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LETTER TO THE EDITOR

# Letter by Aw et al Regarding Article, "Clinical Outcomes and Sustainability of Using CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention"

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*To the Editor:*

We read the recent studies by Lee et al[1] and the IGNITE network (Implementing Genomics in Practice) with much interest and wish to share findings from our cohort of 247 Asians in Khoo Teck Puat Hospital, Singapore. To our knowledge, we are the first Asian group to demonstrate similar interventional cohort findings as those of Lee et al[1] and Cavallari et al from the IGNITE network.[2]

We conducted a single-center, prospective, open label study in 247 Asian patients who underwent percutaneous coronary intervention and received dual antiplatelet therapy consisting of aspirin and clopidogrel. At the time of design, we intended to switch subjects with high-on-treatment response from clopidogrel to prasugrel. Additional blood samples were collected for genotyping. High-on-treatment response was defined then as P2Y12 reaction units >230 using the VerifyNow meter. The rate of major adverse cardiovascular event (MACE) defined by Cutlip classification did not differ between switchers and nonswitchers (4.9% versus 5.3%; *P*=1.0) while clinically-significant bleeding defined by Bleeding Academic Research Consortium classification was significantly greater in the high-on-treatment response group, who were switched to prasugrel (12.2% versus 2.9%; *P*=0.021). Platelet reactivity testing was only able to pick up 20% and 30% of the poor metabolizers (PM) and intermediate metabolizers (IM) subjects to be switched, creating the opportunity of analyzing the impact of switching in PM and IM subjects who were kept on clopidogrel.

*CYP2C19*2, CYP2C19*3*, and *CYP2C19*17* mutations were assayed and classified into *CYP2C19* phenotypes according to the 2013 Clinical Pharmacogenetics Implementation Consortium guidelines. The prevalence rates of rapid metabolizer, extensive metabolizer, IM, and PM phenotypes were 4.9%, 33.2%, 47.4%, and 14.6%, respectively. Comparing CYP2C19 loss-of-function (LOF) mutation rates to published rates for white and black ancestry, we observed a 62% prevalence (n=153); more than twice that in the comparators. Furthermore, 15% were PM (n=36), a 5-fold greater prevalence than that of white and black subjects.[3] In their meta-analysis, Sorich et al[4] reported an over 50% of LOF mutations in Asians. This implies that the problem of increased risk of MACE could be larger in our local Asian population.

We used Cox proportional hazards regression, adjusting for age, ethnicity, sex, diabetes mellitus, smoking, calcium channel blocker use, and proton pump inhibitor use. The risk of MACE was >30-fold greater for PMs on clopidogrel as compared with those with no LOF allele (rapid metabolizer+extensive metabolizer) on clopidogrel (*P*=0.004). Albeit lower for PMs, the risk of MACE for IMs kept on clopidogrel was 9-fold greater when compared with patients with no LOF allele on clopidogrel (*P*=0.042). Other than *CYP2C19* phenotype as a predictor,





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the Malay ethnic group, diabetes mellitus, and proton pump inhibitor (omeprazole) use were significant predictors of MACE.

A larger local study in healthy volunteers showed similar *CYP2C19* phenotype proportions, affirming that the IM and PM phenotype prevalence observed in our cohort was not from a play of chance.[5] With the high prevalence of at least 1 LOF allele in our local population of 62%, it seems probable that *CYP2C19* genotype-guided antiplatelet therapy would be associated with improved clinical outcomes.

Future studies should be designed around the effectiveness and safety of the more potent alternative P2Y12 inhibitors to be used in PMs and potentially in IMs subjects within a larger sample size and whether it would be associated with an increased risk of bleeding as suggested by our study. The out of pocket costs of ticagrelor and prasugrel in our local setting is 30-fold that of clopidogrel to our patients. It is imperative that a health technology assessment of routine genotyping on a background of MACE and bleeding expenditures be performed.

## ARTICLE INFORMATION

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### Disclosures

None.

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