Author's response to reviews

Title: The Association between Statin Therapy during Intensive Care Unit Stay and the Incidence of Venous Thromboembolism: A Propensity Score-Adjusted Analysis

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Author's response to reviews: see over
Dear Nolasco,

We would like to thank the editorial board and the reviewers for their second revision and constructive feedback, which has enriched the manuscript and strengthened the discussion.

We have modified the manuscript according to the reviewers’ comments and changes are marked in RED and track changes. Below see our point-by-point replies.

Sincerely,

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Reviewer 1

Comment: Only one of their replies requires a further comment. In response to the reviewer 1’s comment on the selection of the variables to enter the propensity score, and to the reviewer 2’s comment on the overlooked role of variables (e.g. aspirin use, a history of cardiovascular diseases) possibly related to the outcomes and to statin use, the authors modified the text writing “Variables included in the propensity score generation model were selected according to their relationship to the outcome (VTE) rather than the exposure (statin therapy) as has been shown to reduce bias and variance of estimated exposure effect”, and supported their choice using the following two references:


Actually to select variables associated to the exposure or to select variables associate to the outcome are only two of the possible ways of selecting variables to include in a propensity score. One might select variables associated both to the exposure and to the outcome (i.e. confounders). The two examples provided by the Reviewer 2 were thought to belong to this third option. In fact, the two simulation studies cited by the authors found not only what the authors reported as justification for their selection criteria, but also that confounders performed well; from the PubMed abstract of the article by Austin et al: “(...) We demonstrated that all propensity scores models balanced measured confounders between treated and untreated subjects in a propensity-score matched sample. However, including only the true confounders or the variables predictive of the outcome in the propensity score model resulted in a substantially larger number of matched pairs than did using the
treatment-allocation model (…)”. Therefore, I suggest that the authors leave the sentence as they wrote, and the references as they are, but that they recognize that they could have used that third criteria. They might do that for example, in Discussion, among the limitations (together with the impossibility to take into account the unknown confounders, they should say that they did not look for confounders at all, if not patient age).

Reply: Thank you for the comment. We modified the methods section as follows:

“Variables included in the propensity score generation model were selected according to their relationship to the outcome (VTE) rather than the exposure (statin therapy). However, some of these variables were also related to the exposure. This approach is one of three possible ways (related to exposure and outcome, related to outcome alone, and related to exposure alone) for variable selection. It has been shown to reduce bias and variance of estimated exposure effect [23, 24].”
Reviewer 2

Comment: 1. I have some significant concerns about the survival data. What is now figure 2 (survival analysis) is different from the figure / data presented in the original manuscript. The pattern and number of deaths appears to be different and the authors state in their reply “We have noticed that the coding for the outcome variable during hospital mortality analysis has been corrected” – I presume this means a new analysis has been done on different data from that presented in the original manuscript. Perhaps the authors can clarify exactly what errors existed, what re-analysis has occurred and how this new version of the data has been verified as true and correct. I note that no mortality data is presented in the original published manuscript of the main study to allow external verification.

Reply: Thank you for the comment.

<table>
<thead>
<tr>
<th>Correct coding</th>
<th>Incorrect Old coding</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>484</td>
</tr>
<tr>
<td>1</td>
<td>314</td>
<td>314</td>
</tr>
<tr>
<td>Total</td>
<td>314</td>
<td>484</td>
</tr>
</tbody>
</table>

In the incorrect old coding, 484 patients had been labeled as dead and 314 patient as alive, while in fact the correct counting is 314 patient were dead and 484 were alive.

This mistake stemmed from labeling the variable (alive=1, dead=0) rather than (dead=1, alive=0).
Based on that, the same Cox-regression model was run using the correct coding pattern for hospital mortality and a new table was generated.

**Comment:** I disagree with the conclusion in the abstract and the discussion. It would be better to just state what the study shows – I’m not sure what reported results “support the hypothesis that such association may actually exist”. I think the paragraph that comments on this in the discussion is speculative and doesn’t warrant drawing this as a final conclusion.

**Reply:** Thank you for the comment. The conclusion in the abstract and discussion were changed to read

a. In the abstract, the statement has been modified as follows: “Our study showed no statistically significant association between statin therapy and VTE risk in critically ill patients. This question need to be further studied in randomized control trials.”

b. In the Discussion the statement has been modified as follows: “The direction of the point estimate towards protective effect of statins and the magnitude of the association are similar to previous studies in non-critically ill patients. Accordingly, one cannot dismiss beneficial effect of statin therapy on VTE risk during ICU stay, and therefore, further studies are required.”

c. In the Conclusions the statement has been modified as follows: “Our study failed to show a statically significant effect of continuing statin therapy during ICU stay on VTE risk and 30-day hospital mortality in critically ill patients. We suggest examining this important question in a separate randomized, control trial.”
Comment: 3 Different statistical significance values are presented on figure 2 (log rank p=0.08) from in the text (p = 0.10) and table 3 – please clarify.

Reply: Thank you for the comment. The reported p-value on figure 2 is from the comparison of the two survival curves by log-rank test. This is different from the reported p-value in the text (HR 1.26, 95% CI 0.95-1.68, P= 0.10) which is based on Cox regression model estimate of log hazard ratio (Wald test).

Comment: 4 Aspirin use would seem a logical factor that may influence the results of the study and from my understanding logistic regression methodology does allow for inclusion of variables within a model under such circumstances. Could the authors comment on if this data was collected and found not to relate to the outcome or not collected? – In any case a brief comment in the discussion is warranted.

Reply: Thank you for the comment. We have the data for aspirin use, but we did not think it constitute a significant confounder. However, we re-run the multivariate analysis using aspirin as a confounder and the result did not change the significance of the original analysis on both outcomes (Venothromboemolism or hospital mortality). We will add the following statement to the manuscript:

The potential cofounder effect of aspirin use was tested with multivariate models for both VTE and hospital mortality.

<table>
<thead>
<tr>
<th>Multivariate Model</th>
<th>With aspirin</th>
<th>Without aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR  P value</td>
<td>HR  P value</td>
</tr>
<tr>
<td>VTE incidence</td>
<td>0.58 0.25</td>
<td>0.63 0.32</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>1.03 0.86</td>
<td>1.04 0.79</td>
</tr>
</tbody>
</table>
Comment: 5 Further to my previous comment regarding the clinical detection of the primary outcome. From the data presented I would take this to mean that for every patient that DVT was clinically suspected it was subsequently confirmed with imaging and hence recorded as a positive outcome. Is that correct? Did any patient have a suspected DVT that wasn’t confirmed with imaging or perhaps got some imaging that showed a DVT that wasn’t clinically suspected? My point is that perhaps the discussion needs to acknowledge that it might be possible that not all DVT’s were detected (you would really need to ultrasound everyone in the study to remove all bias) and perhaps the results need to clarify how often it was looked for and how often it was found?

Reply: Thank you for the comment. We have add the following sentences to the discussion part “Our approach was based on clinical suspension and confirmation with Doppler ultrasound. Therefore, it is likely that some non-clinically evident DVTs were missed. This approach, currently, represents the standard of care and it has been shown to be more cost effective than surveillance approach.”

Minor Comments:

Comment1: Abstract wording adjustment: Studies have shown that statins have pleiotropic effects as well as on inflammation and coagulation which may affect the risk of developing VTE. Delete “as well as” to improve clarity

Reply: Thank you for the comment. We have changed accordingly.

Comment: 2 I’m not sure the wording of “block stratified” has meaning in the abstract – it may just confuse the readers – I think this would be best removed from the Abstract
Reply: Thank you for the comment. We have changed accordingly.

Comment: 3 Results – number of DVT = 15 (put in the %) as you have for statin use to keep consistent

Reply: Thank you for the comment. We have changed accordingly.

Comment: 4 I’m unsure if it is reasonable to say that a HR of 1.26 vs 0.98 in the block stratified analysis is “similar” although I agree both are not statistically significant.

Reply: Thank you for the comment. We have add the word Furthermore, instead of similarly.

Comment: 5 Table 2 – could have the n (%) clarified in the column headers (n, %) and n (%)

Reply: Thank you for the comment. We have changed accordingly.

Comment 6: Table 3 heading should include “and Hospital Mortality” and so should read crude and adjusted analysis of VTE risk and Hospital Mortality .... . In addition the * in the footnote needs a mention in the table or header (likely to follow the adjusted analysis sections in both)

Reply: Thank you for the comment. We have changed accordingly