Clopidogrel pharmacogenetics of east, south and other Asian populations

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The pharmacogenetics of clopidogrel metabolism show striking interethnic diversity. Apart from clear differences between white and Asian populations, unique differences in the genetic control of clopidogrel bioactivation exist between major Asian ethnicities. More studies are clearly needed to help us understand the clinical impact of these genetic differences and their environmental interaction in ethnically and genetically diverse Asia.

Clopidogrel, a platelet $P2Y_{12}$ receptor inhibitor, is universally administered to patients with acute myocardial infarction and to patients undergoing percutaneous coronary intervention (PCI) because of its proven efficacy in reducing major adverse cardiovascular events in these populations. Although newer $P2Y_{12}$ inhibitors are now commercially available, clopidogrel, driven by extensive clinical data and the recent availability of generic clopidogrel, is likely to remain the dominant compound in clinical use.

There is wide variability in the level of platelet inhibition with clopidogrel, which is attributable in part to differential bioactivation of the parent compound by the hepatic p450 enzyme system.

Carriers of loss-of-function (LOF) polymorphisms of CYP2C19, namely the *2 and *3 LOF alleles, produce lower levels of the active metabolite of clopidogrel compared with non-carriers, resulting in a decreased antiplatelet effect, and therefore carry an increased risk of major adverse cardiac events after stent implantation.

East Asian populations have a known higher prevalence of CYP2C19 LOF polymorphisms compared with white populations. In a South Korean cohort of 2146 patients who received drug-eluting stents, 47% of the patients carried at least one CYP2C19*2 allele. We showed a similar high prevalence of the CYP2C19*2 allele in a Chinese–Singaporean population as have other groups studying Japanese and Han Chinese populations. We have also shown that Malay–Singaporean subjects, who are Asians of Austronesian descent, and Indian–Singaporean subjects, who are of South Asian descent, have an increased prevalence of the *2 LOF polymorphism when compared with Caucasian subjects. The homozygous *2 genotype, which is associated with the highest level of on-treatment platelet reactivity and is present in 2–3% of the Caucasians, was present in 6% of the Chinese, 9% of the Malays, and 13% of the Indians in our study. The prevalence of *2 polymorphisms among the Indian subjects in our study was higher than that observed in Caucasian populations but similar to other studies on Indian subjects from the Indian subcontinent.

While the CYP2C19*2 polymorphism is found in both white and Asian populations, the CYP2C19*3 polymorphism is found almost exclusively in Asian populations. The *3 polymorphism increased on-treatment platelet reactivity to a similar magnitude as the CYP2C19*2 polymorphism in a South Korean population of 140 subjects treated with 3–5 days of clopidogrel. Man et al. showed that the prevalence of CYP2C19*3 carriers were 24.2% among Japanese, 14.8% among Koreans, and 8.9% among Han Chinese, but only 0.4% among Africans and 0.2% among Caucasians. In our Singaporean population, the *3 allele was present in 10% of the Chinese–Singaporean subjects and 9% of the Malay–Singaporean subjects, compared with only 1% of the Indian–Singaporean subjects.

However, despite the increased prevalence of both the *2 and *3 LOF alleles among East Asians, thrombotic
events after PCI are not higher than in Caucasian populations. Part of reason for this may be that CYP2C19 accounts for less than 15% of the variability in response to clopidogrel and that other environmental factors further modify the response to clopidogrel. Questions in interethnic variability may be best answered by a large study in which patients from multiple ethnic origins are both genotyped and phenotyped (platelet function testing) for clopidogrel response. The recently completed TRILOGY-ACS study will have both genotyping and phenotyping data in a large multinational, multiethnic population (n = 2400) for such comparative studies to connect the dots between genotype, phenotype, and clinical outcomes.

Carriers of a gain-of-function (GOF) polymorphism, the *17 allele, produce higher levels of the active thiol metabolite compared with non-carriers, resulting in a greater antiplatelet effect and an increased risk of bleeding. We have found an increased prevalence of the *17 allele among subjects of South Asian descent (28%) in comparison with subjects of East Asian (2%) and Austro-Nesian descent (5%). More studies are clearly needed to help us understand the clinical impact of interaction between LOF and GOF polymorphisms and the interaction between these genotypes and environmental factors in ethnically and genetically diverse Asia.

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References