Response to Letter Regarding, “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”

We thank Dr Gurbel et al1 for their interest and their comments on our recently published 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 (SHIFT-OVER) study.2

The novel antiplatelet agent, ticagrelor, has several advantages over the long-standing clopidogrel, as the virtual absence of nonresponders and the more powerful platelet inhibition. As highlighted by Gurbel et al,1 clopidogrel nonresponders were excluded from our study, for multiple reasons. First, because it is known that high on-treatment platelet reactivity is associated to a higher incidence of stent thrombosis and adverse events,3 it would have been unethical to randomize those patients. In fact, we do not know how much time it would have taken to reach an adequate level of platelet inhibition in high on-treatment platelet reactivity patients not receiving the loading dose. On the contrary, we found interesting to verify that no adjunctive loading dose is necessary to maintain an already adequate level of platelet inhibition. Finally, giving the sample size required for the SHIFT-OVER, a nonuniform distribution of nonresponders between the study arms could have significantly hindered our evaluation.

Gurbel et al1 also claim that the relatively low baseline platelet function could represent an issue because significant differences in platelet aggregation (PA) between various doses of ticagrelor after switching may be difficult to observe.1 As we already mentioned in the original article, similar PA levels were already reported in the same clinical context.2 Foremost, as also reported in the original article, the addition of baseline aggregation levels as a covariate confirmed the absence of any influence on the study outcome.

Gurbel et al1 also raise the doubt that avoiding the ticagrelor loading dose could lead to a reduction of bleedings because similar PA levels were observed in both treatment arms in the SHIFT-OVER study.1 As we clearly stated in our article, such conclusion cannot be draft from a pharmacodynamic study, such as the SHIFT-OVER, and should instead be tested in an ad-hoc designed clinical end point study. Moreover, as we clearly stated in the original article, the clinical follow-up data were just reported for the sake of completeness and no hypothesis can be generated from these data, which were largely underpowered.

As Gurbel et al1 correctly noticed, percutaneous coronary intervention itself has an effect on PA. However, when the timing of the percutaneous coronary intervention procedure was entered into our model as a covariate, we did not find any influence on PA levels.

Finally, results of secondary end points or subgroup analyses are potentially interesting to the readers. In fact, I reviewer specifically asked to include these analyses in the revised version of the article.

In conclusion, we think that our study was the first demonstrating no significant no additive effect on PA with the administration of a loading dose during the switch from ongoing clopidogrel treatment to ticagrelor in patients with an acute coronary syndrome and generated a hypothesis that should be tested in further prospective clinical end point studies.

Disclosures
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