Author's response to reviews

Title: Early Statin Use in Ischemic Stroke Patients Treated with Recanalization Therapy: Retrospective Observational Study

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Author's response to reviews: see over
Dear Editor

We highly appreciate the thoughtful comments of the reviewers of this manuscript (BMC Neurology/ MS 1500663400134493). The authors agree to the points the reviewers have made, have changed the manuscript as requested, and have described all the changes in a point-by-point response to the reviewers’ critiques in the following pages. Also, we have highlighted the changes in the manuscript. All authors have read and approved the submitted manuscript.

Thank you again for reviewing our manuscript for the journal BMC Neurology.

Sincerely yours,

Hee-Joon Bae, MD, PhD.
1. The major concern is the disease status and result of recanalization may be correlated with earlier, later use or no use of statin. This may also have contributed to symptomatic hemorrhagic transformation and outcome.

We appreciate Reviewer #1’s thoughtful comments. As the reviewer points out, the result of recanalization therapy is a powerful determinant of symptomatic hemorrhagic transformation and other stroke outcomes, and might affect the statin starting time. We had considered including the recanalization status in the models.

However, this study covered all kinds of recanalization therapies including intravenous (IV) only, intra-arterial (IA) only and combined treatments, and unfortunately it was not possible to assess the recanalization status in patients receiving IV only in a uniform manner because of the heterogeneity of angiographic evaluation after IV thrombolysis. For those who were treated by intra-arterial thrombolysis (IA only + combined treatment), we present additional data on the association between recanalization status and statin starting time in Table 1. Post-treatment recanalization status assessed by TIMI grading was not associated with statin starting time (p = 0.97 on Pearson’s chi-squared test). We hope that this result may mitigate the reviewer’s concern.

Table 1 Association between recanalization status and statin starting time in patients receiving intra-arterial therapies

<table>
<thead>
<tr>
<th>Post-treatment TIMI grading</th>
<th>D1 (n = 27)</th>
<th>D2 (n = 35)</th>
<th>D≥3 (n = 19)</th>
<th>No use (n = 48)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>4 (14.8%)</td>
<td>4 (11.4%)</td>
<td>2 (10.5%)</td>
<td>6 (12.5%)</td>
<td>0.97</td>
</tr>
<tr>
<td>2 - 3</td>
<td>23 (85.2%)</td>
<td>31 (88.6%)</td>
<td>17 (89.5%)</td>
<td>42 (87.5%)</td>
<td></td>
</tr>
</tbody>
</table>

TIMI is the abbreviation for Thrombolysis in Myocardial Infarction and TIMI grading used in this analysis is an extension of the original TIMI to assess angiographic cerebral blood flow (ref. Furlan AJ, et al. JAMA. 1999;282:2003–2011.)

*P was obtained by Pearson’s chi-squared test.

2. Another is the time concern hemorrhagic transformation and statin use. Patients
may not receive statin because of occurrence of hemorrhagic transformation.


In response to the reviewer’s concern, we analyzed the association between the timing of symptomatic hemorrhagic transformation (SHT) and statin start timing (Table 2), which showed no occurrence of SHT after starting statin in statin users. However, this retrospective data could not exclude the preferential underuse of statin in patients with a high risk of SHT. This concern can be resolved only by a prospective randomized clinical trial.

To highlight the reviewer’s concern, we revised the Discussion section of the manuscript as follows (page 11, paragraph 1):

“Finally, it should be clearly noted that less frequent symptomatic hemorrhagic transformation and neurologic deterioration in statin users might be attributed to preferential underuse of statin in patients with high risk of hemorrhagic transformation or worse prognosis. A randomized clinical trial would be a more robust setting for answering the questions we posed.”

Table 2  Statin starting time and symptomatic hemorrhagic transformation

<table>
<thead>
<tr>
<th></th>
<th>D1 (n = 45)</th>
<th>D2 (n = 70)</th>
<th>D≥3 (n = 52)</th>
<th>No use (n = 170)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of SHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Day 1</td>
<td>1 (2.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>8 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0 (0.0%)</td>
<td>2 (2.9%)</td>
<td>0 (0.0%)</td>
<td>8 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Minor essential revisions
1. The limitation of observational study can not be neglect. Confounding bias needs mentioned in discussion.

We appreciate Reviewer #1’s comments again. As suggested, we revised the Discussion section of the manuscript as follows:

“First, the study was conducted in a single community-based hospital, and the study subjects were identified in a retrospective manner. Although the patients were enrolled from the prospective stroke registry database and the study outcomes were captured prospectively, we may be dealing with patients who do not represent the community-at large, and thus, our findings may not be representative of other populations. Furthermore, considering the observational nature of our study design, residual or unmeasured confounding effects could be introduced and, hence, our results are not free of risk of inevitable biases despite adjusting for potential confounders through modeling.”
Reviewer #2

Since recanalization itself is a very powerful predictor of outcome it might be not sufficient just adjusting for modality of recanalization. In table 4 the combined treatment has a significant trend for favorable outcome, this suggests that this might be anyway a potential confounder. The number of patients receiving statins at D1 is the same in the iv and in the combined group. In the combined group there were 50% non statin users compared to 17.6% in the iv group.

We agree with Reviewer #2’s concerns. As the reviewer indicates, modalities of recanalization therapy might be a potential confounder and affect the study results in spite of using statistical adjustments.

Table 4 of the manuscript demonstrates better outcomes in statin users than non-users consistently across the modality of recanalization therapy, although statistical significance was observed for a few outcome variables in those receiving combined treatment. Also, the interaction effect between statin starting time and recanalization modality was not statistically significant (p = 0.26 in the multivariable model). The same number of D1 users between IV only and combined treatment as well as the larger number of non-users in combined treatment than IV only can be interpreted as confounding toward the null hypothesis if the outcomes of combined treatment are better than those of IV only. However, the possibility of quantitative interaction could not be excluded, which needs to be addressed through future research on a larger scale.

According to the reviewer’s concerns, the Discussion section of the manuscript is revised as follows:

“Second, subgroups in our analysis were occasionally small and therefore our findings based on multiple comparisons could be a play of chance. However, the subgroup analysis according to recanalization modality suggested possibility of effect modification, although this was statistically not significant. Residual confounding by recanalization modality also cannot be excluded.”

The observation period is very long, as the authors state, the rate of statins given in 2004 was 0% and the increasing to 35% in 2010. How was the development of recanalization therapies at the same time per year?
Did the outcome improve generally over this years?

We highly appreciate the important comments of Reviewer #2. According to the reviewer's suggestions, we analyzed the secular trends of recanalization therapy (Figure 1). The number of patients receiving recanalization therapy increased over time. However, the proportion of excellent outcomes (defined as mRS, 0–1) did not significantly change (Figure 2). As indicated by Reviewer #2, the improvement of outcome by statin use might be attributed to improvement of general care rather than statin by year, although we included calendar year as a covariate in the multivariable models to control for this possibility.

The reviewer’s concerns are addressed in the manuscript as follows:

“We note several potential study limitations. First, the study was conducted in a single community-based hospital, and the study participants were identified in a retrospective manner. Although the patients were enrolled from the prospective stroke registry database and the study outcomes were captured prospectively, we may be dealing with patients who do not represent the community-at large, and thus, our findings may not be representative of other populations. Furthermore, considering the observational nature of our study design, residual or unmeasured confounding effects could be introduced and, hence, our results are not free of risk of inevitable biases despite adjusting for potential confounders through modeling. For example, the rate of statin use increased over time, therefore improvement of outcome by statin use may be attributed to improvement of stroke management over time, although calendar year was included in the multivariable models to adjust for that kind of confounding effect”

Figure 1. Secular trends of recanalization therapy
Minor revision

In the period after MR Clean it is hard to state in the introduction that various therapies (what do the authors mean endovascular approach/ia?) did not show higher successful recanalization rates.

As suggested, the Introduction section of the manuscript was revised as follows:

“additional attempts have been made with a new generation of thrombectomy devices that show much higher successful recanalization rates [2, 3].” (page 1, paragraph 1)