and 75th (in 2005) anniversary of Klein’s pioneering work. Many leading cardiologists and physiologists actively participated at these meetings, including K. Amplatzer, M. Kaltenbach, W. Ganz, M. Bertrand, S.B. King, U. Sigwart, G. Arnold, A. Vahanian, J.P. Bassand, W. Wijns and others. I presented a lecture on Klein and my personal meeting with him in 2000 (published after the symposium), and additional detailed information about his life after emigration was presented by Stern in 2005.

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A double blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days

In reference to the interesting study by von Beckerath et al., we would like to offer the following comments.
The predicted induced platelet aggregation (IPA) of 50% in the 75 mg clopidogrel group is lower than the actual observations of 65% noted in the study controls. Underestimation of the control IPA impacts effect size and study power, and could limit the validity.

Further, the 5 and 20 μM ADP IPA observed in the study control groups receiving 75 mg clopidogrel were 63.3 and 80%, values that are much higher than other reports. One study showed both 5 and 20 μM ADP IPA of ~30% in patients receiving 75 mg maintenance clopidogrel. Another report showed that 20 μM ADP IPA was 42% after a 600 mg clopidogrel loading dose. The higher IPA noted in the study will certainly limit the generalizability of the study findings to other populations with lower IPA. The effect of high dose clopidogrel in subjects with lower IPA remains to be clarified.

Very few female subjects were enrolled, thus limiting the generalizability of the findings to women. It would be interesting to know regarding the gender distribution of all subjects screened and excluded from the study before randomization. Further, by employing a block randomization selection strategy, gender distribution could have been improved.

As diabetes affects platelet function, analysis of the confounding effect of diabetes on platelet activity may be informative. Further, it would be interesting to analyse the data from patients with atherosclerosis in other vascular beds such as those with peripheral artery disease who are known to have abnormal platelet function and are at higher risk for coronary artery disease (CAD).

Clopidogrel pharmacokinetics and pharmacodynamics depends on cytochrome P450 3A inhibition. Therefore, the use of medications that influence P450 3A activity on clopidogrel should be evaluated.

Up to 30% of CAD patients may not have inhibition of platelet aggregation with the standard clopidogrel dose and many studies have recommended increasing the clopidogrel dose. Lack of data on measurements of ADP IPA in this study prevents the comparability of the two groups at baseline, and precludes the assessment of individual platelet responsiveness to clopidogrel treatment.

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**A double blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days: reply**

We agree with them that maximal ADP-induced platelet aggregation was quite high in our recent double-blind randomized study in which we compared the antiplatelet effects of a 150 with a 75 mg daily clopidogrel maintenance dose. Although, light transmission aggregometry (LTA) is the gold standard to evaluate platelet function in response to agonists such as ADP, it is a poorly standardized method which makes it nearly impossible to compare absolute values obtained in different laboratories. Importantly, during the period of this double-blind randomized study, LTA was uniformly performed on a Chrono-log aggregometer as described in the methods section. Therefore, we believe that we describe an existing dose–response phenomenon. This is supported by the data that we obtained with the VerifyNow™ P2Y12 assay. These data also show that the level of platelet aggregation is significantly lower in patients treated with 150 mg per day than in those treated with 75 mg per day. Moreover, at least three other studies have shown that the antiplatelet effects of a 150 mg daily maintenance dose exceed those of a 75 mg daily maintenance dose.

Zhang and Balavenkatesh suggest that the sample size calculation may not be valid since values for platelet aggregation were higher than expected. Interestingly, the relative difference in ADP (5 μM)-induced platelet aggregation 30 days after percutaneous coronary intervention (31 %) amounted quite accurately to what we had assumed. Recalculating the sample size with the absolute values obtained actually increases the power of the study. Moreover, we believe that the sample size of our present study is far too small to allow conclusions on subgroups of patients (e.g., those who are females and those who have diabetes and peripheral artery disease). It should be mentioned, though, that just recently, Angiolillo et al. showed that an increase of the daily maintenance dose of clopidogrel from 75 to 150 mg per day also results in a significant reduction of the level of platelet aggregation in diabetics with a poor response to clopidogrel.

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