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EDITORIAL COMMENT

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).

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Compared with clopidogrel resistance, aspirin resistance, so far, has received little attention in interventional cardiology. In the field of primary or secondary prevention, however, the observation of recurrent events despite aspirin treatment has raised the question early of whether these treatment failures are caused by a defective action of aspirin or by progression of disease despite an appropriate aspirin effect (7).

Aspirin inhibits the conversion of arachidonic acid (AA) into thromboxane A_2 by the platelet through selective and irreversible acetylation of a serine residue within cyclooxygenase [COX]-1 (8,9). The function of COX-1 is thereby disabled for the lifespan of the platelet. An inhibition of more than 95% of the thromboxane-forming capacity is required for the antiplatelet efficacy of aspirin (10). Three distinct types of aspirin resistance have been classified: insufficient bioavailability, including missing compliance, inadequate dosing, or protection of COX-1 against acetylation by certain nonsteroidal anti-inflammatory drugs (type I, pharmacokinetic type); pharmacodynamic ("true") resistance caused by rare genetic changes in the COX-1 protein, disabling acetylation by aspirin, or acquired, transient overexpression of less aspirin-sensitive COX isoforms (type II); and heightened stimulation of platelets by aspirin-insensitive mechanisms (type III) (11).

Apart from direct measurement of serum thromboxane B_2, various assays have been developed for ex vivo identification of aspirin resistance. These include: urinary 11-dehydrothromboxane B_2 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 B_2. 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). In an investigation of 682 patients undergoing coronary angiography, Frelinger et al. (12) found aspirin resistance in only 2%, which always could be attributed to noncompliance or underdosing. Consistently, Gurbel et al. (13) reported aspirin resistance assessed by arachidonic acid-induced optical aggregometry in 2 of 125 stable outpatients with coronary artery disease while on 81 mg aspirin, but in none at an aspirin dose of 325 mg.

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 B_2 (14). At 5-year follow-up, patients with levels in the highest quartile had an almost 2-fold increase in risk for cardiovascular death, myocardial infarction, and stroke. To our knowledge, the investigation by Gori et al. (15), published in this issue of the *Journal*, is the first to address the impact of ex vivo measures of aspirin resistance on clinical outcome after PCI with DES.

Gori et al. (15) report a secondary analysis of the previously published RECLOSE (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis) trial (5) comprising 746 of the 804 patients of the original RECLOSE study cohort. The RECLOSE study primarily showed an association between the 6-month risk of stent thrombosis after PCI with DES and clopidogrel nonresponse. The current analysis also includes aspirin nonresponse, using a generally accepted definition that is platelet aggregation by arachidonic acid (1 mM) ≥20%. Aspirin nonresponse was found in 131 (17.5%) patients, and one-third of them were also nonresponsive to clopidogrel. Within the 6-month follow-up, the incidence of stent thrombosis was significantly higher in dual nonresponders than in the other patients (11.1% vs. 2.1%, $p < 0.001$). Between lone aspirin nonresponders, lone clopidogrel nonresponders, and dual responders the incidences of

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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 A_2 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.

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