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

We would like to kindly thank you for the attention you gave to our paper. After an extensive revision, performed according to the reviewers' suggestion, we think that our work could represent an interesting source of data in the setting of cerebrovascular secondary prevention therapies and a proof of how the real clinical practice can be different from guidelines. Here you will find, as requested, a point-by-point response to the reviewers' queries. Hoping You will appreciate our work and consider it for publication in Your journal,

My best regards,

Dr. Isabella Canavero

N°1: Reviewer's report - Danielle Ni Chroinin

Reviewer's report:
Thank you for the opportunity to review 'Clinical predictors of statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry.' This paper reports the prevalence of statin prescription in the Lombardia Stroke Registry, stratified by multiple patient clinical factors, and utilises a Classification Tree to describe the variables associated with statin use in a step-wise fashion. The authors report suboptimal use of statins, and lack of adherence to existing guidelines. This paper is topical, and the suboptimal practice described echoes recent publications that have described compliance with the Get With the Guidelines-Stroke in other populations [Hseih et al. Circulation 2010; 122(11): 1116-1123; de Carvalho et al. Cerebrovasc Dis Extra 2012; 2(1): 26-35]

We thank the reviewer for her useful comments and suggestions. The manuscript has been carefully revised accordingly.

Essential Revisions:

Methods and Results

How was dyslipidemia defined? Previous physician diagnosis? History of lipid drug treatment? Pre or post-stroke lipid levels?

Risk factors/comorbidities, among which dyslipidemia, were considered as present if the factor was documented on past medical history or the patient was on drug treatment for a specific comorbidity (this sentence has been added to the text).

Was NIHSS assessment standardised/evaluated by trained personnel?

All the physicians operating in our stroke units are certified for the administration of the NIHSS and the modified Rankin scale (this sentence has been added to the text).

Patient factors such as patient preference or agreement to treatment are not addressed, and may have affected rates of statin use at discharge.

We have added to the discussion a paragraph on study limitation, where this and other issues have been discussed.

The authors do not report the treating speciality, or how many patients were admitted to a Stroke Unit, or under the care of a specialist stroke team. It would be interesting to know if these factors are associated with statin prescription.
In the introduction, we added the information on treating specialties and overall number of patients accessing the Stroke Units in the observation period.

In the Discussion, we motivate why we haven’t further elaborated on this point providing some statistics related to the centers.

The separate analysis of large artery strokes is helpful, given that several guidelines differentiate LDL targets on the basis of stroke of atherosclerotic origin, and that SPARCL limited patients to those with stroke/TIA with non-cardioembolic stroke. Potentially the latter fact should be highlighted.

We have addressed this point in the text (Results section – subgroup analysis)

As a hospital-based registry, the study will have inherent biases, which should be acknowledged at some point.

In the Methods section, we added some further detail on how data are inserted into the registry to avoid potential biases.

Discussion

Rather than individually cite each variable associated with statin prescription (or not), and detail potential barriers for each one, the authors might consider an overview of barriers to guideline adherence, referring to the appropriate variables.

We thank the reviewer for this comment. We have now revised the Discussion section using the barriers to guidelines adherence as a guide to discuss the results of our study.

The gender bias is notable, whereby women are less likely to receive statins. However, the authors almost appear to excuse the lack of guideline adherence in women, attributing it to the "well-known higher risk of cardiocerebrovascular pathologies in men", which may or may not have been their intent? Of note, a similar gender bias was seen as regards adherence to lipid management guideline in stroke patients in the North Dublin Population Stroke Study, reported at the European Stroke Conference, May 2013.[Ní Chróinín et al Cerebrovascular Dis 2013; 35(Suppl 3)]

We have addressed this point in the text, adding the suggested citation to the references.


We thank the reviewer for this comment. At the time this paper was initially submitted, some of the suggested papers had still not been published. They have now been included in the references and used in the Discussion to discuss our obtained results.

The authors attribute the association between stroke severity and statin non-prescription, and between antithrombotic use and non-statin use, to a concern on the part of the physician re non-compliance or higher risk of bleeding (with larger infarcts or haemorrhagic transformation). It is more likely that this represents a 'non-prescribing' bias where patients who have had severe strokes and a poor prognosis are not commenced on secondary preventative therapies, e.g. in the context of palliation, or a recognition on the part of the physician that RCTs on which guidelines are based often exclude patients with significant disability or poor life-expectancy.
We agree with the reviewer on this point. Probably the previous version of the paper didn't succeed in clarify this enough. We have now added the following paragraph in the discussion section where we specifically address this point:

“Stroke severity, directly linked to disability and life expectancy, is another factor our model found as influencing prescription. Statin + patients had lower NIHSS scores both on admission and at discharge. These findings suggest that physicians tend to prescribe statins in patients with milder neurological damage, perhaps in order to obtain better compliance. Higher severity could thus represent a 'non-prescription' bias leading physicians to avoid secondary preventive therapies in patients who have had severe strokes and with poor prognosis. Then, as already pointed out, patients with significant disability and poor prognosis are excluded from the dedicated RCTs, whose results cannot be applied to them”

It is interesting that despite the higher rates of statin prescription in patients with DM or hypertension (though still suboptimal), risk factors traditionally associated with small vessel disease, small vessel strokes per se were not associated with rates of statin prescription.

We agree with the reviewer on this point. The point in the text where we address diabetes and hypertension is related to the whole population. In the following of the discussion section, though, a paragraph specifically dealing with small vessel diseases is reported to try to interpret the low prescription rate in that case:

“Concerning small vessel disease, the low rate of prescription we detected could be explained by the complex relationship between statins and lacunar stroke, and by the fact that literature lacks precise indications. Small vessel disease determines both ischemic (lacunar) and hemorrhagic (microbleeds) stroke, and severe arterial hypertension is the main risk factor in both cases. According to these factors, statins could somehow enhance the risk of hemorrhage in patients with lacunar stroke because of the underlying small vessel pathology and unbalanced hypertension. Recent papers have analyzed the connections between statin use and the risk of developing microbleeds, with non-univocal results. Day et al [42] found that previous statin therapy was not associated with the prevalence or degree of microhemorrhages in patients with acute ischemic stroke or transient ischemic attack. Haussen et al [43] found instead that statin use was independently associated with microbleeds in patients with ICH. Some authors [44] underline that patients with non-atherosclerotic causes of stroke should not be treated with statins and that statin therapy should be initiated only after a careful consideration of all the potential risks and benefits that could derive from them”

“The classification tree applied on the subgroup of LVD patients lets us to conclude that statins, in the absence of dyslipidemia, are almost randomly prescribed even in the presence of well-defined atherosclerosis.” The fact that the rate approximated randomisation 2:1 does not necessarily justify the implication that physicians are 'randomly' assigning statin treatment. There may be some rationale, but the factors influencing such decision-making have not been explored in this study.

We have rephrased our considerations according to the reviewer’s note.

"Unexpectedly, thrombolytic treatment...seems to enhance statin prescription": This most likely represents a marker of better stroke care and probably increased specialist input in patients who have received thrombolysis, which should be mentioned.

We thank the reviewer for the suggestion. We added the following sentences in the text:

“We could also hypothesize that patients treated with thrombolysis are more likely to be managed following guidelines, and this could perhaps explain why they are more likely to receive the recommended statin regimen at discharge.”

It would be worth including a brief paragraph outlining the authors' own ideas as to the strengths and weaknesses of the current study.

Our ideas are outlined in the final part of Discussion and in Conclusions. In the Discussion section, we have added a paragraph on the study limitations, highlighting several points raised by the reviewer.
It is also probably worth referencing THRAST in relation to IV lysis and statin use. [Cappellari et al. Neurology. 2013 Feb 12;80(7):655-61. doi: 10.1212/WNL.0b013e318281cc83]

We agree with that. We added the reference as suggested.

Conclusion

The authors conclude that there is 'need for concensus on the matter, in order to get improved and precise guidelines, easier to put into practice by physicians'. This fails to acknowledge that there are guidelines in existence that are both evidence-based and directive. This study shows failure to adhere to well-established parameters for statin initiation, the problem would seem to reflect a failure on the part of treating physicians to utilise existing guidelines. It is possible that physicians may be unaware of the guidelines, believe them to be inappropriate for individual patients, or perceive them as imprecise, but this study did not investigate this further.

We thank the reviewer for this comment, on which we agree. We have modified the Conclusions section to clarify our opinion on the findings presented in this work.

Other comments/Discretionary revisions:

While the authors present an analysis of the clinical factors associated with statin use, information regarding other physician-related factors influencing adherence to guidelines would also be of interest. If unable to provide such information, the authors might develop this more in the discussion. They do not really characterise the "factors interfering with statin prescription" as is suggested in the Introduction, and the focus should be made clearer.

We have tried to explain better our study design, and the consequent limitations, with the following sentences:

“As for patient-related factors, those able to influence their attitude to comply with therapy (after discharge) are usually identified in the literature as patients' demographic, social and cognitive features. On the contrary, clinical factors detected during hospitalization are not usually considered as being among those that influence physicians' prescription.”

“To overcome this limitation, our work tried to identify those patient-specific clinical and care factors that are able to influence physicians’ decisions to prescribe statin after an acute ischemic stroke.”

Do the authors have information regarding statin use post-discharge? Might primary care physicians have introduced statins following hospital discharge? Might patients who went home on statin not have continued it post-discharge?

As the reviewer correctly pointed out, we have not included this information in our study. We have addressed this point in the text, as follows:

“Although our registry is provided with a follow-up section, in this study we have not included information on post-discharge statins use. The motivation underlying this choice is twofold. On the one hand, the follow-up is only partially completed for our patients. On the other hand, for those patients who died during follow-up, the registry doesn’t allow physicians to enter treatment information (even if antecedent to death). This would cause a bias, as the patients who died would result as not continuing the treatment even if they were”

Figures

Figure 1 could potentially be placed online as supplemental material, or incorporated into Figures 4 or 5.
We have created an enhanced version of Figure 4, containing also the explanations previously reported separately in Figure 1.

Figure 2 is probably unnecessary, as the increased rate of statin prescription is mentioned in the text.

**Figure 2 has been removed from the paper.**

Additional comments:
There are a number of grammatical and phrasing errors that may represent inexact translations to English (particularly in the abstract and Intro), which should be corrected if for publication.

Thanks for this comment, the manuscript has now been revised by a native English speaker.

A qualitative study investigating physician factors influencing statin prescription would be of interest, and maybe should be considered for future study?

Thanks for this comment. This kind of study would be of great interest but, as we now acknowledge in the Discussion, there are some issues that prevented us to go further on this.

Level of interest:
An article of insufficient interest to warrant publication in a scientific/medical journal

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

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

Declaration of competing interests:
No conflicts of interest to declare

**N°2: Reviewer's report – Cheng-Hsien Lu**

REFEREE'S COMMENT SHEET - Ms. Ref. No.: BMC Neurol 1447457830108645 Title: Clinical predictors of statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry. This is a clinical study to identify the factors influencing statins prescription by Stroke Unit physicians at hospital discharge. In this study, the authors try to the impact of demographic, risk factors, tPA treatment, in-hospital procedures and complications on statins prescription rate at discharge. We appreciate the amount of hard work that has gone into your study, but feel that the role of these biomarkers in the prediction of statins prescription rate at discharge can not be reliably assessed without controlling the other parameter of vascular risk factors (e.g. glucose, total cholesterol, HDL, LDL) and inflammatory biomarkers (e.g. high sensitive CRP), and blood pressure. The major shortcoming is its methodology. There are several concerns in this study which may influence the statistical results and have a statistical bias. First, this study only provide the categorical data of vascular risk factors (e.g. diabetes mellitus, coronary artery diseases, hypercholesterolemia, etc) rather than the level of the vascular risk factors (e.g. glucose, total cholesterol, HDL, LDL etc). Second, the usage of class and
dosage of statin (e.g. Rosuvastatin, Simvastatin, Fluvastatin, and Vytolin, etc) depends on the preference of the attending physician, this may cause potential bias in statistical analysis and in drawing conclusions. The level of these biomarkers may be influence by other drugs (e.g. calcium channel blockers) or underlying conditions, which may cause potential bias in statistical analysis. Finally, the statistical results are too complicated and are hard to understand for the reader of BMC Neurology. Consequently, the conclusions that can be drawn are very limited.

We thank the reviewer for the useful comments and suggestions. Now we are trying to explain the reasons of the limitations the reviewer had observed, that are mostly a priori determined by the study design and the Registry tool.

The data analyzed in this paper are strictly connected with the nature of the registry they come from. This is a repository where mostly “qualitative” and process information is stored. More precisely, data related to raw values of blood test results (e.g. blood glucose, cholesterol, inflammatory markers,...) are in fact unavailable. Only the clinical implications of such results are stored. So, for example, if a patient shows LDL cholesterol levels above 100 mg/dl, we record that he has dyslipidemia, not tracing the exact LDL value but focusing on the diagnosis. This choice has been made to stick to clinical practice guidelines formulation, usually more oriented to the “disease” rather than to laboratory values. Moreover, the detailed information about pharmacological prescriptions is lacking. As for this aspect, the only information that is recorded is whether the patient was discharged with a statin, regardless of its pharmacological name and dosage. Our Registry was built and set up to easily reflect guidelines recommendations, and in fact current clinical practice guidelines are not specific as well, recommending to use a statin without specifying which type.

However, we understand the reviewer’s comment and, having not the possibility to retrieve the required data from our Registry, we acknowledged these limitations in the final part of the Discussion section.

This said, we tried to clarify as much as possible the statistical analyses and we enhanced the discussion section to make it more fluent and easy to understand, though addressing additional issues.

Level of interest:
An article of importance in its field
Quality of written English:
Needs some language corrections before being published
Thanks for this comment, the manuscript has now been revised by a native English speaker.

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