Letter by Gurbel et al Regarding Article, “Administration of a Loading Dose Has No Additive Effect on Platelet Aggregation During the Switch From Ongoing Clopidogrel Treatment to Ticagrelor in Patients With Acute Coronary Syndrome”

To the Editor:

We read with interest the article by Caiazzo et al comparing the pharmacodynamics of 180 versus 90 mg ticagrelor in 50 clopidogrel responsive patients with acute coronary syndrome. The authors challenge the ticagrelor dosing strategy of the large landmark Platelet Inhibition and Patient Outcomes (PLATO) trial. The authors hypothesize that a 180-mg ticagrelor load may not be necessary based on a similar reduction in platelet aggregation (PA) observed with both ticagrelor doses and that a 90-mg ticagrelor dose could be associated with a reduced bleeding risk. We have the following concerns and questions about the authors’ conclusions:

1. Detailed information on the definition of and the methodology to evaluate responsiveness, an entity that requires an assessment of both baseline and postclopidogrel platelet function, is entirely missing. The study included only clopidogrel responders. Were patients actually screened to enroll 50 clopidogrel responders and these data not reported? The authors should have also studied clopidogrel nonresponders, in whom the added antiplatelet effect of switching to ticagrelor therapy is more pronounced.

2. Given the low mean PA (≈25% maximal aggregation, ≈30 aggregation units by multielectrode aggregometry) during clopidogrel therapy, significant differences in PA between various doses of ticagrelor after switching may be difficult to observe as supported by a previous study in which a mean PA of ≈40% final aggregation was observed in patients with acute coronary syndrome treated with clopidogrel before switching. In contrast to the results of Caiazzo et al, in a previous detailed pharmacodynamic study conducted in patients with stable coronary artery disease correctly screened for clopidogrel responsiveness, an enhancement of platelet inhibition occurred when 180 mg ticagrelor was loaded in the presence of clopidogrel responsiveness, an entity that requires an assessment of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding.

3. How can the authors hypothesize that “avoiding the loading dose of ticagrelor when switching could be associated with a reduction in the incidence of bleeding complications” when low and similar PA values were observed with both ticagrelor doses studied? These low PA values have been associated with bleeding cutoffs reported in a recent consensus document.

4. The timing of ticagrelor switching and PA measurements with respect to the occurrence of revascularization was not noted. The revascularization procedure itself is known to influence PA and antiplatelet response.

5. The study is greatly underpowered for any subgroup analyses, multivariate analyses, and most importantly to comment on any relation to clinical outcomes.

The authors’ statements that “...ticagrelor treatment without the administration of a loading dose of ticagrelor seems to be safe” and “the administration of a loading dose of ticagrelor has virtually no additive effect on platelet aggregation or the onset of drug action in patients with ACS who were responders to dual antiplatelet therapy with aspirin and clopidogrel” are unsupported by the data they show.

Disclosures

Dr Gurbel reports serving as a consultant for Daiichi Sankyo, Sankyo, Eli Lilly, Bayer, AstraZeneca, Accumeetrics, Merck, Medtronic, CSL, and Haemonetics; receiving grants from the National Institutes of Health, Daiichi Sankyo, Eli Lilly, CSL, AstraZeneca, Haemonetics, Harvard Clinical Research Institute, and Duke Clinical Research Institute; receiving payment for lectures, including service on speakers’ bureaus, from Eli Lilly, Daiichi Sankyo, and Merck; and receiving payment for development of educational presentations from Merck, the Discovery Channel, and Pri-Med. Dr Gurbel is holding stock or stock options in Merck, Medtronic, and Pfizer and holding patents in the area of personalized antiplatelet therapy and interventional cardiology. The other authors report no conflicts.

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References


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