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: 06 Oct 2018

Reviewer: André Denault

Reviewer's report:

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.

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.

   o 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

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

   o 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.

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

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..

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.

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)

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.

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

Minor comments:

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

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

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.
"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.

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)

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.

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

"intuional review board": change for institutional

"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. "

"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"

References
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