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CYTOCHROME P450 2C19 POLYMORPHISM AND PLATELET AGGREGATION IN CLOPIDOGREL-TREATED PATIENTS AMONG MALAYSIAN MULTIETHNIC POPULATION

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Objectives Cytochrome P450 2C19 (CYP2C19) *2 (681G>A; rs4244285) and CYP2C19*3 (636G>A; rs4986893) null alleles are responsible for the phenotypes of poor CYP2C19 enzyme function, hence adversely affecting the ability of clopidogrel to inhibit platelet aggregation. In recent years, a novel CYP2C19 gene variant, CYP2C19*17 (–3402C>T; rs11188072), has been identified and is associated with ultrarapid metabolism of CYP2C19 substrate. To date, there is limited data on CYP2C19 prevalence rates in a multiracial Malaysian population with coronary artery disease planned for percutaneous coronary intervention (PCI), and their impact on clopidogrel-mediated platelet aggregation (CPA). Therefore, the primary objective of this study was to assess the impact of CYP2C19 *2, *3 and *17 on CPA in patients planned for PCI.

Methods From the 323 consecutive patients planned for PCI, 237 patients≥18 years of age, underwent either aspirin alone or both aspirin and clopidogrel therapy, were recruited from Sarawak General Hospital Heart Centre (Kota Samarahan, Malaysia). Venous blood samples were collected from each participant before their scheduled appointment for PCI. The CYP2C19*2, *3 and *17 were genotyped by PCR—restriction fragment linked polymorphism (PCR-RFLP) method. The antiplatelet effect of clopidogrel, as assessed by ADP-induced platelet aggregation, was measured by Multiplate impedance aggregometry.

Results Of the 237 subjects (mean age 57.6±11.1), 77.6% were male and 22.4% were female. Ethnic group distribution was: Chinese 50.6% (n=120), Malay 21.1% (n=50), Iban 19.0% (n=45) and other races 9.3% (n=22) The allelic frequency of the CYP2C19 *1, *2, *3 and *17 were 63.0% (95% CI 62.1% to 59.0%), 29.0% (95% CI 28.7% to 29.3%), 6.0% (95% CI 5.9% to 6.1%) and 2% (95% CI 1.6% to 2.4%), respectively. Genotype determination revealed that 38.8% were extensive metabolisers (EM: *1/*1, *2/*17), 45.1% intermediate metabolisers (IM: *1/*2, *1/*3), 12.7% poor metabolisers (PM: *2/*2, *2/*3, *3/*3), 3.0% intermediate ultrarapid metaboliser (IUM: *1/*17) and 0.4% ultrarapid metaboliser (UM: *17/*17). The frequencies of the CYP2C19*2 variant allele and of the homozygous genotype were higher in Chinese descent individuals (35.8%; 12.5%) compared with other ethnic groups (p=0.010; p=0.022, respectively). Meanwhile, a similar proportion of CYP2C19*3 allele was observed in all ethnic groups (p=0.071). Overall, the PM genotypic prevalence rate was 15.0% in Chinese, 10.0% in Malays, 8.9% in Iban and 18.2% in other subjects (p=0.042). One Chinese subject shown to be homozygous *2 and heterozygous *17, hence resulting in a new combination of *2/*17. The predicted metabolic phenotype for this combination is unknown and we assume that the ultrarapid clopidogrel metabolism by *17 allele may be suppressed by loss-of-function *2 alleles, thus resulting in a functional metabolising enzyme phenotype. Hence, we grouped this individual as EM. Linkage disequilibrium analysis showed that the *17 were in different linkage disequilibrium with *2 and *3. Among the 118 subjects who underwent a similar double antiplatelet loading strategy (75 mg loading doses of aspirin for at least 2 days+75 mg loading doses of clopidogrel for at least 4 days), the prevalence rate of PM remains high within Chinese group (17.5%) compared to other ethnic groups (p=0.036). The CPA was observed to be higher in PM (333.6 aggregation unit×min (AU*min)), followed by IM (319.7 AU*min), EM (278.7 AU*min) and lowest in IUM (264.5 AU*min) (p>0.05). The *2 and *3 carriers also demonstrated higher platelet aggregation (310.6 AU*min) compared to *17 carriers (264.1 AU*min) (p=0.412). The absence of statistically significant differences between the different phenotypic groups could be attributed to the relatively small sample size. Nevertheless, there was a significant influence of CYP2C19 polymorphism on CPA in Chinese subjects only (p=0.032) even after adjustment for various cardiovascular risk factors.

Conclusions The CYP2C19*2 is found at high frequency in Malaysians, especially in Chinese subjects, consistent to that found in other Asian populations of Chinese ethnic origin. Other CYP2C19 polymorphisms, particularly *17 were rare in the Malaysian population. However, carriers of *17 demonstrated better CPA compared to *2 and *3 carriers. Our findings indicate a broad inter-ethnic difference in CYP2C19 allelic frequencies. As both the presence of certain genotypes especially *2, and a lower CPA, have been shown to be associated with higher adverse cardiovascular event rates in patients prescribed clopidogrel, subsequent outcome studies in our multiethnic population are warranted.