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Reply

We thank Dr. Jeong and colleagues for their comments with regard to our study (1). We well know that previous studies investigated on-clopidogrel platelet reactivity (PR) through follow-up (2,3). Nevertheless, these findings were observations in studies planned for other aims. Our study is the first investigating the incidence of clopidogrel poor response at baseline versus that at 1 month as the primary endpoint and assessing the different influence over time of genetic and environmental PR determinants. Principally, 3 points were raised: the first concerns the timing of measurements with respect to the last dose administration, the second refers to the occurrence of adverse events, and the third touches on the independent determinants of bleeding. Firstly, in our study, the maintenance dose of clopidogrel was taken in the morning, and the blood sample to evaluate PR was collected 1 to 5 h later. Considering both the time between drug intake and blood sample and the degree of platelet reactivity (PRU) value variation between "acute" and "chronic" phases, we believe that the potential influence related to timing of measurement may be minimal. Secondly, one of our aims was to assess the predictive role of 1 month PRU value as compared to baseline value. So, as clearly reported in the Methods section, clinical events that occurred after 1 month and up to 1 year of follow-up were deliberately considered for this purpose. Patients with adverse events during the first month were excluded. Third, it is plausible that *CYP2C19*17* carriership indicates a "chronic" tendency to have lower PRU values. Nevertheless, other environmental factors may still influence PRU values irrespective of **17* carriership. This aspect could explain partially why both *CYP2C19*17* and PRU values emerged as independent predictors of bleeding complications. This observation is intriguing and deserves further investigation, as it alone would strongly reinforce the concept that both phenotype and genotype should integrate the clinical decision making about the more appropriate choice of oral $P2Y_{12}$ inhibitor. Therefore, we agree with Dr. Jeong and colleagues when they affirmed that, in the future, comprehensive algorithms including clinical, genetic, and laboratory findings are needed to permit us to optimize antiplatelet therapy in each individual patient. Our study is one of the first efforts in this direction, and the value of integrating this working algorithm into clinical practice versus a purely clinically driven choice of $P2Y_{12}$ inhibitor is currently being tested as a pre-specified substudy of the MATRIX (Minimizing Adverse Haemmhorragic Events by Transradial Access Site and Systemic Implementation of Angiox) study.

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