Author’s response to reviews

Title: Head to head comparison of Prasugrel versus Ticagrelor in patients with Acute Coronary Syndrome: A systematic review and meta-analysis of randomized trials

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POINT TO POINT RESPONSE TO REVIEWERS

Reviewer reports:

Simone Brogi, Ph.D (Reviewer 1):

The authors previously declared that only an indirect comparison between prasugrel and ticagrelor have been conducted until now and the aim of this work is: "we aimed to perform a head to head comparison of the adverse clinical outcomes associated with prasugrel versus ticagrelor in patients with acute coronary syndrome (ACS)". So, firstly, I think is impossible to carry on a meta-analysis study.

After that, they said that they are going to compare the recently published cohorts, citing [5], where the authors effectively compare the two antiplatelet drugs. So this first part of the paper results a little bit confusing and need some clarifications.

Author’s response: I think the reviewer did not understand our point. Due to lack of data comparing prasugrel with ticagrelor, only network meta-analyses were published whereby there was an indirect comparison between prasugrel and ticagrelor because at that time, there was
hardly original studies which directly compared prasugrel with ticagrelor. Prasugrel was often compared with clopidogrel, but not with ticagrelor. Ticagrelor was also often being compared with clopidogrel, but not with prasugrel.

However, in our meta-analysis, we directly compared prasugrel with ticagrelor in patients with acute coronary syndrome since we have been able to extract direct data from recently published studies. Presently, with the availability of direct data from recently published trials, a meta-analysis could easily be conducted.

Through a meta-analysis, we have systematically compared drug A with drug B. The authors meant that no study has systematically compared ticagrelor with prasugrel using direct data obtained from randomized trials. Therefore, our aim was to directly compare these 2 drugs through a meta-analysis of randomized controlled trials. Thank you.

Simone Brogi, Ph.D (Reviewer 1):

page 6 The authors built a statistical analysis based only on 563 patients?? A meta-analysis study used to assess previous research studies to derive conclusions about that body of research. And so the benefit of this kind of study is to obtain a quantitative review of a large literature. So the selection of only 4 publications for a total of 563 patients, seems too weak for this kind of study.

Author’s response: Thank you for raising up this point. However, after a thorough search, we ended up with only 4 trials which directly compared prasugrel with ticagrelor. In addition, one study had a larger number of patients compared to the others, but in order for the result of this analysis not to be influenced by the result of the trial with the large number of patients, we had to reduce its number of patients to 200, and then include this number in our analysis. Hope the reviewer will be able to understand our two strong points: 1. Only 4 randomized trials were available, therefore we had no option to include more trials. 2. One among the studies had more than 500 patients being treated with ticagrelor and prasugrel respectively. However, because all the other 3 studies had small number of patients, and in order for the result of this analysis not to be influenced by the one study with large number of patients, we had to include only a proportion of 200 patients for each group to maintain a balance, or else the results would have been affected.

These points have been mentioned in the limitation section of the manuscript too. Thank you.
Simone Brogi, Ph.D (Reviewer 1):

page 1 row 48 while OR and CI are defined P is not define please define it.

Author’s response: Thank you. This has been defined appropriately.

Simone Brogi, Ph.D (Reviewer 1):

page 3 row 12 published till date should be published until date

Author’s response: thank you. Appropriate changes have been made.

Simone Brogi, Ph.D (Reviewer 1):

page 3 row 20 Morici et al should be Morici et al. please correct it also in the main text

Author’s response: thank you. We have corrected it appropriately.

Simone Brogi, Ph.D (Reviewer 1):

page 5 ref 10 should be formatted following the journal guidelines

Author’s response: Thank you. We have formatted it appropriately.

Simone Brogi, Ph.D (Reviewer 1):

page 6 row 14 In order to level out all the numbers presented, the authors have to add "ninety-seven" or have to remove the others.

Author’s response: Appropriate changes have been made. Thank you.

Simone Brogi, Ph.D (Reviewer 1):

page 6 row 52 Motovska2016 and Laine2014 the refs should be formatted following the journal guidelines. Please check also the bibliography format at the end of the manuscript

Author’s response: Thank you. Appropriate changes have been made.
QiPing Feng, Ph.D. (Reviewer 2): The authors conducted a meta-analysis of head-to-head comparisons of Prasugrel and Ticagrelor. It is an interesting topic. Here are some concerns.

(1) ~500 is small for meta-analysis.

Author’s response: Thank you very much. As mentioned above, we have already given our solid reasons why only a small number of patients was included. 1. Only 4 randomized trials were available, therefore we had no option to include more trials. 2. One among the studies had more than 500 patients being treated with ticagrelor and prasugrel respectively. However, because all the other 3 studies had small number of patients, and in order for the result of this analysis not to be influenced by the one study with large number of patients, we had to include only a proportion of 200 patients for each group to maintain a balance, or else the results would have been affected.

These points have been mentioned in the limitation section of the manuscript too. Thank you.

QiPing Feng, Ph.D. (Reviewer 2):

(2) It is not clear to me, I suggest the authors to add more discussion of why comparison of Prasugrel and Ticagrelor is clinically important. They have different mechanisms? They target different patients? One is more efficacious or safer than the other.

Author’s response: Thank you. The discussion section has further been improved accordingly.

QiPing Feng, Ph.D. (Reviewer 2):

(3) I suggest to add some discussion among Prasugrel, Ticagrelor and clopidogrel.

Author’s response: Thank you. We have added some discussions about these 3 drugs.

QiPing Feng, Ph.D. (Reviewer 2):
(4) Even though some endpoint were only measured in one out of four studies, it would still be interesting to discuss some of them.

Author’s response: Thank you. We have discussed those endpoints too in the revised manuscript (nephropathy and dyspnea were mentioned, and platelet activities were already discussed).

QiPing Feng, Ph.D. (Reviewer 2):

(5) Is it possible to adjust/or stratify by T2DM?

Author’s response: No. This would be interesting but however, it was impossible to compare because only 1 among the 4 studies reported patients with diabetes mellitus. The other studies had a mixture of the general population with acute coronary syndrome. Therefore, an analysis strictly based on patients with diabetes mellitus was not possible. Thank you.