Title: Prognosis of concomitant users of clopidogrel and proton-pump inhibitors in a high-risk population for upper gastrointestinal bleeding

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Author's response to reviews:

Dear Editor,

We appreciated for all of the further comments on our manuscript entitled “Prognosis of concomitant users of clopidogrel and proton-pump inhibitors in a high-risk population for upper gastrointestinal bleeding”.

All the comments have been addressed point by point and manuscript has been revised accordingly. We also invited an English editor for further linguistic check-up. Hereby, we uploaded two versions of manuscripts together with this response letter. One manuscript has been highlighted with yellow and another one was the updated manuscript without any revision markers.

All co-authors have contributed, read and approved the latest version of the manuscript. Hopefully the revised manuscript will be suitable for publication in the BMC Pharmacology and Toxicology.

Yours sincerely,

Yunxia

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Reviewer's report:

Thanks for your responses and revisions. I believe you have adequately addressed most of the comments. However, I have questions regarding my comment #5 in Major Revisions section. The comment is about outcomes definition in Table 2. It appears that in each of the two cohorts (CVD and MI) you ran two models, each for "death" as an outcome and for "recurrent CVD" as an outcome. My question regards the censored categories in these models. When death was the outcome, you included in the censored group all those that did not die (including those with cardiovascular disease or myocardial infarction related re-hospitalization). It implies that you also included in the censored group all those who neither died nor had CVD or MI. My concern is that you are comparing death with both the healthy (those who did not die and did not have CVD or MI) and the sick (those having CVD or MI) at the same time. The censored group appears to be a mix of different types and is not a clean group. Therefore, the comparison (hazard ratios) between death and the censored group is confusing. Same is true for the comparison between the recurrent CVD group and the censored group in that model. Please clarify how you can draw meaningful comparisons given the mixed censored groups, and further, what exactly the hazard ratios in Table 2 mean or imply.

Response: Thank you very much for the comments. This is a question about survival analysis which was performed for the study. In survival analysis, the risk of outcome was measured considering the length of time to reach the outcome. For example, when outcome is death, survival analysis calculates the conditional probability of death considering time. The comparison is not between the groups of subjects who reach the outcomes (e.g., death) and the censored group (e.g., re-hospitalization). Actually it compares the conditional probability (risk) of outcome in the exposed group (e.g. use of clopidogrel) with the conditional probability (risk) of outcome in the reference group (e.g., concomitant use of clopidogrel and PPI). The hazard ratio (HR) means that the risk of death in the exposed group compares to the reference group. For instance, in Table 2, the HR of current only PPI users was 2.02 (1.19-3.44) compared to the current clopidogrel and PPI user when outcome was death. It meant that PPI only users has around 2 times of risk of death compared to the patients who concomitantly
used clopidogrel and PPI.

Reviewer's report
Title: Prognosis of concomitant users of clopidogrel and proton-pump inhibitors in a high-risk population for upper gastrointestinal bleeding

Version: 2 Date: 20 January 2014
Reviewer: Kathryn Momary

Reviewer's report:
Thank you for providing me with the opportunity to re-review this manuscript. The authors have made significant improvements.

Major Compulsory Revisions

- While the authors cannot analyze the data for each separate PPI, I do feel that the manuscript would benefit from at least a description of the number of patients receiving each PPI. Can this be added to table 1?

Response: Thanks for comments. It is very difficult to describe the number of subtype of PPI user in Table 1 because the patients got mixed prescriptions of PPIs during the follow-up period. We added the description of such information in the Results section on page 8 and page 9.

Revisions: On page 8, lines 24 to 25 and page 9, line 1, text has been added “In patients who only used one type of PPI, there were 878 omeprazole users, 162 esomeprazole users, 96 lansoprazole, 95 pantoprazole and 5 rabeprazole users.”

- While the authors addressed my question about previous GI bleed, I still believe that they need to provide literature support for this point. Specifically, how do you know that having a GI bleed increases future risk of the same event? If there literature to support this?

Response: Previous studies have reported the recurrence of GI bleeding is very high if someone had a history of GI bleeding. I added two more literatures (ref 31 and ref 32) in the manuscript on page 8 lines 3.

Response: Thank you for updating the paper to include a more thorough review of the PPI interaction with clopidogrel. However, lines 16-18 on page 10 are confusing. It is unclear if the authors are stating that pantoprazole does or does not interact with clopidogrel.

Response: Because several studies concerned about the safety of pantoprazole,
it is unfortunately we cannot measure it in our study. Therefore, we have to
confront the weakness of the current study but expect more studies with possibly
separating the analysis of pantoprazole. In order to express it clearer, we added
text on page 10 at lines 19-20.

Revisions: on page 10, lines 19-20, new text has been added “More studies with
large sample size for possibly separating of analysis of subtype of PPIs are
warranted.”