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.

(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 platelet function and clinical outcome- a systematic review. Heart. 2013 Apr;99(8):520-7. doi: 10.1136/heartjnl-2012-302371. Epub 2012 Jul 31. Review. PubMed PMID: 22851683.).

(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.

(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?
(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?

(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.

(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.

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.

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

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

(4) What do you mean by “emigrated” patients or “migration” of patients? How did it impact your cohort?

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

(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.

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

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.