Reviewer’s report

Title: IMPACT OF RENIN-ANGIOTENSIN SYSTEM INHIBITORS CONTINUATION VERSUS DISCONTINUATION ON OUTCOME AFTER MAJOR SURGERY: PROTOCOL OF A MULTICENTER RANDOMIZED, CONTROLLED TRIAL (STOP-OR-NOT TRIAL)

Version: 0 Date: 08 Oct 2018

Reviewer: Iacopo Cappellini

Reviewer's report:

Dear Authors,

congratulations for the trials you created on this topic still debated. However, based on latest recommendation, it is not still suitable for publication and need major revisions. You will find comments as bullet points referring to page and line in the manuscript.

Best Regards

Abstract

Methods: repetitive word randomized in "this is a multicenter randomized, open-labeled randomized…"

Background

Page 1 line 14 and 19: 8 and 9 references are the same article

Page 2

Line 6: the sentence "we aim at evaluating the impact of a strategy…..". The authors already stated the purpose of the study at the end of page 1

Line 12: repetitive word randomized in "this is a multicenter randomized, open labeled randomized…"
Line 14: word to be corrected "intuitional" with institutional. It is also necessary to provide ethical committee registration number.

Line 17: title of the study in clinical trials.gov is "Impact of Renin-Angiotensin System Inhibitors Continuation on Outcome After Major Surgery (STOPorNOT)" and is slightly different from the one indicated in the present manuscript. Is there a reason for this adjustment. Anyway the title in the present protocol is more appropriate than the one in clinicaltrials.gov.

Line 18: authors need to be more specific about randomization. It is necessary to provide how electronically you performed the allocation (i.e. a website). If it is block randomization (i.e. 1:1, variable block). Allocation concealment is not mentioned. It is suggestable to follow guidelines in BMJ 2016;355:i5663 "Allocation concealment in randomised controlled trials: are we getting better"

Line 40: considering that is not possible to perform a double blind study, is it possible to know clinicians or research assistant involved in the study are blind to treatment regimen arm? Please specify.

Line 50: why did you choose 48 hours for withholding RASi. It is necessary a reference

Page 3

Line 10: did the authors included only patients undergoing general anesthesia or also considered patients candidate to receive neuraxial anesthesia or peripheral nerve block? Why orthopedic surgery was not included? Why is not mentioned in the inclusion and or exclusion criteria?

Line 23: why did you considered only patients treated RASi for more than three months?

Page 4

Line 13: do the authors have any expectations on primary endpoint (i.e. a percentage of reduction of overall postoperative complications)? I guess that, based on sample size calculations at page 6 line 35, it is expected the continuation of RASi is beneficial than withholding these drugs. Please specify
Line 53: as in the primary endpoint do you have any expectations about secondary endpoint?

Page 5:
Line 45 what's the role of endpoint adjudication committee? Assessing the relevance of complications occurred? Please specify

Page 6
Line 6 How do the authors manage missing data, internal inconsistencies and range errors. Did the authors plan a statistical analysis plan (SAP)?

Line 37 statistical analysis is well described in supplementary materials but both in the latter and in the manuscript there is no reference of which software has been used to perform the calculation and will be used for statistical analysys.

Line 40 Based on my sample size calculation 2188 patients are necessary. Did the authors considered a drop-out number. Please specify.

Line 42 Here is the primary endpoint. It is suggestable to mention 20% relative decrease also in page 4 line 13

Page 7
Line 13 Are the authors sure that results of this trial should result in "new guidelines regarding best management of medications"? actually, as the authors mentioned in the manuscript, RASi continuation has an evidence IIa level b of recommendation; maybe the results of the present study will reinforce and improve this level.

Line 30 I guess the study has been registered on December 15 2017 (instead 2018)
Line 11 Please specify consent for publications, availability of data and materials and number of ethical committee approve

Spirit Checklist

13 schematic diagram is missing. It is suggestable to have it
17 a and b blinding measure. If not applicable specify
18 b you need to specify plans to promote participant retention and complete follow up
22 and 23 specify reporting adverse events and management
25 any communications about protocol amendments
31 a b c please specify authorship eligibility

Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

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

Not suitable for publication unless extensively edited

Quality of figures
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

Statistical review
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.
**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

Were you mentored through this peer review?

No