vivo identification of aspirin resistance. These include: urinary 11-dehydrothromboxane B2 excretion, AA-stimulated expression of surface receptors, optical platelet aggregometry after stimulation with AA, and various assays measuring platelet aggregation induced by other agonists. To a variable degree the results of these assays are influenced by mechanisms other than aspirin resistance. Hence, there is only partial overlap between the various tests and, in particular, with the gold standard, direct measurement of serum thromboxane B2. Depending on assay, cut-point, clinical setting, and aspirin dosage, putatively defective pharmacodynamic action of aspirin is found in <1% to 65% of the patients (7).

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stent thrombosis were almost identical (2.3%, 2.2%, and 2.1%, respectively). On multivariable analysis, only the interaction term for aspirin and clopidogrel nonresponse, but not aspirin and clopidogrel nonresponse by themselves, showed a significant independent association with stent thrombosis. The investigators conclude that dual nonresponsiveness to aspirin and clopidogrel identifies patients at very high risk of stent thrombosis after PCI with DES.

Two questions arise:

1. What is the reason for the stunning difference in the incidence of aspirin resistance between the RECLOSE study cohort and other studies on cardiac patients?

2. Do we still need clopidogrel in patients who respond well to aspirin?

Based on recent studies on aspirin nonresponse in cardiac patients, the expected incidence of aspirin resistance is <2%, whereas it was 17.5% in the RECLOSE study. Underdosing cannot serve as an explanation because the RECLOSE study administered a high dose of aspirin (325 mg). However, there may be an issue with noncompliance, particularly in the 43% of patients with delayed testing at day 6 after administration of abciximab. An important difference from previous studies on aspirin resistance is the high proportion of patients with acute coronary syndromes in the RECLOSE study, with acute myocardial infarction in 26.0% and unstable angina in 39.9% of the current analysis of patients. Platelets are highly activated in acute coronary syndromes (16–18). Thus, it is conceivable that a high baseline platelet reactivity may have limited the ability of any drug to achieve adequately low levels of platelet reactivity (type III aspirin resistance). This interpretation is supported by the observation in the RECLOSE study that clopidogrel nonresponders were more likely to be aspirin nonresponders than clopidogrel responders and vice versa (odds ratio for dual nonresponse: 6.6 [95% confidence interval: 4.1 to 10.6]). In addition, there is the possibility that the increased platelet turnover in acute coronary syndromes may lead to the release of young platelets still able to form thromboxane A2 or to an overexpression of the aspirin-insensitive COX-2 isoform (type II aspirin resistance).

Concerning the second question, the finding in the RECLOSE study that the stent thrombosis rate in responders to a single antiplatelet agent is similar to the event rate in dual responders is puzzling. It may appear that clopidogrel nonresponse does not matter and that single treatment with aspirin may be sufficient when responsiveness is confirmed by laboratory testing. We have to realize, however, that the current analysis of the RECLOSE study cohort did not have the power to support such conclusions. The strong mechanistic interdependence of clopidogrel and aspirin nonresponse limits the ability to detect the independent contribution of each of the 2 variables. Apart from the fact that the number of patients presenting with lone nonresponsiveness to either clopidogrel (n = 45) or aspirin (n = 86) is low, we have to consider that 58 of the patients of the original RECLOSE study cohort were not included in the current analysis. This resulted in 5 events less with further reduction of power. In addition, we cannot fully exclude selection bias, because the event rate of patients not included was significantly higher than that of those included (8.6% vs. 2.7%, p = 0.01). Therefore, the current analysis does not rule out an independent contribution of high on-clopidogrel platelet reactivity to clinical outcome. Indeed, multivariable analysis even of the current RECLOSE study data set maintained a trend in this direction (adjusted hazard ratio for stent thrombosis of clopidogrel nonresponse: 2.23 [95% confidence interval: 0.85 to 5.82, p = 0.10]).

It is the merit of the current study to put aspirin resistance on the map of interventional cardiology. Gori et al. (15) remind us that nonresponse to aspirin is a neglected risk after PCI with DES, particularly when combined with clopidogrel nonresponse. Ongoing large-scale studies, such as the ADAPT-DES (Assessment of Dual Anti-Platelet Therapy with Drug-Eluting Stents) trial (19), will delineate the incidence of abnormal ex vivo platelet responses to aspirin-sensitive stimuli in various patient subsets and will reveal the clinical risks associated with such abnormalities.

**REFERENCES**


Key Words: aspirin • clopidogrel • antiplatelet drug resistance • percutaneous coronary intervention • drug-eluting stent.