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RESPONSE TO LETTER TO THE EDITOR

Response by Lee and Stouffer to Letter Regarding Article, "Clinical Outcomes and Sustainability of Using *CYP2C19* Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention"

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In Response:

We thank Aw et al for their letter and commend them on their study of clinical outcomes in 247 patients at Khoo Teck Puat Hospital in Singapore who underwent platelet reactivity testing to guide antiplatelet therapy after percutaneous coronary intervention and also had *CYP2C19* genotype testing performed.

We highlight 3 key findings from their study, which complement our recent single-center study at the University of North Carolina at Chapel Hill and the multi-center study conducted by the Implementing Genomics in Practice Network.[1,2] First, Aw et al report that the frequency of *CYP2C19* loss-of-function alleles was ≈2× higher (62% prevalence) in individuals of Asian ancestry than in white Americans and blacks in our study (30% prevalence). Second, high-on-treatment response to clopidogrel, as determined by VerifyNow platelet reactivity testing, failed to detect 70% to 80% of CYP2C19 intermediate metabolizers (IMs) and poor metabolizers (PMs). Third, treatment of CYP2C19 IMs and PMs with clopidogrel was associated with a markedly higher rate of major adverse cardiovascular events (MACE) compared with patients without an loss-of-function allele who were prescribed clopidogrel, consistent with the findings of our study. The magnitude of these associations (over 30-fold greater for PMs and 9-fold greater for IMs) was higher than observed in our study and may reflect different end point definitions, patient selection, timing of *CYP2C19* genetic testing, and population differences. Prior work has highlighted the importance of these differences.[3]

The significantly higher risk of MACE in both CYP2C19 IMs and PMs prescribed clopidogrel reported by Aw et al at their institution in Singapore is consistent with observations in multiple other populations that treatment of IMs and PMs with an alternative $P2Y_{12}$ inhibitor can reduce MACE. Most notably, the multi-center Implementing Genomics in Practice Network analysis of 1815 patients found that IMs and PMs who received alternative therapy with prasugrel or ticagrelor had a lower risk of MACE over 12 months after percutaneous coronary intervention compared with IMs and PMs who received clopidogrel.[2] More recently, the multi-center PHARMCLO trial (Pharmacogenetics of Clopidogrel in Acute Coronary Syndromes) of 888 patients hospitalized for an acute coronary syndrome found that patients randomized to the genotype-guided arm had a lower risk of MACE or major bleeding events at 12 months compared with the standard of care arm.[4] Taken together, the study by Aw et al contributes to a rapidly growing evidence base in the United States,[1,2] Europe,[4,5] and Asia,[6] demonstrating that *CYP2C19* genotype-guided antiplatelet therapy results in better clinical outcomes in patients undergoing percutaneous coronary intervention.

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ARTICLE INFORMATION

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Disclosures

None.

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