CYP2C19 loss-of-function alleles: A common but overlooked problem associated with clopidogrel resistance

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Antiplatelet agents are important in the prevention of cardiovascular diseases. However, unlike antihypertensive or antidiabetic drugs, the effect of antiplatelet cannot be easily and quickly assessed. A certain population has high on-treatment platelet reactivity (HTPR), namely antiplatelet resistance. The loss-of-function single nucleotide polymorphism of cytochrome P450 family 2 subfamily C member 19 enzyme (CYP2C19) is a known cause of HTPR when using clopidogrel. Clopidogrel is a commonly prescribed antiplatelet second to aspirin, and is often prescribed with aspirin as dual antiplatelet therapy (DAPT). Therefore, the "clopidogrel resistance" caused by CYP2C19 loss-of-function alleles is an important issue, which may be detrimental to those under the prevention of cardiovascular diseases.

The two CYP2C19 loss-of function alleles, CYP2C19*2 (681G>A) and CYP2C19*3 (636G>A), are more common in East Asian than in Western population. However, the prevalence data in Taiwanese are still lacking. Dr. Lee's study published in the current issue of *the Journal of the Chinese Medical Association* reported the prevalence of CYP2C19*2 and CYP2C19*3 in 868 patients with stroke and 557 nonstroke controls, which is the largest study of CYP2C19 loss-of function alleles in Taiwan up to now.[1] In this study, more than half (51%-58%) patients and controls were CYP2C19*2 carriers, and about 10% patients and controls were CYP2C19*3 carriers. Moreover, 13% to 14% patients and controls had at least 2 CYP2C19 loss-of-function alleles (poor metabolizers), which was substantially higher than the prevalence of 26% single CYP2C19 loss-of-function allele carrier and 2% poor metabolizers in Western population.[2] It was found that the prevalence of CYP2C19*2 was not different between patients and controls, and was not different between different stroke etiologies, so the genetic polymorphism itself did not influence the risk of stroke.[1]

It was found that the carriers of CYP2C19 loss-of-function alleles had higher risks of coronary stent thrombosis and ischemic stroke when they were treated with clopidogrel.[3–5] In the trial of DAPT with clopidogrel and aspirin in Chinese patients with minor stroke or transient ischemic attack, the DAPT was superior to aspirin alone in reducing the recurrent stroke only in patients without CYP2C19 loss-of-function alleles.[6] In Taiwan, the efficacy of stroke prevention was equal between aspirin and clopidogrel users, whereas the mortality rate was higher in clopidogrel than in aspirin users,[7] which might be due to the high prevalence of CYP2C19 loss-of-function alleles.[1]

According to the aforementioned findings, about half of the East Asian people have clopidogrel resistance when it comes to stroke prevention. Since the cost of clopidogrel is much higher than most of the other cardiovascular drugs, and clopidogrel resistance might lead to severe cardiovascular events, it is better to confirm the patient's responsiveness when clopidogrel treatment is considered. Rapid genotyping techniques are available nowadays,[8] and many platelet reactivity assays are also available for HTPR detection.[9] However, it is still unclear whether the genotypes or the platelet reactivity would be better in the prediction of clinical outcomes when using clopidogrel. Clinical trials of CYP2C19 genotype-guided antiplatelet therapy in coronary artery disease are ongoing, and study participants assigned to genotype-guided therapy will use ticagrelor or prasugrel instead of clopidogrel if they are carriers of CYP2C19 loss-of-function alleles.[10,11] If successful, genotype-guided treatment will provide a good example of precision medicine.

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