Will the epidemic of metabolic syndrome raise the prevalence of antiplatelet drug resistance?

Aspirin, mentioned in a medical Egyptian papyrus dating to 1534 BC, and the subject of the first recorded medical trial, circa 1763, has since enjoyed a remarkable career in relieving pain, inflammation, fever, and more recently, in the treatment of cardiovascular disease (CVD).[1] Subsequently, low-dose aspirin was found to irreversibly inhibit the platelet-dependent enzyme cyclooxygenase (COX)-1, acetylating a hydroxyl group on Ser530 of COX-1, thereby blocking access to arachidonic acid, resulting in reduced levels of thromboxane A2 (TXA2), a potent promoter of platelet aggregation.[2] These antithrombotic effects were effective and useful in acute occlusive stroke, secondary prevention of stroke, and primary and secondary prevention of coronary heart disease (CHD), particularly in patients with acute coronary syndrome (ACS). Approval by the Food and Drug Administration (FDA) followed, and additional studies lent further credence to the aforementioned clinical applications.[3,4] Use of aspirin in primary prevention, however, remains controversial since an uncertain reduction in thrombotic events must be weighed against major hemorrhage, the chief feared side effect of antiplatelet therapy.[4,5]

During the 2000s, aspirin "resistance" – actually interindividual variability – gained traction, manifested by failure of aspirin to prevent thrombosis, raise the bleeding time, lower production of TXA2, and/or reduce platelet activity or aggregation. Estimates of aspirin resistance vary, there is no rigorous definition, and no gold standard exists for diagnosis. A number of mechanisms have been proposed, and several biochemical, functional, and genetic tests measuring individual drug response are available for diagnosis and subsequent choice of treatment. The essential concept is that confirmed aspirin resistance or unresponsiveness, recently referred to as high on treatment platelet reactivity, is associated with a higher risk of (further) episodes of myocardial ischemia, recurrent adverse events, and cardiovascular death. Under these circumstances, determining unifying principles that characterize patients with stable, constant phenotypes of true pharmacological resistance to aspirin (and other antiplatelet agents), such as genetic causes, rather than pseudoresistance, perhaps "caused" by poor adherence or the enteric coating of aspirin, could clarify the approach to this vexing issue.

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As compared with aspirin, the availability of the family of platelet adenosine diphosphate receptor (P2Y12) inhibitors; clopidogrel (an irreversible P2Y12 blocker, a commonly-used prodrug with high individual variability), prasugrel (quicker conversion to its active metabolite, higher incidence of bleeding), ticagrelor (a nonthienopyridine, reversible, rapidly-acting P2Y12 inhibitor), and cangrelor (an intravenous, direct, reversible, extremely rapidly acting thienopyridine P2Y12 antagonist) offered greater potency and faster onsets of action.[6-8] Aspirin, in part by raising nitric oxide availability, and ticagrelor, by inhibiting P2Y12 induced vasoconstriction and suppressing inflammation and restenosis, tend to have more pleiotropic effects. The P2Y12 receptor is of immense importance in the ADP-stimulated activation of glycoprotein IIb/IIIa (gpIIb/IIIa), an integrin complex on platelets which is an avid fibrinogen receptor. During thrombosis, exposure of subendothelial collagen to platelet receptors results in the release of platelet agonists TXA2 and ADP, which activate gpIIb/IIIa. The interaction of ADP with the platelet P2Y12 receptor is necessary for platelet actuation, and by blocking the P2Y12 pathway, thienopyridines, and ticagrelor prevent the ensuing conformational change in platelet gpIIb/IIIa receptors that induces binding to fibrin.

Interfering with platelet activation, degranulation, and aggregation through different, complementary methods, so-called "dual oral antiplatelet therapy", has become the guidelines-recommended treatment for patients with ACS and following PCI with stent placement. Most often aspirin with a drug which blocks P2Y12 for up to a year is used, although the optimal duration remains unknown. Finally, each of the antiplatelet agents has individual properties not mentioned above, which differ among clinical subpopulations.

In the pages of this journal, a paper compares the prevalence and associations of antiplatelet drug resistance in 47 patients with metabolic syndrome (MetS) and ACS, as part of a total cohort of 94 patients with ACS.[9] The authors measured

resistance to aspirin and clopidogrel then correlated the findings with clinical data and plasma levels of glucose, lipids (including apolipoprotein B), fibrinogen, and C-reactive protein (CRP). There were 28 cases of antiplatelet drug resistance in the group with ACS and MetS, compared to 12 instances of resistance in the group with ACS without MetS. Not surprisingly, patients with MetS had higher CRP and fibrinogen levels, which correlated with antiplatelet drug resistance.

Although this is a case control study in a modest number of patients without follow-up, the report evokes considerable thought, since (i) not only is resistance to antiplatelet agents of clinical concern, but (ii) the increasing number of patients with MetS is an enormous global public health challenge.

Patients with MetS constitute a spectrum of proinflammatory, prothrombotic, and prooxidative phenotypes with raised CV risk. Each element connects with others forming a complex web of interrelated genetic, metabolic, immunologic, and vascular processes with rich crosstalk. Presence or greater severity of hypertension, visceral obesity, low high density lipoprotein cholesterol and/or high triglyceride values, insulin resistance, kidney disease, elevated CRP levels, and endothelial dysfunction amplify cardiometabolic risk in most instances. Obesity,[10] hypertension,[11] diabetes,[12] dyslipidemia, high CRP levels,[13] and other individual risk factors/biomarkers are connected with antiplatelet drug resistance. These data suggest that, although such resistance frequently occurs in patients without MetS, additional features that intensify the thrombotic, inflammatory, and hyperglycemic burdens, particularly those that thwart availability of nitric oxide through potent prooxidative mechanisms, may increase the likelihood of antiplatelet drug resistance.

One must also recall that apart from being effector cells in hemostasis, platelets are heavily involved in signaling pathways modulating transcriptional regulation, innate and adaptive immunity, endothelial adhesion, and the atherothrombotic process.[14]

All told, the results of larger, randomized studies delineating the etiologies of antiplatelet drug resistance, and their associations with individual components of cardiovascular risk, will undoubtedly contribute significantly to improve future patient outcomes.

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