Author's response to reviews

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: see over
Dear Editor,

It is very grateful for the comments on our manuscript titled “Prognosis of concomitant users of clopidogrel and proton-pump inhibitors in a high-risk population for upper gastrointestinal bleeding”.

In this response letter, we have addressed all of the comments and made responses point by point. Manuscript has been revised and done the language check-up accordingly. 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 current status of the manuscript. Hopefully the revised manuscript will be suitable for publication in the *BMC Pharmacology and Toxicology*.

Yours sincerely,
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Reviewer's report

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

Version: 1 Date: 13 September 2013

Reviewer: Qayyim Said

Reviewer's report:

Major Revisions:
(1) This study sought to explore the effect of concomitant use of clopidogrel and proton pump inhibitors (PPIs) on the risk of re-hospitalization for cardiovascular diseases (CVD). This topic, though controversial, has been much researched in the last few years. Several observational studies across various settings have investigated the relationship of concomitant use of clopidogrel and PPIs with CVD. Therefore in order for a new study in this area to be published a strong case must be made. The authors need to provide a stronger justification and more explanation of new contribution of this study. The authors do refer to the fact that they focused on patients with high risk of both cardiovascular disease and upper gastrointestinal bleeding. However, they should provide some citations from the literature showing that this type of population was not studied before. The authors should further describe how their study improves upon previous studies in terms of design, methods, or data.

Response and revisions: I totally agree with the comments. On page 3 lines 19-25, and page 4, lines 1-8, more text for justification of the current study has been added and more references have been quoted.

(2) Further, there are some issues in this study regarding methods in relation to treatment selection bias. More information must be provided as to the baseline characteristics of patients in each of the four treatment groups. This is important since “non-randomised, retrospective studies, with apparent differences in baseline characteristics and prescription bias” may drive the results in one direction or the other (please see this review [citation 31 in your study] for further information: Focks JJ, Brouwer MA, van Oijen MG, Lanas A, Bhatt DL, Verheugt FW. Concomitant use of clopidogrel and proton pump inhibitors: impact on

Response: We have tried to add more baseline information as suggested. We described the baseline information for most of the available variables including age, sex and diagnoses. The variables actually are very limited because of register-based data sources. Also we have discussed the weakness regarding the potential bias with citation of the above review (PMID: 22851683).

Revisions: On page 8, lines 16-21, more relevant baseline information has been described.

(3) In the drug exposure section, you mention that typical PPI and clopidogrel prescriptions are for 90 days. Does it mean that you looked for only one 90-day prescription for each of these drugs (clopidogrel and PPIs) while categorizing patients into four drug exposure cohorts? Did you have patients with 30-day or 60-day prescriptions? If so, did you distinguish between different lengths of exposure? Please clarify.

Response: We did not restrict any prescriptions which may prescribe for 90 days, 60 days or 30 days. We identified our exposures from 30 days before entry day (the discharge date for cardiovascular disease) to 90 days after entry. As we know, the typical prescription for clopidogrel and PPIs is 90-day which meant our follow-up period could cover most of the prescriptions. It means if the patients have prescriptions for 30-day or 60-day, it will be definitely included in the study period.

(4) Further, it is mentioned that you did analysis with a 180-day and 360-day follow up? How did you define drug exposure for the patients in each of these longer follow up cohorts?

Response: Yes, we have analysed data with the 180-day and 360-day follow-up. We used the similar method to define drug exposure.
**Revisions:** On page 4, lines 20-24, some explanations have been added in the Method Section.

(5) In Table 2, the outcome definitions are not clear. For example, when analysing death as an outcome, who were included in the group that did not die (i.e., survived)? Did it include those with a CVD or MI related re-hospitalization? Similarly, in the CVD group, who were included in the non-CVD group? Also, please provide numbers in each of the outcome groups in Table 2. Finally, in Table 2, do the columns with heading “Cardiovascular disease” refer to re-hospitalization due to cardiovascular disease?

**Response:** We analysed our data as a cohort study design. In Table 2, when we analysing death as an outcome, all those did not die (including those with cardiovascular disease or myocardial infarction related re-hospitalization) were treated as censored. When we analysed cardiovascular disease as outcome, all of other status were regarded as censored.

In Table 2, the columns with heading “cardiovascular disease” do refer to re-hospitalization due to cardiovascular disease.

**Revisions:** We added numbers for the different groups of outcomes in Table 2.

(6) Comparing Tables 1 and 2, the columns are presented differently which is confusing. Specifically, Table 1 is classified into “Death” and “Re-hospitalization for cardiovascular disease” cohorts, whereas Table 2 is classified into “Cardiovascular disease” and “Acute myocardial infarction” cohorts. Please clarify why it was done that way.

**Response:** Sorry for any confusion. We agree with your points and now the tables have been re-arranged in the same format.

**Revisions:** Table 1 and Table 2 have been re-organized for the same style.

(7) Please provide numbers at each level of cohort selection, i.e., how many were selected in the upper GI group during 1987-2009 period, and then how
many were identified with first CVD event during 2006-2009. Further, please report how many died, had second event, migrated, and survived until 90 days. Finally, please report characteristics of the final cohort before you subdivide them into sub-cohorts in Table 1.

**Response:** In Table 1 and Table 2, “cardiovascular diseases” cohort is the main cohort. Cohort of acute myocardial infarction was the part of the “cardiovascular diseases” cohort. The related number has been added.

**Revisions:** In page 8, lines 16-21, more text has been added.

**Minor Revisions:**

1. Please clarify the actual study period. Specifically, the abstract and Figure 1 mention 2008 as the end of the period whereas in the text it is 2009.

**Response:** Sorry for the error. The correct study period is until 2008.

**Revisions:** The number “2009” has been replaced by “2008” on Page 4, line 14 and line 16.

2. In the Data Source section, is the “dispatch date” same as “prescription fill” date?

**Response:** Yes. In the discussion section (Page 10, lines 13-15), we have discussed the weakness to use “dispatch date” as “prescription fill” date in this register-based study.

3. Please provide more description of the “Swedish Prescribed Drug Register.” What information does it exactly contain for each of the prescribed drugs?

**Response:** More information of the “Swedish Prescribed Drug Register” has been provided.

**Revisions:** On page 5, lines 4-10, more descriptions of the Swedish Prescribed Drug Register have been added.

4. What do you mean by “emigrated” patients or “migration” of patients? How did it impact your cohort?
**Response:** “emigrated” patients or “migration” of patients in this study means the cohort members who moved to other countries from Sweden. We identified the cohort excluding subjects who moved out of Sweden before entry. Those patients may move into Sweden again shortly and can be possible to be included in the study cohort. Theoretically, those patients are different from the general populations because they may have specific medical demands.

(5) In the statistical analysis section, please clarify the difference between “study period” and “observed time period” to remove confusion for the reader.

**Response:** The two phrases are the same to describe the time period for study. In order to make it clearer, we replaced “observed time period” with “the defined study period”.

**Revisions:** Revision has been showed at Page 8, line 1-2.

(6) On page 9, in the section entitled “Patients with diagnosis of upper gastrointestinal bleeding before entry”, the sentence starting with “Current use of only clopidogrel….” is not clear. Please clarify.

**Revisions:** The sentence has been revised on page 9, lines 22-25.

(7) Please be consistent with using acronym (GI) or using full word for gastrointestinal. Same for CVD or cardiovascular.

**Revisions:** Acronyms GI have been used for all “gastrointestinal” now. Full words for “cardiovascular diseases” have been used instead of acronyms of “CVD”. Revisions have been done all through the manuscript.

Il Reviewer's report:

**Version:** 1 **Date:** 7 October 2013

**Reviewer:** Kathryn Momary

Thank you for providing me with the opportunity to review this manuscript assessing CVD risk in patients receiving concomitant PPIs and clopidogrel. The authors explore this question in a unique patient population.
Major concerns:

• The authors do not differentiate between those PPIs most likely to effect clopidogrel and those less likely. This needs to be at least discussed or mentioned in the background and methods.

Response: It is very appreciated for the pertinent comments. We did try to differentiate PPIs to see if different types of PPI affected clopidogrel differently. The major PPIs types available in Sweden included omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. Unfortunately, it is not possible to analyse PPI separately due to limited sample size. This has been described in the Method Section at page 6, lines 4 to 6. We also added some text in Discussion at Page 10, lines 16 to 18.

Revisions: More text has been added in Discussion Section at page 10, lines 16 to 18.

• The inclusion criteria as it relates to CVD are quite wide. Specifically the inclusion criteria are AMI, stroke and angina. In the US, clopidogrel is not routinely used for stroke or angina. Please justify the inclusion of these disease states into your study.

Response: The cohort members we defined in this study included acute myocardial infarction, stroke and angina. It would be good to have a cohort include potential patients as many as possible which guaranteed a stable comparison between clopidogrel use and concomitant use of clopidogrel and PPIs. We also separated acute myocardial infarction from other cardiovascular disease. The result of the sub-group is consistent with the overall cohort.

• Since the majority of CVD patients will receive both aspirin and clopidogrel, their exclusion makes this data difficult to interpret. This definitely limits the clinical applicability of this manuscript and this needs to be addressed by the authors.

Response: We agreed that aspirin might be prescribed commonly along with clopidogrel which has been discussed in the Introduction section. However, some studies discouraged the dual anti-platelet treatment because it increased risk of GI bleeding. For this study, we focused on the combined effect of clopidogrel and PPIs in cardiovascular disease with high risk of gastrointestinal bleeding. Obviously
aspirin may confound the real effect of concomitant use of clopidogrel and PPIs. Although, we analysed data including aspirin initially, we decided to exclude aspirin from this study in order to focus on the study aim.

- The different PPIs used needs to be described in table 1.

**Response:** As we described, we have tried to differentiate different PPIs in the analysis but cannot because of few cases in the different types.

- The authors do multiple sub-group analyses (time of bleed and different types of CVD). This is complicated and the text in the results does not clearly outline the different groups. Perhaps breaking the results up into section by subgroup analysis would make this clearer.

**Response:** The results have been re-organized. Based on Table 1 and Table 2, we divided the Results Section into three parts. The first part is about general characteristics of the cohort members. The second one is about results of cardiovascular disease cohort. The third one is about results of acute myocardial infarction cohort. Sub-analysis based on time of bleeding has been combined into the latter parts regarding results of two cohorts.

**Revisions:** More text for description of acute myocardial infarction has been added on page 9, lines 13-18.

- The authors only cite and discuss literature that supports an interaction between PPIs and clopidogrel. However, there is a significant amount of literature where no interaction was seen. The 3rd paragraph of the discussion section needs to more clearly describe the totality of literature related to this topic.

**Revisions:** More text has been added at the 3rd paragraph of the Discussion Section (page 11, lines 9-25; page 12, lines 1-7) regarding interaction or no interaction between PPIs and clopidogrel.

**Minor comments:**
- Abstract: Please explain what CVD encompasses in the abstract.
**Revisions:** On page 2, lines 5-6, text for description of specific cardiovascular disease has been added.

• Please provide a reference for the co-morbidity scoring system used.
**Response:** We developed the co-morbidity scoring system based on the Swedish Patient Register. Reference has been added on page 7, line 6.

• The authors state in the last paragraph of the methods section that patients who had a GI bleed after the study period are at increased risk of bleed during the study period. This needs a reference to support the statement.
**Response:** Sorry for the confusion raised. What we would like to present is that if a patient have any experiences of GI bleeding, no matter it happens before the cardiovascular disease diagnosis, or after the cardiovascular disease diagnosis, it indicated the patient is liable to suffering from GI bleeding. In this study, the mainstream of study subjects are patients who had history of GI bleeding. They contributed to the main results which we analysed it specifically. Both of results are quite similar.

• The second sentence in the results section does not make any sense. Please revise.
**Response:** The sentence has been modified.
**Revisions:** On page 8, lines 16-21, the sentence has been revised.

• While table 2 shows both the CVD cohort and the AMI cohort, this is never clear in the text and the different results aren’t discussed.
**Response:** As we discussed above, the results section has been re-organized. Now the different results from CVD cohort and the AMI cohort has been discussed and compared.
**Revisions:** On page 9, lines 5-18, the results section has been re-organized and revised.

• The last sentence of paragraph 2 in the discussion section does not make sense.
**Revisions:** On page 11, lines 5 to 7, the last sentence of paragraph 2 has been rewritten.