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To Have and Have Not: Intrinsic Platelet Hyperreactivity?

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Coronary artery disease is a complex and progressive disease process involving plaque and thrombus formation. The key role of thrombus formation was identified several years ago and is considered not only critical for plaque growth but also as a cause of acute coronary syndrome (ACS). Platelets are key drivers of these events.[1] They have several activation pathways, and some of them have emerged as therapeutic targets during ACS. Aspirin induces an irreversible inhibition of cyclooxygenase enzymes reducing thromboxane A2 formation and inhibiting this pathway of platelet activation. Another critical pathway for platelets is the ADP receptors and, in particular, the $P2Y_{12}$ receptor. This receptor is of crucial importance in the second phase of platelet activation and aggregation and is considered the main therapeutic target to prevent thrombus formation during ACS and percutaneous coronary interventions.[1,2] During the past decade, several investigators have demonstrated that, in patients experiencing an ACS, the outcome of percutaneous coronary interventions was dependent on the level of $P2Y_{12}$ activity undertreatment, as measured by various platelet assays. They demonstrated that patients with a high on-treatment $P2Y_{12}$-ADP receptor activity had an excess in-stent thrombosis or recurrent myocardial infarction.[3] However, the relationship between platelet reactivity (PR), in particular $P2Y_{12}$-ADP receptor activity, and outcome in other settings, including percutaneous coronary intervention for stable disease, medically managed ACS, or stable coronary artery disease and primary prevention, is not established to date.

In this issue of *Journal of the American Heart Association* (*JAHA*), Puurunen et al[4] performed an elegant substudy investigating PR in a patient cohort issued from the Framingham Heart Study. In this prospective study, the authors aimed to determine if baseline PR to multiple agonists was related to long-term ischemic events in patients naïve of antiplatelet agent and in primary prevention.[4] They include ≈2800 participants who were followed up for >2 decades. PR was assessed by light transmittance aggregometry using 3 different agonists: ADP, collagen, and epinephrine. Intrinsic hyperreactivity to low-dose ADP identified subjects at higher risk of myocardial infarction or stroke (hazard ratio, 1.69; 95% confidence interval [CI], 1.02–1.33), whereas >1 μmol/L ADP doses were not predictive. Of importance, hyperreactivity to the other agonists, epinephrine or collagen lag-time, which are other contributors to the platelet activation process, was surprisingly not associated with clinical events.

These findings further reinforce the central role of the ADP pathway in arterial thrombosis. Previous aggregation studies performed ex vivo showed that all the other platelet agonists are dependent, to some extent, on released ADP to elicit maximal platelet aggregation, although this dependence varies with the agonist and is dose related. They are also in line with experimental studies demonstrating that platelet ADP receptors play a key role in the development and extension of arterial thrombosis. The P2Y1 receptor has a limited function, mainly inducing platelet shape change and initiating platelet activation. On the other hand, the $P2Y_{12}$-ADP receptor is critical for the generation of platelet-mediated thrombus. It triggers platelet adhesion/activation, thrombus growth, and stabilization but also modulates the inflammatory response.[1,5] It also triggers a positive feedback loop in which nearby platelets are recruited in the thrombus. This ADP receptor is, therefore, considered the gatekeeper of platelet activation state. It is, therefore, to date the main therapeutic target during ACSs to prevent thrombus growth and improve the clinical outcome for patients.[1] One originality of the present results is to suggest that the activity of the ADP pathway predicts adverse cardiovascular events in healthy volunteers. It may position the activity of this pathway as a precipitating factor for these events. Consistently, intrinsic PR

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may, in the future, represent a cardiovascular biomarker alongside C-reactive protein or low-density lipoprotein to assess the long-term ischemic risk of apparently healthy subjects. If the results were to be confirmed in large cohorts with a reproducible and easy-to-use platelet assay, a perspective would be to screen and select at-risk patients before a first cardiovascular event.

The present findings may also support the potential interest of $P2Y_{12}$-ADP receptor blockers in primary prevention. In a meta-analysis of randomized controlled trials published in 2013, Sutcliffe et al[6] found that the reduction in all-cause mortality obtained with aspirin in primary prevention was questionable (relative risk, 0.94; 95% CI, 0.88–1.00; at 8 years), whereas the benefit on cardiovascular mortality was uncertain (relative risk, 0.85; 95% CI, 0.69–1.06). On the opposite, the rate of major bleedings was significantly increased with aspirin (relative risk, 1.62; 95% CI, 1.31–2.00).[6,7] More recently, the US Preventive Service Task Force proposed to tailor primary antiplatelet prevention in the general population by stratifying the patients who can most benefit from such a strategy in the long run.[8] These guidelines highlight the delicate situation of primary prevention that may cause unwanted iatrogenesis in healthy subjects. In the study by Puurunen et al, PR to epinephrine and collagen was not predictive of events, which may suggest that these pathways of platelet activation are not critical to the occurrence of cardiovascular events and, thus, question the use of aspirin in primary prevention.[4] On the other hand, the predictive value of PR to ADP suggests that this could represent an effective therapeutic target in primary prevention but also a mean to select patients who would benefit from a therapeutic intervention, thus reducing iatrogenesis. Although performed in a secondary prevention setting, the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial compared $P2Y_{12}$-ADP receptor inhibition with clopidogrel with aspirin to reduce ischemic events.[9] This study randomized >19 000 patients with peripheral arterial disease, recent myocardial infarction, or ischemic stroke to aspirin or clopidogrel. Clopidogrel was superior to aspirin to reduce the combined ischemic primary end point of myocardial infarction, ischemic stroke, or cardiovascular death: relative risk reduction, 8.7% (95% CI, 0.3%–16.5%; P=0.043). The study by Puurunen and colleagues[4] gives an insight in the potential reason underlying the benefit of clopidogrel over aspirin.

Although the results and perspectives of the study by Puurunen and colleagues[4] are promising, there are some limitations to the present work and some hurdles to overcome before they could be implemented in clinical practice. First, the sample size is relatively small given the long-term follow-up. Second, the predictive value of PR to ADP was only identified with 1 concentration of agonist. Third, studies have observed that PR did vary over time and, therefore, the optimal timing and setting for the assessment should be investigated. The investigators should be congratulated on their important work, which opens up an entire field for biomarkers and preventive therapy.

Disclosures

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