Author’s response to reviews

Title: Consequences of continuing renin angiotensin aldosterone system antagonists in the preoperative period: a systematic review and meta-analysis

Authors:

Qiong Ling (lingqiong2000@163.com)
Yu Gu (hospitalgirl7@aliyun.com)
Jiaxin Chen (chenjx1298@163.com)
Yansheng Chen (gammac@126.com)
Yongyong Shi (syy211@hotmail.com)
Fenggao Zhao (zhaogaofeng_97@163.com)
Qianqian Zhu (zhu.qian.qian123@stu.xjtu.edu.cn)

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Author’s response to reviews:

Savino Spadaro

BMC Anesthesiology Editorial Office

Dear Professor Savino Spadaro,

Thank you very much for the Reviewers’ Comments concerning our manuscript entitled “Consequences of continuing renin angiotensin aldosterone system antagonists in the preoperative period: a systematic review and meta-analysis (BANE-D-17-00313)”.

We studied the comments carefully and took all the comments into full account in revising our manuscript. We agree that all the comments have helped improving our manuscript.

A list of responses according to the Reviewers’ Comments is appended below.
We wish our revised manuscript is acceptable for publication in BMC Anesthesiology.

Yours sincerely,

Qianqian Zhu
M.D., Ph.D.

Responses according to the Reviewers’ Comments and Editorial Policies

Reviewer 1 question #1: Information about the type of included studies (RCT, observational, etc.) are not well presented. Please include these information in the abstract and in the table of included studies and add information of patient numbers to the table of included studies.

Response: We thank the Reviewer very much for this suggestion. We included the type of studies and number of participants in Table 1 in revised manuscript.

Reviewer 1 question #2: As critical complications after general anaesthesia and elective surgery are rare, please comment if patient numbers in the included studies are big enough to show a significant difference in developing these types of complications.

Response: We thank the Reviewer very much for this comment. It is true that critical complications after general anaesthesia and elective surgery are rare, especial in single study. The present systematic review and meta-analysis was aimed to investigate the difference of complications between patients who taking and not taking ACEIs/ARBs on the day of their scheduled surgery. A systematic review and meta-analysis could include as many studies and participants as possible to make the number of participants big enough to show a statistical significant differences which was could not be concluded in a single study because of rare incidences. However, the results of meta-analysis were depended on the included studies totally. We have to admit that the included studies varied in design and quality, and no RCT identified that involved a large number of participants which would limit the statistical power of the results of the present study. We thank the Reviewer for this comment again and mentioned the limitation of our study in the Discussion part.
Reviewer 1 question #3: Today discontinuation of ACEIs/ARBs before elective surgery is mostly performed for surgery with a high-volume need (e.g. intraabdominal or large orthopaedic surgery). Do studies make a differentiation between these types of surgeries. Can you perform a subgroup analysis for this type of surgery?

Response: We thank the Reviewer very much for this suggestion. There are two studies (Calloway, 2014 and Zainudheen, 2017) involved in large orthopaedic surgery. We performed a subgroup analysis and the results are listed in Table 2. We could not perform a meta-analysis about intraabdominal study because there is only one study included is pertinent to elective bariatric surgery (Salvetti, 2016).

Reviewer 2 question #1: The manuscript should be revised by a native Speaker

Response: We thank the Reviewer very much for the concerns. We have English native speakers from language editing service to help edit our manuscript. The certificate was submitted.

Reviewer 2 question #2: Why was Hypotension Chosen as main endpoint rather then harded endpoints (those defined as secondary)

Response: We thank the Reviewer for this concern very much. Firstly, ACEIs/ARBs are primary used as antihypertensive medications, but also for treating chronic heart diseases or other diseases. It was noted first that these drugs were related to hypotension and even refractory hypotension during the administration of anesthesia. Then, some hard endpoints like cardiac complications or kidney complications were noticed most because of hypotension. Therefore, the hypotension was chosen as main endpoint for it was the main reason of other hard endpoints. Secondly, the incidences of hypotension were much higher than other complications which were fairly rare. The hypotension was reported in more studies that the hard endpoints which were not mentioned or did not happen in some studies. We define the hypotension as main endpoint would include as many studies as possible. Last but not least, we analyzed hard endpoints as detailed as possible though only seven studies reported these complications.

Reviewer 2 question #3: Define and justify substudies in methods; why was not a subgroup analysis of RCT vs observational design conducted? There was a relevant heterogeneity how in the subgroup analyses;

Response: We thank the reviewer very much for these suggestions. We mentioned subgroup in the methods in the revised manuscript. Meanwhile, we did sensitivity analysis according to the type of included studies according to the suggestion of Reviewer which was listed in Table 2.
Reviewer 2 question #4: There was a significant heterogeneity also in the subgroup analyses; alternative subgroups to explain this?

Response: We thank the reviewer very much for these concerns. The included studies varied in design and quality which might account for the significant heterogeneity. Though we did subgroup analyses, the heterogeneity still existed because the varied types of studies. We mentioned these as limitations in revised manuscript and add sensitivity analyses help to strengthen the understanding of results. The added results are list in Table 2. The quality of observational studies was also assessed with the use of the Newcastle–Ottawa Scale (NOS). (Table 1)

Reviewer 2 question #5: Cardiac surgery is a quite different Setting compared to noncardiac surgery, it should be justified why the authors decided to pool both types of surgery

Response: We thank the reviewer very much for this comment. The included studies were involved in cardiac surgeries and noncardiac ones. We pooled both types of surgeries for all of them were elective operations. We want to know the general effects of continuing ACEIs/ARBs on patients who were scheduled for elective surgeries. However, we thank the reviewer very much for the concern and add subgroup analyses for cardiac surgery, major vascular surgery and noncardiac surgery. The results are list in Table 2.

Reviewer 2 question #6: How did you take into account confounders for the results in observational studies

Response: We thank the Reviewer very much for this concern. An “excellent” meta-analysis should include all RCTs without heterogeneity existing between studies. However, the present study included more observational studies than RCTs. In order to investigate the effect of continuing ACEIs/ARBs from as many study as possible, we not only pooled the results of all the included studies but also make subgroup and sensitivity analyses to help know more about the effects. Thank the reviewer very much for this comment and we add sensitivity analyses including observational studies and RCTs superlatively. The results are list in Table 2.

Reviewer 2 question #7: Please assess and report formally Quality of evidence

Response: We thank the Reviewer very much for this suggestion. The quality of observational studies was assessed with the use of the Newcastle–Ottawa Scale (NOS) added to Table 1.
Reviewer 2 question #8: Half of the available publications (12/24) was excluded based on "endpoint conflict and no available data"; please expand on this, further please state if you contacted the others of the publications were data were not available.

Response: We thank the Reviewer very much for this concern. We are very sorry that we did not state clearly only published data were included in the present study. We add the statement in methods part in our revised manuscript. The blood pressure in the excluded studies was expressed as median with 95% confidence interval, MAP, or definite change value. No available published data could be extracted and meta-analyzed with the included studies.

Reviewer 2 question #9: Please check the correctness of line 167 ("the difference remained significant...")

Response: Thank the Reviewer very much for the comment. We have revised it in our revised version. Thank the Reviewer again.

Editorial Policies

We have read the editorial policies and provided the information required.