Author’s response to reviews

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)

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Author’s response to reviews:

Dear Editor,

We would like to thank you for giving us the opportunity to submit a revised version. We also thank the reviewers for their careful assessment of the manuscript and their comments, which allowed us to improve the quality of the manuscript. We have replied point-by-point to the reviewers’ comments. Our replies are provided below. All modifications appear in red in the revised version of the manuscript.

As before, all authors have approved the revision and none of the contents have been published elsewhere.
We hope that this revised version of the manuscript will satisfy the editorial team and the reviewers. We remain at your entire disposal for any further indication.

Sincerely yours

Pr Legrand, on behalf of the authors

Reviewer #1: na

Reviewer #2: Thank for the opportunity to review the manuscript entitled: "RENIN-ANGIOTENSIN SYSTEM INHIBITORS CONTINUATION VERSUS DISCONTINUATION ON OUTCOME AFTER MAJOR SURGERY: PROTOCOL OF A MULTICENTER RANDOMIZED, CONTROLLED TRIAL (STOP-OR-NOT TRIAL)". This is a protocol for a randomized controlled trial in which the intervention is the timing of RASi discontinuation before major surgery. This is a very important clinical question and this trial aim is to inform clinical practice. The results may lead to a rapid change in prescription habits before major surgery.

Reply : thank you for your encouraging comments.

Below is a summary on major and minor issues with this manuscript:

Major comments:

1. I am very concerned about the primary outcome for this study which is a rather inclusive definition of major post-operative complications after cardiac surgery. As suggested by multiple authors[1-4], the components of a composite endpoint should be 1) Similar in importance for the patient, 2) Occurring by a similar frequency and 3) likely to be affected to a similar degree by the intervention. Unfortunately, I feel that none of the above apply to the selected composite outcome. Please consider the following:

   o De novo AF or urinary tract infection will be considered to have an importance similar to death, stroke or dialysis. Moreover, K=5.6 would not be considered severe hyperkaliemia and only one administration of insulin/glucose should not be together with death in a composite outcome.
It is likely that some components will not move in line with each other with the proposed intervention (e.i. hyperkaliema/hypertensive crisis vs cardiogenic shock

Some components are unlikely to be affected by the intervention: venous thrombosis, infection...

Reply: we thank the reviewer for rising this important point. We agree that the primary endpoint might include outcomes of different severity. We however consider these outcomes as important considering the global outcomes after major surgery.

Regarding the opposite direction of hyperkalemia, we believe this remain an important outcome which should be included in the primary endpoint since it is considered as an important side effect of patients treated with ACEi or ARB, especially when renal failure occurs. In this line, incidence of AKI and hyperkalemia are expected to move in the same direction. Furthermore hyperkalemia has been associated with increased risk of poor outcome and death in many observational studies. This reinforces the relevance of this outcome.

Others items of the combined endpoint are expected to be affected but the renin-angiotensin system blockage. Thrombosis has been linked to the angiotensin activity (we provide extra references with this respect[1][2][3]). Finally, angiotension II-associated vascular dysfunction and the microcirculation is likely to impact global post-operative outcomes including surgical complications[4][5]. These points guided the scientific committee of the study to propose this combined endpoint.


Additionally, there is some imprecisions:

In the main text, AKI is not in the primary composite (only dialysis is) but it is in the detailed definition in the supplementary material. Is AKI (KDIGO) in the composite outcome or not? Furthermore, is both the creatinine criteria and the urine output criteria will be used.

Reply: We thank the reviewer for her/his careful reading of the manuscript. This point was indeed unclear. AKI was part of the composite endpoint (not only dialysis). Only the creatinine biomarker will be considered due to lack of accuracy of urine output monitoring after major surgery (especially for patients outside the ICU). We have clarified these different points in the discussion.

For respiratory complications: I suppose it refers to re-intubation and exclude the use of PPV immediately after extubation?

Reply: this is correct. This excludes any « preventive » use of ventilator support. We have mentioned this point in the revised version of the manuscript.
For the outcome: Episodes of hypotension requiring vasopressors administration during anesthesia and surgery, I would recommend being more specific. Minimum duration? What agents are considered vasopressors. Only bolus counts of increase in infusion rate. Etc..

Reply : Thank you for allowing is to develop this point. The definition of hypotension is indeed not consensual. The scientific committee of STOP-or-NOT therefore suggested defining hypotension as a mean arterial pressure below 60 mmHg. We agree that the type of vasopressors was not mentioned and we added it in the revised version (i.e. ephedrine, epinephrine, norepinephrine, or neosynephrine). Bolus and continuous infusion will be considered. Lowest arterial pressure, duration of hypotension and total doses of vasopressors will be collected and reported as well.

Duration of vasoactive agents would be important to report because this is a criteria that will prevent patients to be discharge from the intensive care unit

I think this merits careful consideration and honestly think this important study should include hard patient-centered outcomes as the primary outcome considering a sample size of more than 2000.

Reply : we thank the reviewer for the comment. The use of vasopressors in the post-operative period and un-planned admission to the ICU or prolonged stay in the post-recovery room for vasopressors infusion will be collected.

2. Concerning the stratified randomization. Will the heart failure category only include HFrEF or also HFpEF. (RASi have not been formally proven to reduce mortality in HFpEF).

Reply : even though LVEF will be collected when available, stratification will be based on the NYHA status (NYHA ≥2). We have specified this point in the revised version.

3. I would suggest to note the nature of the medication because some agents have longer half-life (telmisartan, trandolapril) and this might be a good idea to do a post-hoc sensitivity analysis.
In an ideal situation, obtaining blood levels and comparing them (as a substudy) would further support the hypothesis.

Reply : we thank the reviewer for the proposal. Performing such a ancillary study will be possible since the nature of the treatment will be collected.

4. Will the timing for re-institution of the RASi be reported?

Reply : We suggest the attending physician to resume the treatment as soon as possible after surgery. The date of re-institution is indeed being collected.

Minor comments:

Please include a sentence to say if the mineralocorticoids antagonists are included in the intervention (spironolactone, eplerenone, amiloride)

Reply : the mineralocorticoids antagonists are not included in the intervention. We added a sentence which reads : « Patients treated with angiotensin converting enzyme inhibitors or angiotensin receptors antagonists will be included. Mineralocorticoids antagonists are not included in the intervention ».

Please verify if patients are on Entresto. This has a potential to influence the outcome.

Reply : Treatment with Entresto is being collected indeed.

Figure 1 is confusing for the reader. The nature of the "profile A, B, C" is not entirely clear to me and the legend does not explain.
Reply: The profile of « A, B or C » refers to the treatment scheme (medication usually taken, on the morning, the evening or both). We have mentioned this point in the legend of the Figure.

"These recommendations are based on few data suggesting an increased risk of overall complication after RAS inhibitors discontinuation in the peri-operative setting while intra-operative hypotension can be managed with available vasoactive drugs during anesthesia. " Please offer reference supporting this sentence.

Reply: We have added the following references supporting this sentence[6][7][8].


Please review the manuscript for grammatical errors:

Introduction:

"It is much likely" change for "It is most likely…"

"American heart association": capitalize each words

exclusion criteria: remove: Inability to obtain informed consent from the patient (redundant with inclusion criteria)

Reply : we apologize for the typos and have made the corrections.

Design:

"We aim at evaluating the impact of a strategy of RASi continuation or discontinuation on perioperative complications in patients undergoing major non-cardiac surgery. " This sentence is more appropriate in the introduction.

Reply : We have moved this sentence at the end of the introduction.

"This is a multicenter randomized, open-labeled randomized controlled trial in more than 30 French centers. " Randomized is here two times in the sentence.

Reply : sorry for the mistake. We corrected the sentence.

"intuitional review board": change for institutional
Reply: sorry for the mistake. We corrected the sentence.

"The randomization will be performed after the anesthesiology consultation after information provided and patient written consent being obtained. " Change for "The randomization will be performed after the anesthesiology consultation after informed written consent has being obtained."

Reply: Thank you. We corrected the sentence.

"print out" change for printed

"hand" to handed

"….and good appliance to the protocol. " Change to and proper application

"In the experimental group, RASi will be continued with a intake the day of the surgery, while the treatment will be stopped 48h prior the surgery in the control arm (Figure 1). " Change for : In the experimental group, RASi will be continued including of the day of the surgery, while the treatment will be stopped 48h prior in the control arm (Figure 1). "

"All patients will receive a leaflet in which they will record the stopping or RASinhibitors continuation. " Change for "All patients will receive a leaflet in which they will record the discontinuation of the RASinhibitors"

"The authors have been founded by": change for "…have been funded by"
Reply: Thank you. We addressed these points and made the corrections.

References


Reviewer #3: Dear Authors,

congratulations for the trials you crated on this topic still debated.

Reply: Thank you for the encouraging comment.

However, based on latest recommendation, it is not still suitable for publication and need major revisions. You will find comments as bullet points refereing to page and line in the manuscript.

Best Regards
Abstract

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

Reply: thank you for your careful reading. We made the correction.

Background

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

Reply: We made the correction.

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

Reply: We removed this sentence.

Line 12: repetitive word randomized in "this is a multicenter randomized, open labeled randomized…"

Reply: We made the correction.

Line 14: word to be corrected "intuitional" with institutional. It is also necessary to provide ethical committee registration number.

Reply: We made the correction.

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.

Reply: there is not reason for the title to be different. However, since it is not possible to modify the clinical trial, we have chosen to keep the later title.
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”

Reply : Thank you for the suggestion. We have provided more details regarding randomization. The text now reads: “The randomization will be performed at the CRU “Lariboisière-St Louis” and stratified by center and on the chronic heart failure status (NYHA stage >=2). The randomization list will be developed by a different biostatistician from the biostatistician who will conduct the final analysis within the CRU “Lariboisière- St Louis”. The list will be inserted into the Clean Web-based software and then forwarded to the sponsor’s quality insurance team for validation. The randomization will be performed on the day of written consent obtainment by Web (CleanWeb) software, which assigns the patient a randomization number. Randomization will be performed randomly by blocks of 4 or 8 with allocation concealment.”

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.

Reply : Indeed, research assistant and experts of the adjudication committee will be blinded of the group assignment. Clinicians in charge of the patients will not be blinded. We have mentioned this point in the revised version of the manuscript.

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

Reply : We have chosen 48 hours to avoid any remnant effect on the renin-angiotensin-system blockage after stopping the treatments. We have added a reference on this point.
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?

Reply: only patients receiving general anesthesia could be enrolled. However, patients having combined general anesthesia together with neuraxial anesthesia or peripheral nerve block could be enrolled. This information is being collected.

Orthopedic surgery could be included. Since the submission of the current manuscript, the definition of major surgery has been slightly adjusted and now reads: « surgery with an expected duration of more than 2 hours from the surgical incision and a post-operative hospital stay of at least 3 days »

These points have been mentioned in the revised version of the manuscript.

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

Reply: We didn’t want to include patients recently treated with ACEi-or ARB due to possible changes in hemodynamic status or renal function soon after initiation of these treatments.

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

Reply: that’s correct. We have mentioned the sample size calculation and the expected decrease of the incidence of the primary endpoint in the revised version of the manuscript.

Line 53: as in the primary endpoint do you have any expectations about secondary endpoint?
Reply: the secondary endpoints are exploratory and we do not have a sample size calculation. We do however expect that continuation of the treatment won't increase the incidence of potential side effects (i.e. AKI, hyperkalemia).

Page 5:

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

Reply: The role of endpoint adjudication committee is to increase internal validity of the trial. Since a double-blinded RCT was not feasible (too many placebos would have been necessary), we have chosen to validate the endpoint by a blinded adjudication committee.

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)?

Reply: We detailed the statistical analysis in the supplement. The statistical plan will be finalized before validating the final dataset.

The main analysis will be performed on all patients included in the trial, according to the intention to treat principle. Only patients who have withdrawn their consent may be excluded from the analysis; patients who have decided to stop follow-up or who have been lost to follow-up will be included in the analysis. Any missing value will be replaced by the previous value if available (so-called "last value carried forward" method). Sensitivity analyses to missing values will also be carried out, using a multiple imputation method (MICE, multiple imputation by chain equations).

Regarding internal inconsistencies and range errors, automatic checking procedures have been implemented into the electronic CRF. Moreover, random verification procedures will be carried out regularly to look for potential source of inconsistencies.

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 analysis.
Reply: We have specified the software used in the revised version of the manuscript. All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

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

Reply: The sample size calculation indicates 2222 patients after 2 interim analysis. These points are mentioned in the supplementary file.

<table>
<thead>
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<th>P value</th>
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<td>0.0375</td>
</tr>
</tbody>
</table>

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

Reply: thank you for the suggestion and have mentioned this point.

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.
Reply: we agree with the reviewer and have mentioned that the study « would impact guidelines on the strategy of RASi continuation or withholding before major surgery ».

Line 30 I guess the study has been registered on December 15 2017 (instead 2018)

Reply: The first version was published on December 15 2018 and last updated in July 2, 2018. We modified the text.

Page 8

Line 11 Please specify consent for publications, availability of data and materials and number of ethical committee approve

Reply: We modified the text. We added this information and have further detailed the chapter on data management.

Spirit Checklist

Reply: we have mentioned that the protocol follows the SPIRIT guidelines.

13 schematic diagram is missing. It is suggestable to have it

Reply: we have included a schematic diagram as suggested as a Table at the end of the manuscript.

Selection visit

Day -60 to

Day -3
### Inclusion

- **Day -30 to Day -2**
  - (anesthesia consultation)
- **Day -1 Day 0**
  - (surgery)
- **Day 1 Day 2 Hospital discharge or Day 7**
  - Follow up visit by Day 28

**Verification of inclusion and exclusion criteria**
- X
- X

**Informed consent**
- X
- X

**Signature of consent**
- X

**Medical history / comorbidities**
- X
- X

**Clinical examination/ arterial pressure measure**
- X
- X
- X
- X
- X
- X
- X

**Anesthesiology consultation**
- X

**Concomitant medication**
- X
- X
- X
- X
- X
- X
- X
- X

**Pregnancy test**
- X
- X*

**Randomization**
- X

**Phone by study clinical technician**
- X (Day-3)

**Drug intake**
- X
- X (Day-2)
- X
- X
- X
- X
- X
- X

**RAS-i discontinuation**
- X
- X
- X

**Blood sample for local biological assessment**
- X
- X
- X
- X

**Retrieval of Adverse Events**
- X
- X
- X
- X
- X
- X

**Assessment of morbidity and mortality**
- X
- X
- X
- X
- X

17 a and b blinding measure. If not applicable specify
Reply: we have specified this point in the revised version of manuscript.

18 b you need to specify plans to promote participant retention and complete follow up

Reply: We have specified this point in the data management chapter.

22 and 23 specify reporting adverse events and management
25 any communications about protocol amendments
31 a b c please specify authorship eligibility

Reply: We modified the text accordingly.