Endothelial progenitor cells and erectile dysfunction: reply

Fadini et al. mention that antibodies used and staining performed in our study were not described. In order to condense the methods section, we referred to the publication of the EPCAD study (Circulating Endothelial Progenitor Cells and Cardiovascular Morbidity and Mortality in Patients with Coronary Artery Disease Study), in which the patients from our study were enrolled from. Flow cytometry and staining procedures are described in detail in this publication. This study demonstrated a clear and significant association of EPC and cardiovascular outcome in patients with coronary artery disease. Moreover, we could demonstrate that EPC are an independent risk factor for erectile dysfunction. Thus, in our opinion, event counts used in both studies are adequate, especially regarding the high number of patients included.

We could demonstrate in our study that only CD133+, but not CD34+, cells correlate with erectile function. We discussed this finding in the paper, but explanations remain speculative. CD133+ cells are precursors of CD34+ cells with an increased potency for endothelial repair. This finding was clearly demonstrated by Friedrich et al.2 in vitro as well as in vivo in a mouse model and in humans. Hence, those experiments can be translated to the ex vivo determination of circulating EPC, particularly with flow cytometry, which is, at this time, the only and most validated method for EPC measurement. In the cardiovascular high-risk patients of our study, CD133+ cells might be upregulated because of the increased endothelial dysfunction. Hence, these increased CD133+ cell counts might allow to detect associations of CD133+ cells with target variables more reliably. In contrast, consumption of CD34+ cells into vascular lesion areas in these patients might result in decreased cell counts without the opportunity to detect distinct differences in our study population.

Fadini et al. criticize that EPC, in our study, was not further differentiated. We agree with this suggestion, but when the study was performed, detailed information about differentiation in CD133+/CD34+ or CD133+/CD34- cells were not yet available. Thus, we further agree with the conclusion of Fadini et al. that consensus on EPC definition and evaluation is needed.

References

3. Magnus Baumhäkel Department of Cardiology University Hospital of the Saarland Kirrbergerstr Hamburg 66421 Germany E-mail address: magnus@baumhaekel.de
4. Michael Böhm Department of Cardiology University Hospital of the Saarland Kirrbergerstr Hamburg 66421 Germany

Acute coronary syndromes, response to clopidogrel, and worsened cardiovascular outcomes: the hen and the egg dilemma

I enjoyed reading the quality paper by Geisler et al.3 that tried to link low response to clopidogrel with the incidence of major cardiovascular events and death in a broad spectrum of post-stent patients. The team should be acknowledged for the effort, clean data, and the realistic assessment of the frequency of low response (5.8%) after loading with 600 mg clopidogrel. The major home-take message the authors try to deliver to the readership is that at 3 months after stenting the incidence of death and AMI was higher in the low clopidogrel responders. However, such conclusions are not fully supported by the presented evidence, and deserve at least some clarification, and/or adjustment.

The major limitation of the index analysis is the fact that almost all of the low responders (81.8%, or 18 out of 22 patients) underwent emergency revascularization, whereas only the minority (43.1%, or 147 out of 341 average responders) experienced acute coronary event (Table 1). In contrast, the majority of patients from the control group was subjected to the elective angioplasty and stenting, and did not suffer an acute event at the time of intervention. In short, low response cohort was not stable, experienced more myocardial damage, and probably worsened outcomes even before clopidogrel therapy. How fair and balanced is to declare low response to clopidogrel as a major risk factor to such harmful association remains to be seen, especially when patients were already at higher risk, and platelet glycoprotein IIb/IIIa inhibitors were not allowed. Although ISAR-REACT 2 trial revealed that addition of abciximab to 600 mg loading with clopidogrel improves cardiovascular outcomes in the troponin-elevated ACS patients,2 the index patients were deliberately denied the benefit, substantially limiting the practical value of the study. Obviously, the thrombotic burden in some patients with ACS exceeds the ability of even high dose loading with clopidogrel to prevent secondary events. However, it is not reasonable to generalize such clinical scenario, and blame clopidogrel’s low response for recurrent events, especially acknowledging that no-load 75 mg clopidogrel saved 119 lives and provided an absolute mortality benefit after AMI in the COMMIT trial.3

Another critical baseline difference in the index study is the 14.6% less use of statins in the low responders group with highly significant (P = 0.001) hyperlipidaemia when compared with the average responders. Recent meta-analysis of 13 trials with almost 18 000 patients strongly suggests that statins reduce death and cardiovascular events after 4 months of treatment in ACS patients.4

There are also certain shortcomings of the study design that limit our ability to adequately interpret the platelet data. Although the definition of low response, and lack of baseline platelet function assessment are questionable, but still acceptable, random non-pre-specified sample collection times cannot be advocated. Indeed, the single platelet test was performed after at least 6 h after clopidogrel loading, but with the broad mean of 34.8 ± 25.9 h after stenting. In common terms, it means that some patients were already treated with the maintenance clopidogrel dose for 1 or 2 days, and the data analysis should be adjusted accordingly. This is especially important because platelet activity after acute thrombotic events is not consistent, nor unchanged, but rather undergoing phasic changes,5 which in turn are dependent on the success of reperfusion. Therefore, single platelet aggregation test done randomly, not at the pre-specified time after coronary intervention, may be

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used as a reliable screening laboratory tool, but falls way too short to provide clinically meaningful conclusions.

In fact, the index study is timely to provide some important insight that ACS patients exhibit worse cardiovascular outcomes after stenting, reinforce the protective role of statins (directly), and platelet glycoprotein IIb/IIIa inhibitors (indirectly). However, multiple unadjusted variables with regard to group composition, baseline characteristics, and lack of strictly pre-specified time point for the platelet assessment limit the clinical utility of the study.

References

**Figure 1** Scatter-plot showing the correlation between time-point of platelet function assay and platelet aggregation in 363 patients with coronary stenting after administration of 600 mg loading dose of clopidogrel. Correlation curves and coefficients are presented for the subgroups of patients with stable angina and acute coronary events. No further attenuation effect of clopidogrel on platelet aggregation was observed at time-points later than 6 h after the loading dose.

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Acute coronary syndromes, response to clopidogrel, and worsened cardiovascular outcomes: the hen and the egg dilemma: reply

We thank Dr Serebruany for his interest and careful reading of our article entitled “Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation”.

He critically remarked the influence of acute coronary syndromes (ACS) on response to clopidogrel in our patient cohort. We agree with Dr Serebruany that acute coronary events may have substantial influence on measured platelet activity and, of course, also influence cardiovascular outcome. The very justified comment is supported by previous clinical studies.1,2

Our aim of the present manuscript was to provide data on platelet response after administration of 600 mg loading dose of clopidogrel in an unselected consecutive patient cohort undergoing coronary stenting and to investigate its association on cardiovascular outcome. The measurement was done in a clinically practical way by a single measurement. We found that patients identified as low responders showed an increased incidence of cardiovascular events within 3 months. In univariate analysis we found ACS to be significantly associated with low response to clopidogrel. We agree that the lower response of platelet inhibition in ACS may be related to a higher degree of platelet activation. However, multivariate analysis of potential variables that may influence cardiovascular outcome including ACS shows that low response to clopidogrel and severe left ventricular dysfunction was independently associated with adverse cardiovascular events.

We are absolutely aware that multiple factors may have an impact on response to clopidogrel, which were not regarded in this study and that low response cannot be considered as a sole risk factor for cardiovascular events. However, the published data suggest that residual platelet activity after administration of 600 mg clopidogrel loading dose represents an additional risk factor for recurrent cardiovascular events and that point-of-care testing of platelet function detects patients at risk for upcoming cardiovascular events. Besides, the data fit well to previously published data on the clinical relevance of response to clopidogrel measured by platelet function tests.3 In the study by Matetzky et al.4 high-risk patients with acute myocardial infarction who received eptifibatide for 14 ± 2 h, clopidogrel-resistant patients expected an increased risk of atherothrombotic events despite intensive antithrombotic treatment by GPIIb-IIIa antagonists.

Importantly, the aim of the presented study was not to question the benefits of a dual antiplatelet therapy in cardiovascular risk patients as already proved by several studies including the CURE trial and the quoted COMMIT trial. As demonstrated by the relatively small proportion of low responders in our patient cohort, our results do not stand in contradiction to the