Genetic testing in antiplatelet therapy – not effective for perioperative bleeding

Wiktor Kuliczkowski

Department of Cardiology, Wroclaw Medical University, Wroclaw, Poland

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Nowadays the populations of the developed countries are becoming older, with an obvious increase in the incidence of cardiovascular diseases. This implies a higher risk for complications of invasive treatment and of prolonged antiplatelet therapy in older patients. Additionally, in the era of prasugrel and ticagrelor, the problem of stent thrombosis and recurrent target-vessel ischemic events has declined and is replaced by bleeding complications. If we give strong antiplatelets, we should be aware of their strength, trying to minimize the risk of long-term bleeding. However, we should also be mindful of the risk of periprocedural bleeding, which can be related to technique, medications or possibly genetic factors.

Sianova *et al.* [1] decided to perform a genetic analysis of single nucleotide polymorphisms (SNPs) of crucial hemostatic platelet receptors (GPIa, GPVI, P2Y12) and correlate their presence with the risk of periprocedural bleeding complications related to coronary angiography or percutaneous coronary intervention (PCI). From a presumably large database of several centers, they selected 73 patients who developed some sort of bleeding events during 30 days after the procedure, unfortunately excluding patients with the most severe types of bleeding (intracranial or fatal bleeding) because "it was impossible to obtain an informed consent for genetic testing from those critically ill patients". Controls consisted of 331 patients without bleeding. They found no significant association of the SNPs of GPIa 807C/T, GPVI 13254T/C, P2Y12 32C/T, P2Y12 H1/H2 haplotype with increased risk of periprocedural bleeding in patients with ischemic heart disease undergoing coronary angiography or PCI. There was only a trend for higher (according to authors) bleeding risk in the homozygous form of P2Y12 H2 haplotype patients. The most common perioperative bleeding event included was access site hematoma (82.2%), with others below 5%. This is what one could expect, as access site hematoma is most frequent and can even influence outcomes in acute coronary syndrome [2]. It can be due to femoral access, but exact data are missing in the paper, although it is mentioned that in "most participating centers the radial access is preferred". Instead of genetic factors, the authors found that bleeding was linked with older age, lower body mass index, more frequent arterial hypertension, renal insufficiency, history of previous bleeding, a higher level of leucocytes, lower admission hemoglobin and hematocrit levels and higher international normalized ratio (INR). Additionally, acute coronary syndrome and PCI was associated with more bleeding. So the problem depends on the clinical picture of the patient more than the platelet membrane receptor genetic profile. What is more, it seems that at the time of radial access for coronary intervention the more potent blockade by newer antiplatelet drugs does not influence the frequency of local hematoma occurrence [3].

The problem with genetic studies is most frequently the number of individuals included, which should be sufficiently high to obtain meaningful results. Once we obtain a significant correlation between a given SNP and a clinical outcome in the whole group, the question arises as to how it applies to the individual patient. Should we change the treatment or the technique in the given patient to achieve/avoid a clinical outcome? When it comes to bleeding, including perioperative, we know one allele – CYP2C19*17 – that is associated with a higher risk of bleeding [4]. It does not influence the structure of platelet receptors but causes more efficient liver metabolism of clopidogrel into an active drug. We are fairly certain about the effect of the CYP2C19*17 allele, but we do not know what to do, if anything, with a patient possessing it. We still lack the prospective randomized data, and in the era of ticagrelor, which is not influenced by this mutation [5], it is rather unrealistic to obtain such information.

Corresponding author:
Wiktor Kuliczkowski MD, PhD, Department of Cardiology, Wroclaw Medical University, 213 Borowska St, 50-556 Wroclaw, Poland, phone: +48 71 7364200, fax: +48 71 7364209, e-mail: wkuliczkowski@wp.pl
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Looking into the results of the discussed study, we can ask one more question. Are platelets really the most important cause of bleeding events listed in Table II? In my opinion, they may account for gastrointestinal bleeding (in 1 patient), urinary tract bleeding (in 1 patient), epistaxis (in 2 patients) or other (in 5 patients). If we investigate the link between platelets and bleeding, these events should be of our interest, but as we see, they are very few, and it would be challenging to obtain meaningful results.

So what would be the future of genetic testing in predicting bleeding events in invasively treated patients? It is rather futile to look for genes influencing ticagrelor metabolism, as it is not a prodrug. Another direction would be to look, like the authors, for the genetic difference in a wide range of platelet receptors, but together with their influence on the response to the current antiplatelet regimens [6]. Although this approach has shown mixed results so far [7], knowing such an influence would prompt investigation into antiplatelet treatment changes in those with a given mutation.

Conflict of interest

The author declares no conflict of interest.

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