Aspirin resistance: more emphasis on definition and appropriate use of platelet function tests is needed

Commentary on

The influence of aspirin resistance on non-fatal coronary events following percutaneous coronary interventions

Alp B. Catakoglu[1], Saide Aytekin[1], Huseyin Celebi[2], Murat Sener[1], Hilal Kurtoglu[1], Cemsid Demiroglu[2], Vedat Aytekin[1]

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Armen Y. Gasparyan

Dudley Group of Hospitals NHS Trust, Dudley, West Midlands, United Kingdom

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Corresponding author:
Assoc. Prof. Armen Yuri Gasparyan, MD, PhD
Dudley Group of Hospitals NHS Trust
Dudley, West Midlands DY1 2HQ
United Kingdom
Phone: +44-1384-244842
Fax: +44-1384-244808
E-mail:
armen.gasparyan@dgoh.nhs.uk
a.gasparyan@gmail.com

Despite the availability of a variety of new potent drugs inhibiting platelet function [1, 2], aspirin still remains the most widely used anti-platelet agent worldwide, and it comes to prove that 'old drugs work well'. Although anti-inflammatory and anti-pyretic potential of the decoction of willow bark, a source of salicylic acid, was recognized millennia ago, and it was used for treatment of arthritis and other inflammatory disorders, the chemical structure of salicylic acid and its anti-platelet mechanism of action were clarified only in the past century. Aspirin is now regarded as an anti-aging agent [3], which, first and foremost, underlines its protective role against cardiovascular disease.

Irreversible acetylation of cycloxygenase-1 (COX-1) and disruption of the arachidonic acid cascade with subsequent disruption of thromboxane A_2 (TxA_2) synthesis in platelets constitute the basis of cardiovascular protection with aspirin. Relatively well-tolerated, safe at low doses and inexpensive, aspirin has become a cornerstone of primary and, especially, secondary cardiovascular prevention [4-6].

A meta-analysis of 287 randomized anti-platelet trials with a total of 135,000 patients at high vascular risk proved that aspirin alone (75-150 mg daily) or in combination with other anti-platelet agents (clopidogrel, ticlopidine, dipyridamole) substantially reduces the incidence of non-fatal myocardial infarction (MI) and stroke [7]. The impact of this study on the strategy of cardiovascular prevention in patients after MI or stroke, or in those with diabetes or other high risk conditions, is hardly possible to overestimate. However, the rapidly growing pharmaceutical industry and expanding market of anti-platelet agents have forced researchers to revisit this strategy and to explore opportunities of further reduction of cardiovascular risk. As a result, the concept of so-called aspirin resistance has emerged and multiple attempts have been made to define it. A multitude of possible mechanisms of failure of aspirin to inhibit hyperactive platelets, to block the release of TxA_2 and other platelet-derived inflammatory and prothrombotic agents has been thoroughly studied

within the framework of laboratory and biological (clinical) aspirin resistance. The fact that most patients treated with aspirin may still be at risk or may actually experience adverse vascular events was referred to as being a consequence of 'clinical aspirin resistance' or 'aspirin treatment failure' [5].

A recent meta-analysis of 11 prospective studies with a total of 1952 cardiovascular patients treated with aspirin and followed for 4 years demonstrated significantly increased risk of cardiovascular events in those with baseline hyperactivity of platelets (relative risk [RR] 3.11, 95% CI 1.88-5.15, $p < 0.0001$) [8].

Improved understanding of aspirin resistance has become possible with the advent and widespread use of modern platelet function tests, measuring diverse parameters of platelet activation. Differences in principles, laboratory standardization and reproducibility of these tests have disclosed complexity of the phenomenon and uncertainties with estimation of its prevalence. In fact, with the use of optical aggregometry, which is a gold standard of platelet function assessment, it was estimated that the prevalence of laboratory aspirin resistance in cardiovascular disease is 6%, whereas relatively new point-of-care platelet function tests, particularly Platelet Function Analyzer™ -100 (PFA-100), revealed much higher prevalence (26%) [9].

The message of most studies on aspirin resistance is, seemingly, straightforward - to switch from aspirin therapy to dual (aspirin plus clopidogrel) [10] or even triple anti-platelet therapy (aspirin plus clopidogrel or ticlopidine plus cilostazol) [11]. While this approach seems to be efficient in some patients [12], in others it can lead to dual or triple anti-platelet resistance [13], and in a worse case scenario it can be complicated with major bleeding. Importantly, those who fail to respond to anti-platelet drugs (e.g. patients undergoing coronary angioplasty, those with diabetes, heart failure, inflammatory disorders) are also prone to major bleeding and other life-threatening complications, and that should be carefully weighed before implementing the strategy of aggressive multi-drug therapy [14, 15].

Taken together, lessons learned from numerous previous studies on aspirin resistance indirectly point out the following. First of all, aspirin with its unique mechanism of action secured its deserved place in cardiovascular protection of patients at high risk of vascular atherothrombotic events, and its replacement with thienopyridines, such as clopidogrel, is not justified, unless there are absolute contraindications (previous history of idiosyncratic or allergic reactions to salicylates). Platelets have numerous targets for a variety of anti-platelets, and aspirin acts on only one, but obviously crucial target, arachidonic acid cascade and TxA_2 synthesis. Also, aspirin possesses pleiotropic anti-atherosclerotic effects linked to inflammation, oxidative stress, nitric oxide synthesis and lipid profile [16], which are important assets for primary and secondary cardiovascular prevention, and these should be taken into account when 'aspirin resistance' is concerned.

In this issue of the Journal, Catakoglu *et al*. [17] present the results of their study on aspirin resistance in patients undergoing percutaneous coronary interventions with stenting. Aspirin resistance was defined by PFA-100™, as a closure time of collagen/epinephrine cartridge of less than 186 s, despite aspirin therapy.

Of note, PFA-100 is designed to imitate a capillary vessel, through which the whole blood passes under a high shear stress and is exposed to platelet activating agents (in this case, collagen and epinephrine of the cartridge membrane, which activates the arachidonic acid cascade). A resultant plug formation closes the aperture of the vessel over a certain period of time, which is a surrogate measure of platelet function. Sufficient suppression of the arachidonic acid cascade with aspirin delays thrombocoagulation and closure in the capillary vessel of the analyzer, whereas its failure results in shortening of the closure time.

The authors of the index study found that aspirin resistant patients had higher incidence of vascular events over a 2-year period, compared to aspirin responders (22.4 vs. 5.9%, $p = 0.021$), and a conclusion was drawn, distinguishing aspirin resistance as an independent risk factor of non-fatal coronary events. These results are in line with the data of numerous previous similar studies, and, unavoidably, there are shortcomings characteristic for most of them. First of all, PFA-100™ was designed to imitate the vascular system under shear stress. The latter underscores the need for measuring markers related to shear stress (i.e. von Willebrand factor) [18]. Besides, aspirin resistance is not a static phenomenon and, to better understand its implications, repetitive measurements are more appropriate. As far as efficiency of aspirin (aspirin resistance) over a long period of time (2 years in the index study) is concerned, one should also take into account non-compliance to this drug, which can cause inadequate suppression of the arachidonic acid cascade in about one third of patients with chronic coronary artery disease and can mask 'true aspirin resistance' [19]. Finally, coronary intervention itself is a low-grade inflammatory condition, where an increased platelet turnout and sustained hyperactivity are subjected to the effects of multiple prothrombotic and inflammatory agents, and, from this standpoint, measurement of activity of only one pathway (arachidonic acid cascade in this case) is not sufficient.

Obviously, the current study indicates the need for long-term and properly designed studies to explain the multifaceted nature of aspirin resistance and to ascertain its implications in different clinical conditions, including those largely influenced by low-grade inflammation. It once again highlights the complexity of factors affecting platelet function and the lack of a universally accepted definition of this phenomenon, despite an avalanche of studies on aspirin resistance over the past decade.

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