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Are Patients Getting Their Aspirin's Worth in Ischemic Stroke?

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Given its long history, established safety profile, and efficacy, low-dose aspirin remains the major antiplatelet therapy utilized in secondary prevention. Recurrent ischemic events occur despite prescription of antiplatelet therapy. Residual platelet activation following agonist stimulation can be present during treatment with antiplatelet therapy at standard doses. This phenomenon, known as high on-treatment platelet reactivity, has been linked to worse cardiovascular outcomes.[1,2] The majority of research in this field has focused on clopidogrel on-treatment reactivity in coronary artery disease, most commonly in the context of percutaneous coronary intervention.[1] Clopidogrel "resistance" has a strong mechanistic link to reduced-function polymorphisms in the cytochrome P450 CYP2C19 allele that decrease clopidogrel bioactivation, in addition to other factors.[3] In contrast, aspirin nonresponsiveness is more poorly understood in terms of pathogenesis, less clearly linked to genetic polymorphisms, and not as rigorously studied regarding its clinical implications. Nevertheless, data suggest that patients with high on-aspirin platelet reactivity (HAPR) have worse cardiovascular outcomes.[2] Similar to clopidogrel, most of this research has focused on patients with coronary artery disease, with less emphasis on ischemic stroke.[4]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Kim and colleagues expand our understanding of the association between aspirin nonresponsiveness and vascular outcomes by focusing exclusively on patients presenting with ischemic stroke.[5] More than 1400 patients who presented to their institution with ischemic stroke, mostly minor in severity, were screened for analysis. Patients were excluded if the stroke mechanism was likely cardioembolic or if new atrial fibrillation was detected, or if patients had hematologic abnormalities, bleeding diathesis, long-term nonsteroidal anti-inflammatory use, thrombocytopenia, or chronic liver or renal disease. Residual platelet reactivity was demonstrated by the ability of arachidonic acid, which in the absence of aspirin is catalyzed into thromboxane A_2 by cyclooxygenase, to activate platelets using the validated point-of-care VerifyNow platform and standard cutoffs for aspirin nonresponsiveness (≥550 IU). The final prospective enrolment included 805 patients who had aspirin reaction unit (ARU) testing performed on the fifth day of aspirin administration (termed ARU-5). Ninety-nine patients (12.3%) demonstrated HAPR at ARU-5. Patients were followed for 1 year with few being lost to follow-up. The main finding was that patients with HAPR at ARU-5 were more likely to experience the composite end point of stroke, myocardial infarction, or vascular death compared with those with normal on-aspirin platelet reactivity (18.8% versus 10.9%, respectively, P=0.048). This difference in end points was driven by higher rates of myocardial infarction in patients with HAPR at ARU-5 (4.7% versus 0.6%, P=0.001), although the absolute numbers of myocardial infarction were small, with just 8 events total. There was no significant difference in recurrent stroke (8.8% versus 6.0%, P=0.38) or vascular death (7.8% versus 5.6%, P=0.37) between patients with HAPR and normal on-aspirin platelet reactivity at ARU-5, respectively.

For 558 patients, ARU was also measured 3 hours after the initial 300 mg aspirin loading dose (termed aARU) and HAPR was detected in 78 of these patients (14.0%). There were no significant differences in the primary outcome between patients with HAPR or normal on-aspirin platelet reactivity based on aARU measurements. The study may have been underpowered to detect a difference in aARU-based outcomes. The use of serial measurements (3 hours after aspirin loading and again after 5 days of therapy) led to some interesting findings, namely, 112 patients who had discordant aARU and ARU-5 measurements. Initial aspirin nonresponsiveness in the setting of stroke may reflect acute

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inflammation or decreased absorption, but the explanation for an initially aspirin-sensitive patient converting to aspirin nonresponder is unclear and raises some concerns about the reproducibility of the assay. This discordant subgroup did not have increased risk of the primary outcome. The 21 patients with persistent HAPR at both aARU and ARU-5, however, had the highest independent risk for the composite primary outcome, with a hazard ratio of 3.11 (confidence interval 1.23–7.36) after adjustment. This difference in outcomes was driven by an increase in vascular death, not by a difference in stroke or myocardial infarction. These findings are exploratory and limited by small sample size, but raise the possibility that serial, rather than static or arbitrary, ARU measurements may identify an especially high-risk group of persistent aspirin nonresponders.

The authors acknowledge the limitations of a single-center study without end point adjudication and the inability to generalize to a larger population given the ethnic homogeneity in their study. Additionally, an inherent concern involves the use of platelet function assays that maximize ease of performance over standardization and have limited correlation with one another.[1] The authors do not provide information on how long after aspirin administration the ARU-5 was measured, as platelet cyclooxygenase activity recovers linearly 12 hours after aspirin administration.[6] Does this cohort have characteristics similar to others with HAPR? In this analysis, patients with HAPR were more likely to have lower platelet count, lower low-density lipoprotein cholesterol, and be prescribed dual-antiplatelet therapy. Lower platelet count is associated with higher mean platelet volume, more immature platelets with increased basal platelet reactivity, and worse outcomes in stroke.[7] The association of HAPR with lower low-density lipoprotein levels was only observed for ARU-5, not for aARU, and in contrast, higher low-density lipoprotein levels have been associated with HAPR in other cohorts.[8] Oxidized low-density lipoprotein and its metabolites can sensitize platelets to activate at a lower threshold.[9] Notably, diabetes mellitus was not associated with HAPR in this cohort, as has been demonstrated in other studies.[6] However, in patients with diabetes mellitus, higher body mass index is a major effector of aspirin resistance[6] and there were very few obese patients in this Korean population. A significantly larger percentage of patients with normal on-aspirin platelet reactivity were on dual-antiplatelet therapy. Combination antiplatelet therapy will lower ARU through inhibition of redundant platelet signaling pathways and may also be expected to reduce vascular events in high-risk patients presenting with ischemic stroke.[10,11] The authors do not state whether combination antiplatelet therapy was linked with a decreased risk of vascular events or, as might be expected, increased bleeding. To that end, it would have been helpful for the investigators to report on bleeding outcomes, as one wonders whether aspirin nonresponsiveness is associated with a decreased risk of bleeding events.

The term aspirin "resistance" is vague and is more accurately represented as the interpatient variability in response to aspirin. The definition of aspirin responsiveness depends on the method of assessment and the outcome of interest. In strictest terms, aspirin nonresponsiveness as determined by the levels of thromboxane metabolites in the serum of patients treated with aspirin may be rather rare.[12] However, as defined by the ability of arachidonic acid to stimulate platelet activation in the presence of aspirin, much more heterogeneity is observed.[12] While platelet activation is the biological end point directly related to the pathophysiology of atherothrombosis, HAPR may reflect higher baseline platelet sensitivity or cyclooxygenase-independent pathways of platelet activation rather than simply the inability of aspirin to inhibit its pharmacologic target. Despite these caveats, aspirin nonresponsiveness as defined by HAPR has been linked with several factors (Figure).[13] Several inflammatory and high-catecholamine states including acute coronary syndrome, heart failure, postsurgery, smoking, and obesity are associated with higher degrees of baseline platelet activation. Diabetes mellitus, particularly hyperglycemia, results in increased platelet turnover and aspirin nonresponsiveness via a higher rate of new platelet generation in between aspirin doses. Nonsteroidal anti-inflammatory drugs also inhibit cyclooxygenase and prevent aspirin binding to the cyclooxygenase active site during aspirin's short biological half-life of approximately 15 to 20 minutes. Polymorphisms of platelet membrane glycoproteins and cyclooxygenase have also been associated with a diminished response to aspirin.

The association of aspirin and clopidogrel nonresponsiveness and recurrent cardiovascular events has naturally led to studies of antiplatelet therapy intensification in patients with high on-treatment reactivity. Unfortunately, this strategy has not produced encouraging results. In a cohort of patients presenting with transient ischemic attack and stroke, antiplatelet therapy was intensified in 23% of the patients with aspirin or clopidogrel nonresponsiveness. This was accomplished by either increasing aspirin or clopidogrel dosing, switching antiplatelet medications, or by addition of a second antiplatelet medication. Compared with no adjustment in antiplatelet therapy, intensification of antiplatelet therapy was associated with an increase in the combined end point of death, bleeding, and ischemic events.[14] Similar strategies of aspirin or clopidogrel intensification in response to high on-treatment reactivity have not resulted in a reduction of ischemic events in patients receiving percutaneous coronary intervention.[15] Compared with those with coronary artery disease, patients who have had a stroke are at higher risk for bleeding during more intensive antiplatelet therapy, including but not limited to intracranial bleeding.[16,17]

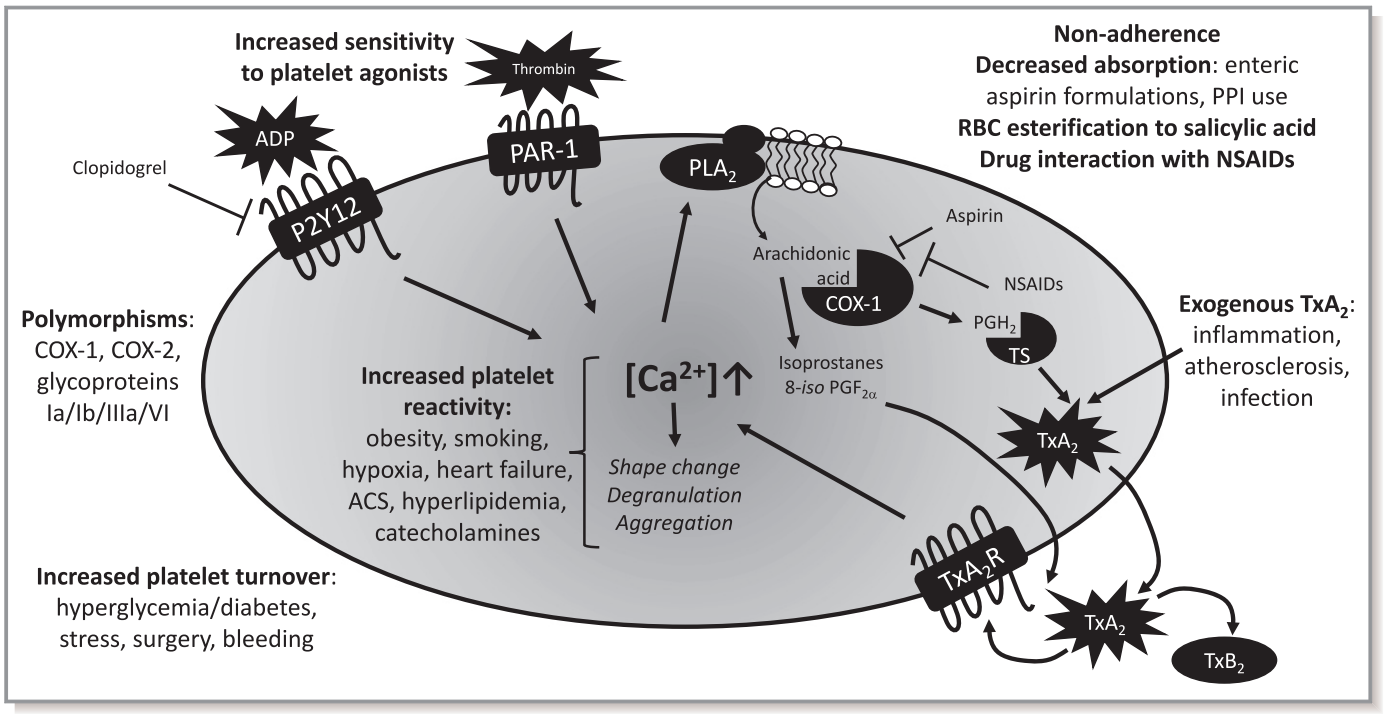

Figure. Potential mechanisms of aspirin nonresponsiveness include clinical factors such as patient nonadherence and decreased drug absorption, genetic polymorphisms, increased platelet turnover, increased platelet reactivity or sensitivity to other agonists, and exogenous thromboxane A_2 from activated leukocytes or endothelium. Isoprostanes are prostaglandin F_2-like compounds produced via COX-independent free-radical oxidation of arachidonic acid, and specifically, 8-*iso*-prostaglandin $F_{2\alpha}$ has been implicated in enhancing platelet activation. ACS indicates acute coronary syndrome; ADP, adenosine diphosphate; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory; PAR, protease activated receptor; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGH_2, prostaglandin H_2; PLA_2, phospholipase A_2; PPI, proton pump inhibitor; TS, thromboxane synthase; TxA_2, thromboxane A_2; TxA_2R, thromboxane A_2 receptor; TxB_2, thromboxane B_2 metabolite measured in urine or serum.

Because of this risk, any prospective trial studying an intensification of antiplatelet therapy in stroke should be performed in a cohort of only patients who have had a stroke, instead of generalizing from studies in other types of atherosclerotic disease.

Rather than simply being a measure of aspirin responsiveness, HAPR perhaps more accurately represents a marker of increased residual risk—be that inflammatory, metabolic, or thrombotic. The implications are that high on-treatment platelet reactivity may be better addressed through aggressive treatment of underlying risk factors such as diabetes mellitus, hyperlipidemia, smoking, or obesity, to name a few. To this end, the current study would have benefitted from analysis of nonvascular death, as one would not expect this to be associated with aspirin resistance. However, if an association does exist, it could suggest that aspirin nonresponsiveness is truly just detecting a sicker population of patients and is less likely to be modified by intensification of antiplatelet therapy.

The goal of aspirin therapy is prevention of atherothrombosis. Treatment failure can be linked to a diverse set of factors, the most important of which may be nonadherence to therapy. Recurrent vascular events in patients adherent to aspirin therapy, but not receiving adequate pharmacologic platelet inhibition, only accounts for a fraction of the residual risk. Most of these events occur despite adequate platelet inhibition. Repeat ischemic events represent a challenging scenario for physicians and a trying setback for patients. To truly provide precision medicine, we require both refined diagnostics and targeted therapeutics. This interesting work from Kim et al enhances our understanding of how platelet function testing might further risk stratify the heterogeneous population of ischemic stroke survivors. The next challenge is how to translate this information into an improved therapeutic approach to decrease recurrent ischemic events.

Disclosures

Dr Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials*

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