Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance': reply to a rebuttal

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See also Michelson AD, Linden MD, Furman MI, Li Y, Barnard MR, Fox ML, Lau WC, McLaughlin TJ, Frelinger AL. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance'. *J Thromb Haemost* 2007; **5**: 75–81; Gurbel P, Bliden KP, Tantry U. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance': a rebuttal. This issue, pp 1087–8.

In their letter, Gurbel *et al.* [1] review their important contributions to the controversial issue of clopidogrel 'resistance' or response variability.

In our work [2], we studied the effects of clopidogrel on platelet response variability to adenosine diphosphate (ADP) in healthy volunteers and in patients. Contrary to the contention of Gurbel *et al.* that in our study there was an 'absence of an analysis of platelet inhibition in the healthy control group', Fig. 1 displays an analysis of platelet inhibition by clopidogrel. Fig. 1 shows the results of measuring the response to ADP in healthy volunteers who had their blood drawn prior to and 5 h after the oral administration of 300 mg clopidogrel. The significant correlation ($P < 0.0001$) between preclopidogrel ADP-stimulated platelet surface P-selectin and postclopidogrel ADP-stimulated platelet surface P-selectin demonstrates that platelet response variability to ADP in the presence of clopidogrel (clopidogrel 'resistance') is largely accounted for by pre-existent variability in platelet response to ADP in the absence of clopidogrel. This led us to the hypothesis that the variation in response to ADP of a patient population exposed to clopidogrel would not be different from the variation in response to ADP of a patient population not exposed to clopidogrel. We therefore performed a cross-sectional patient study, summarized in Fig. 2 [2]. Thus, unlike the healthy volunteers shown in Fig. 1, all 613 consecutive cardiac catheterization patients shown in Fig. 2 were analyzed for their response to ADP at a single time-point prior to cardiac catheterization, irrespective of whether or not they were receiving clopidogrel at that time-point. In addition to permitting evaluation of patients exposed to clopidogrel for varying durations, our study design avoided the confounding effects on platelet response of a percutaneous coronary intervention performed between pre- and postclopidogrel time-points. Our statistical analyses compared the variation observed in the untreated population (wherein everyone should respond to ADP) with the variation observed in the subsets of patients exposed to clopidogrel for varying lengths of time (wherein, if clopidogrel resistance were present, some individuals would respond normally to ADP while most would respond poorly to ADP, resulting in greater variation of response for the population). The data from this large number of patients ($n = 613$) (see Fig. 2) were consistent with the data from the normal volunteers (see Fig. 1), i.e. platelet response variability was not increased by clopidogrel administration.

We agree with Gurbel *et al.* [1] that in individual subjects it is optimal to measure platelet function before and after clopidogrel therapy in order to evaluate response; as we did in our study of normal subjects. However, our population-based patient study was a statistically valid design, with some methodological advantages as described above. In any event, as we stated [2], the conclusion from our 613-patient population-based study, that pre-existent variability in platelet response to ADP accounts for clopidogrel 'resistance', is consistent with the data obtained in four smaller, previously published studies – two by Gurbel's group [3,4] and two by Angiolillo *et al.* [5,6] – that measured platelet function before and after clopidogrel therapy.

Disclosure of Conflict of Interests

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References

1 Gurbel PA, Bliden KP, Tantry US. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance': a rebuttal. *J Thromb Haemost* 2007; **5**: 1087–8.

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