Author's response to reviews

Title: Clinical predictors of statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry

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Version: 4 Date: 28 January 2014

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

Here enclosed you can find the revised version of the manuscript "Clinical predictors of statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry".

In the following you will find (in bold) a point-by-point reply to all the reviewers' comments. As regards Reviewer#2’s concerns, mainly focused about lack of raw biomarkers levels, we have tried to motivate our choices through a better explanation of the claim of the paper. To this end, we have added further evidence coming from the very last clinical guideline on the treatment of blood cholesterol, which supports our statements and methodologies.

Hoping you will appreciate our work, Our Best regards!

the Authors

Reviewer's report#1
Title: Clinical predictors of statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry
Version: 3
Date: 26 November 2013
Reviewer: Danielle Ni Chroinin

Reviewer's report:
Thank you to the authors for diligently addressing each of my concerns/queries. After revisions, I would recommend publication in BMC Neurology. May I also apologise for the erroneous indication of 'Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal', which should have read 'An article of SUFFICIENT interest...', in keeping with my Review/comments.

Thank you for these comments!

Minor/discretionary revisions prior to publication:
- Hospital-based registries can be inherently prone to biases (where community sources not included), but I appreciate the authors detailing the inclusion criteria for the registry.
- In the Results section, the results of multivariate analyses might be better presented in tabular form.

In the paper we already have two tables. Following this suggestion, the number of tables will increase to five. If the Editor approves this number of tables, we don't have any problem to provide them.

- The statin-haemorrhage link is slightly over-stated in the Discussion, and might be best modified from: "...another factor in patients with higher stroke severity being less frequently treated with statins is the supposed increased risk of hemorrhagic transformation..." to "...less frequently treated with statins is the EITHER 'concern re' OR 'possibility of' increased risk..."

The text has been modified according to this comment.

- One or two typographical errors, e.g. epatopaty for Hepatopathy, 'In literature' for 'In the literature' should be adjusted pre-publication.

Thank you for highlighting the errors, we have now fixed them.

- Finally, given the recent launch of the revised AHA lipid guidelines, the authors may wish to include a single line mentioning the newest recommendations for (atherosclerotic) stroke patients. I realise these are very recent, and couldn't have been included before now, but a citation would keep the manuscript up to date and topical.

Thank you for this comment, it has been very useful to highlight our claim. We have included a sentence in the Introduction and a sentence in the Discussion Section referring to the results presented in the last AHA guidelines. Moreover, we have included the paper in the references, adding also the related work by Keaney et al "A Pragmatic View of the New Cholesterol Treatment Guidelines" published on NEJM in January 2014.

Level of interest:
An article of importance in its field

Thank you for this comment!

Quality of written English:
Acceptable

Statistical review:
No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests
I declare that I have no competing interests
The paper is greatly improved over the previous version, but some issues remain.

Thank you for appreciating our effort!

The major issue is that data related to raw values of blood test results (e.g. blood glucose, cholesterol, inflammatory markers,...) are in fact unavailable. In my opinion, the level of cholesterol, HDL and LDL, the stroke subtype of TOAST classification (Large vessels diseases and Lacunar stroke), and the underlying diseases for statin prescription (e.g. Hepatitis B and C, and myopathy, etc) were the major factors for the statins prescription or not.

It’s true that raw blood test results are not available, due to the study and registry design; after the first revision, we acknowledged this limitation in the final paragraph. However, we think that their absence does not affect seriously our Results and Conclusions (see below).

Instead, the stroke subtypes of TOAST classification are available and have been considered in the analysis, as it has been specified in the Materials and Methods section (“Clinical variables”). In Figure 1 and in the text at the beginning of page 7, we present the distribution of the stroke subtypes. At the end of page 8 we describe an analysis carried out on the subgroup of patients with large vessels disease. We also discuss the relationship between statin prescription and stroke subtype in the discussion section from page 11. The fact that TOAST classification is not pointed out by the classification tree is one of the main finding of our work.

Regarding underlying diseases that could represent a contraindication to statin prescription, on page 4 we specified:

“For this study, we considered only the patients discharged alive, with a diagnosis of ischemic stroke or TIA, and without clinical contraindications to statin prescription (e.g. hepatopathy or hemorrhagic diathesis).

In brackets we reported just a few examples of contraindications, but in fact we excluded patients with any contraindication [123 patients have been excluded from further analysis for this reason, as reported in the Results section; all the patients we considered are eligible to receive a statin]. Contraindications were identified both through a specific item present in the registry and indicating that a patient has a contraindication (i.e. “Contraindications to statins”) and by checking the discharge diagnosis codes (ICD9-CM classification). Since, as suggested by the reviewer, also myopathy is one of the most important exclusion criteria, we now added it to the list of our examples in brackets.

The LDL cholesterol levels above 100 mg/dl, is recorded as dyslipidemia in this study; however; to my opinion, the level of cholesterols being 101 or 180 mg/dl is quite critical for the physicians to decide whether to prescribe statin or not, and it may influence the statistical results and have a statistical bias. Consequently, the conclusions that can be drawn are very limited.

Since current guidelines recommend statins prescription in any case of non-cardioembolic stroke, one of the main claims of our paper is that we found that, on the contrary, this is not true in our dataset. The main driver for statin prescription resulted in fact the presence of dyslipidemia.

We agree that, in the real medical practice, the raw level of LDL cholesterol (101 or 180) could influence statin prescription. However our study is focused on guideline adherence in non-cardioembolic stroke patients. In this case, to adhere to the guideline, statins have to be prescribed independently of the raw LDL cholesterol value. Recent AHA guidelines [Circulation. 2013 Nov 12] confirm and highlight this point. In the work “A Pragmatic View of the New Cholesterol Treatment Guidelines” by JF Keaney et al [NEJM, January 2014], the Authors describe how the recent guidelines suggest the elimination of the assessment of LDL cholesterol (“because target levels are no longer emphasized”), C-reactive protein and calcium scores in patients with defined ASCVD. Our patients are all included in the definition of ASCVD given in the guideline (page 13). For this reason, we think that having classified patients in having or not having dyslipidemia (defined with the currently agreed threshold for LDL of 100 mg/dl) does not affect our claim. Specifying the LDL level would not enhance our analysis because, according to the guideline, we shouldn’t consider it. On the contrary, our result can be read as follows: “stroke patients are more likely to receive a statin if they have a LDL of at least 101 mg/dl, that differs from guideline recommendations”.

Level of interest:
An article of limited interest

We do not understand this rating because in the first review the reviewer reported: “Level of interest: An article of importance in its field”.

Quality of written English:
Not suitable for publication unless extensively edited

For the first revision, the manuscript had already been revised by a native English speaker.

Statistical review:
Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests