Reviewer’s report

Title: Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in chemoprevention of hepatocellular carcinoma: A nationwide high-risk cohort study

Version: 0 Date: 25 Sep 2017

Reviewer: Michael Barone

Reviewer’s report:

The study of Ho et al., enrolling a large number of patient, describes the effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in chemoprevention of hepatocellular carcinoma. Although, the statistical approach of the study is well done, there is a major problem in the study design since they compare the effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in two groups that both assumed the two drugs and differ only for the length of treatment.

In addition, they found that the therapy with ACEI or ARB even increase the risk of HCC development in patients without cirrhosis and other major risk factors (aOR, 4.53) but neither give the "p" value for their results, nor declare the exact number of patients that developed HCC in the two groups, nor give any explanation for this result that is just mentioned in the discussion.

Minor comments:

1. Both in the abstract and materials and methods, the difference in ACEI or ARB exposure between the groups with "Initial exposure" and "Initial non-exposure" is not mentioned at all and the reader has to wait for table 2B to find out this description.

2. In the first page of the introduction (pages are not numbered) (lines 52-55), references 16 and 17 report controversial data on metformin and NSAIDs, but the phrase is misleading since it comes after a larger list of drugs, including ACEI and ARB. Moreover, the authors should include a broader spectrum of studies in favour of the protective effect of ACEIs and ARBs to offer to the reader a more objective and equilibrated picture of the issue (Facciorusso et al. J Gastroenterol Hepatol 2015).

3. The same papers should be mentioned in the following page together ref. 25 and 26.

4. The point 3 (lines 55-58) of the second page describing "cohort selection" is not clear.

5. In the "Statistical analysis" section (line 52), HBC should be HBV.
6. In the 4th page of the "Results" it is reported that "In the subgroup without any comorbidity (cirrhosis, DM, and hyperlipidemia), ACEIs and ARBs posed a significant risk in the HCV cohort (aHR: 4.53, 95% CI: 1.46-14.1)"; what about "p" value?

7. The discussion does not take in consideration the differences/comparison with the studies supporting a role of ACEI and ARB in HCC prevention, trying to explain the opposite conclusions of the present study.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.