RESPONSES to REFEREES

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Kidney dysfunction and long-term outcome in post-PCI acute coronary syndrome patients treated by high-dose tirofiban: the role of creatinine clearance

REFEREE 1: He/she said: “The paper is confusing and needs to be rewritten into 2 separate papers or two separate section one on Measurement of KD and one on the influence of IIa/IIIb inhibitor. The authors should devoted equal amount of time to each of the measures of renal dysfunction. They also need to examine EGFR more closely as it is now a quality mandate in my health systems. The graphs and tables should show the sCr, CrCl and eGFR data so the reader can review and should also provide some data the validity of each measure to KD. What is the true gold standard for measuring KD. The authors should stratify the final one year outcomes of patients in regard to progression of KD / dialysis. The discussion should be more focused on PCI and KD.

Responses of the Authors: Now that the MS has been reformatted according to the Journal style and that headings and subheadings have been included we feel that the overall aspect and presentation is much more understandable and probably clearer. We disagree with this Referee’s opinion that this MS actually needs to be split into 2 separate MS: one presenting the predictive data on KD and a second one on the influence of Tirofiban. In fact, as we have repeatedly quoted in this MS, the large majority of controlled studies on GP IIa/IIIb inhibitors consider KD as an excluding factor with the result that the concomitant information is either absent or minimal. On the other hand, it is important to know whether in presence of KD there might be an incremental risk (especially long-term) in patients treated by GP IIa/IIIb inhibitors. This was the most interesting and provocative information of the Study and we maintain that it should be provided in a single MS.

Graphs and Tables do provide information about CrCl and eGFR (by 2 formulae) and precisely what is important in this MS is that Table 2 illustrates the results of forced Cox models whereby these parameters are comparatively challenged: however they do essentially provide a very similar information. The Cox models were not provided for sCr since Fig. 1 (as compared to Fig. 2) very clearly showed that sCr should not be used for predictive purposes. It is quite clear, in addition that further providing these data should expand this MS further, which is in contradiction with the idea of keeping it at a reasonable length.

We did not stratify in accordance with KD/dialysis since the predictors (either crCl or eGFR) were considered CONTINUOUS variables and the Cox models run were forced, meaning that all variables stay in the model. This further means that the risk illustrated by the risk factors is continuous and KD (as signified by these predictors) add or not to the overall predictivity. In this perspective it is not relevant to stratify since the conclusion from Table 2 is that yes KD does make a difference as a predictor for long-term outcome as defined in this Study.

We have focused the Discussion on the 2 elements outlined by this Referee: PCI and KD

We hope that this Referee will appreciate our efforts and replies.
REFEREE 2: Zuo, Li, Department of Nephrology, Peking University First Hospital wrote:

1. The authors gave two results in their abstract: one, CrCl is predictive of future CIE; two, high dose tirofiban use was possibly associated with lower risk of CIE. These two results did not answer the question raised in the manuscript title: was there any interaction between tirofiban and CrCl?

2. The title should be carefully rewritten. If the author wanted to study the interaction between KD and high-dose tirofiban, they should study only this part of patients. But it seemed that the authors wanted to report all patients using different dose of AAD.

3. Text needed to be polished, because it was very hard to read and to understand.

   The description about Cox model was not sufficient: how many models were they established, what were all the covariates?

Responses of the Authors:

1. precisely speaking the evidence provided by our MS was that a) CrCl is predictive of future CIE; b) high dose tirofiban, which in several different studies was useful to lower the risk of CIE (HR around 0.82 but with 95% limits crossing the unit and then not statistically significant), what could be suspected in presence of KD. Moreover, there is no formal question in the MS Title “was there any interaction between tirofiban and CrCl?” and the Title is just descriptive with no allusion of interactions.

2. We have pointed to Referee 1 a concept that apply to Referee 2 as well “… it is important to know whether in presence of KD there might be an incremental risk (especially long-term) in patients treated by GP IIa/IIIb inhibitors. This was the most interesting and provocative information of the Study and we maintain that it should be provided in a single MS. In fact, as we have repeatedly quoted in this MS, the large majority of controlled studies on GP IIa/IIIb inhibitors consider KD as an excluding factor with the result that the concomitant information is either absent or minimal.”. This is why we did not split this Ms. By the way we kept the previous Title since we believe that it fully describes both the scope and the results of this investigation.

3. We have carefully reviewed and at places simplified the Text and, particularly about the Cox model we provided further specifications and details.

We hope that this Referee will appreciate our efforts and replies.