Author`s Reply

To the Editor,

We would like to thank you for your comments on our article (1) entitled "The first six-month clinical outcomes and risk factors associated with high on-treatment platelet reactivity of clopidogrel in patients undergoing coronary interventions" published in Anatol J Cardiol 2016; 16: 967-73, about high on-treatment platelet reactivity of clopidogrel (HTPR), clinical outcomes, and associated risk factors and for the opportunity to discuss the clinical outcomes further.

It was discussed that in a meta-analysis of 17 studies consisting of 20839 patients treated with clopidogrel showed a 2.7-fold higher risk for stent thrombosis (ST) and a 1.5-fold higher risk for mortality following percutaneous coronary intervention (PCI) in HTPR patients (2). However, we found no statistically significant difference between the study and control groups in terms of ST (2.9% vs. 2.6%, p=0.82) and cardiovascular mortality (2.9% vs. 4%, p=0.34) in the first 6-month follow up (1). First of all, in the abovementioned meta-analysis, non-Western patients were excluded from the study because of different pharmacodynamic response to P2Y12-inhibitors across races. In addition, there is no long-term outcome follow-up (just the first month follow up data were available) in 6 of the 17 studies compromising 4694 of 20839 patients. Despite these methodological differences there may be some confounding variables altering our study results as previously mentioned in the limitations section:

One of the major reasons for ST and stent malapposition could not be evaluated in our study because there was no feasibility of IVUS or OCT when the stent deployed. Another issue about ST is that this entity could be affected by the type and size of stent. In our study, as we specified in limitation section, we do not have data enclosing stent size and type (BMS or DES). We accept that not covering stent type and size could have played a role in evaluation of results.

The prevalence of HTPR varies from study to study. There are many reasons for this disharmony: race, dietary habitudes, concomitant drug use, time from clopidogrel ingestion to study platelet functions, technique used, and cut-off levels for platelet reactivity. In our study, platelet functions were studied only once (24 hours after clopidogrel ingestion) and Multiplate analyzer was used. Platelet function assessment more than once, as performed in GRAVITAS (3) trial, could predict more accurate outcomes regarding mortality and ST. Another issue concerning platelet function is cut-off levels of assays. In the GRAVITAS (3) trial, when HTPR cut-off level is chosen as 230 PRU (Verify Now), <230 PRU was not associated with a lower risk of the primary end-point at 60 days [hazard ratio (HR), 0.62; 95% confidence interval (CI), 0.25–1.51; p=0.30] and at 6 months after PCI (HR, 0.71; 95% CI, 0.41–1.23; p=0.22). However, when the cut-off level is chosen as 208 PRU, <230 PRU showed a lower risk of the primary end-point at 60 days (HR, 0.18; 95% CI, 0.04–0.79; p=0.02) and at 6 months (HR, 0.43; 95% CI, 0.23–0.82; p=0.01). In our study, Multiplate analyzer was used and HTPR was defined with a cut-off level of 200 and the area under the aggregation curve as described by the manufacturer. According to a previously conducted study with Multiplate analyzer (4), an ADP test value >468 AU seems to be the optimal cut-off level to separate patients with high risk of stent thrombosis. Our study was conducted to evaluate not only ST but also find the prevalence of HTPR and associated risk factors, and a cut-off level of 200 was more reasonable than 468. However, there could be a more precise conclusion about ST and mortality if we have chosen 468 as the cut-off level.

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References

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