Reviewer’s report

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

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Reviewer: Maura Marcucci

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Dr Shmeylan and colleagues explored the association of the statin therapy with the incidence of venous thromboembolism (VTE) and the overall mortality during the hospital stay in critical ill medical/surgical/trauma patients, as a post-hoc analysis of a prospective observational cohort and using a propensity score to adjust for relevant variables. The topic and the methods used are interesting and the manuscript overall well written. However the authors should clarify some points.

Major Compulsory Revisions

1. Methods. The following issues should be clarified:

i) timing of the primary outcome: it is quite understandable that the authors mean “the incidence of VTE during the hospital stay”. Yet, when they show the results of the Kaplan-Meier analysis they say to have censored the analysis at 30 days of follow up, and that might be confounding for the reader. To be more understandable, please specify for how long the patients were followed up (during the hospital stay or up to 30 days from the hospital admission independently of the length of the hospital stay, i.e. even after discharge for some patients?). Hence, how do the patients who were discharged without symptomatic VTE before 30 days enter the survival analysis? Were they censored?

ii) therapy with aspirin might be a relevant variable (expected to be associated with the statin therapy and maybe with the outcomes). Why was this data not collected or included in the analysis? A similar question might be posed for a positive history of cardiovascular diseases/diabetes.

iii) variable for heparin: please specify in Methods that the included variable for heparin (unfractionated or at low molecular weight) corresponds to heparin for DVT prophylaxis, as stated only in the foot notes of tables 2 and 3. The authors should also clarify how they considered in their analyses the treatment with heparin for other acute reasons, for example for an acute coronary syndrome (which does not correspond to a chronic use of heparin, but either to a DVT prophylaxis).

iv) covariates adjustment: please clarify what the authors mean when they say that “Multivariate Cox regression was also used to control for any residual confounding not taken [into] account for by propensity score adjustment or blocks stratification”. Do they mean that they include again all the variables used to build
the propensity score as covariates in the Cox, together with the propensity score? If so, there is no technical reason to do that, also because in this way the advantage of using a propensity score (i.e. to avoid the concern about the over-parameterization) is lost. Usually, and not necessarily, only a subset of variables believed “major”, or for which the balancing property after adjusting for the propensity score is not satisfied, is included again as covariates.

v) was there any missing data? If so, how did the authors manage them? They may represent a limit when the STATA command pscore is used.

2. Results. In Methods the authors state that they performed 3 different Cox analyses with propensity score: a blocks stratification, a propensity score adjustment and an additional propensity score and covariates adjustment. Why did they report only the HR for one of those analyses (block-stratification) and did not mention at all the results for the other analyses?

Minor Essential Revisions
1. Abstract. The authors should clarify in the abstract, as well in the main text, the timing for the primary outcome: “incidence of VTE”, when? The reviewer also suggests the authors specify in the Methods section of the Abstract that a survival analysis, and in particular a Cox regression, was performed.
2. Abstract, page 3, line 3: please change “if they reduce the odds” with “if it reduces the odds”.
3. Background, page 4, line 8: please change “for both primary and secondary indications” with “when administered for both primary and secondary indications”.
4. Results. Like for the occurrence of VTE, please provide the percentage of patients died in hospital, overall and in the statin and non-statin groups.
5. Results, page 8, lines 3-5: please rephrase “Similarly (…) blocks-stratified analysis (…),” which is not grammatically clear.
6. Discussion: in Background (page 4, lines 20-21) the authors state that there are “limited studies” examining the association between statins and VTE in critical patients, whereas in Discussion (page 10, line 22) they write that the study described is “the first study” on this topic. Please clarify.
7. Along the manuscript there are several small typos/grammatical errors: please carefully revise it.

Discretionary Revisions
1. Background. How the background is framed in the main text is inconsistent with how the Background is framed in the abstract. Indeed, in the abstract, the statins’ property of modulating inflammation is advocated as the possible biological link with the development of VTE, whereas, in the main text, their antithrombotic properties on the venous side are primarily presented as the driving mechanism (in fact, in part by the interaction with the inflammatory system, but this is a mechanism not explicitly mentioned in the text). The reviewer would suggest the authors slightly reorganize the first part of the Background in order to make the structure of the manuscript more consistent.
2. Methods. The choice of the variables to include in the propensity score might be commented and the type of variables described, for example distinguishing those which were really confounders (associated both to the treatment with statin and to the outcomes), those which were only associated to the treatment with statin, those associated only to the outcomes, those eventually not associated either to the treatment or to the outcomes.

3. Discussion. The authors report extensively the existing evidence in the literature on the association between statins and VTE. This part might be synthesized and/or the authors should at least emphasize the difference in the setting between the study here prescribed and most of the cited evidence (population-base cohorts, long term follow up, outpatients).

4. Discussion. The reviewer suggests the authors to rephrase the sentence “However, we have adjusted for those imbalances using multivariate and propensity score analysis” (page 11, lines 17-18), making clearer that they adjusted for some putative confounding variables but not all (i.e., to completely overcome the “imbalance” in an observational setting is not possible).

5. Among the limits of the analyses, the "competing" nature of the two outcomes, which would have required a specific survival method for competing risk, and which may be particularly relevant in a patient population at high in hospital mortality, might be mentioned.

6. Figures. The reviewer suggests the authors invert the order of figure 1 and 2 according to the “order” of the outcomes.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests