Author's response to reviews

Title: Pretreatment with statins improves early outcome in patients with first-ever ischaemic stroke: a pleiotropic effect of statins or a beneficial effect of hypercholesterolemia?

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Author's response to reviews: see over
AUTHORS’ COMMENTS TO SUGGESTIONS OF Dr. LUCA MASCITELLI

We appreciate very much the helpful comments of the reviewer. Following your reasoning, a potential benefit role of hypercholesterolemia is more extensively discussed in the Abstract, Discussion and Conclusions.

Introduction: “... a high levels of total cholesterol were associated with an increased rate of recovery from disability in basic activities of daily living among hospitalized older adults [8] and decreased risk of physical disability after stroke [9].”

In the Discussion section, we have added this comment: “It has been shown that elevated cholesterol concentrations were associated with improved short-term health outcome after acute stroke of any type [35], short-term mortality following ischaemic stroke is higher in older patients with low total cholesterol levels independent of a large number of factors [36] and elevated levels of cholesterol were associated with increased rate of recovery from disability in basic activities of daily living among acutely ill hospitalised older patients [8]. Alternatively, we cannot exclude that elevated cholesterol may simply represent an indicator of good nutritional status. In line with this hypothesis, previous observations have identified strong correlations between specific clinical markers of nutritional status (in particular serum proteins) and the risk of subsequent in-hospital adverse events [37].” All supporting references are added in the reference list.

Conclusions are modified as follows: “The present findings indicate that pretreatment with statins, hypercholesterolemia or both in ischaemic stroke patients could have neuroprotective effects with reduced neurological deficits at presentation, lower early death and dependency rate, thus increasing the chances for good outcome.”

The characteristics of the patients included in the present study (sample collected up to 2004) are not influenced by thrombolytic treatment. Thrombolytic therapy was introduced in our hospital in 2006 and the stroke code system was fully implemented in the metropolitan area of Barcelona in 2006.

Six of the recommended references are incorporated in the new version.

The potential neuroprotective role of hypercholesterolemia is more extensively commented on in the Discussion: “Accordingly, hyperlipidemia may be considered, on the one hand, a cardiovascular risk factor, but on the other hand, and paradoxically, through a mechanism of neuroprotection of the brain would be related to a lower neurological deficit and decreased mortality in patients with acute cerebral ischaemia. In this respect, when prescribing pharmacological treatment, an excessive reduction of total cholesterol levels may be avoided in order to control the stroke risk factor without affecting the neuroprotection mechanism of hypercholesterolemia. On the basis of this hypothesis, a prospective randomised trial with statins assessing the relationship between functional outcome and mortality with different blood lipid levels in the acute phase of cerebral ischaemia would be necessary.”
When the present study was finished (in 2004), treatment with statins was only indicated in patients with hypercholesterolemia. From the results of SPARCL study in 2006, the indication of statin therapy was expanded. We have added this sentences in the Discussion: “Presumably, baseline cholesterol levels of the statin-treated patients in this study were higher than those of non-statin treated patients. Unfortunately, cholesterol levels were not considered in the study.”

This comment of the SPARCL study is also included: “The Stroke Prevention with Aggressive Reduction in Cholesterol (SPARCL) study found that –as compared to placebo- the use of high-dose atorvastatin in accurately selected patients who had a stroke or TIA was associated with a non-significant 13% risk reduction of non-fatal stroke during a 5-year follow-up without improving survival [30].” The reference is also added.

The subtitle suggested by the reviewer “a pleiotropic effect of statins or a beneficial effect of hypercholesterolemia” is added.
Reference: MS 1161952358342879 “Pretreatment with statins improves early outcome in patients with first-ever ischaemic stroke: a pleiotropic effect of statins or a beneficial effect of hypercholesterolemia?”, Adrià Arboix et al., revised version

AUTHORS’ COMMENTS TO SUGGESTIONS OF DR. MATHEW J. REEVES

Major Compulsory Revisions

1. The frequency of favourable outcome and the mortality rate (although with a decreasing trend) showed no differences when data of three periods (1986–1992; 1993–1998; 1999–2004) were analyzed. These data are included in the text and in a new table (Table 3) in the Results section: “As shown in Table 3, the frequency of favourable outcome and in-hospital mortality in relation to the use of statins when the study period was divided into three periods (1986–1992; 1993–1998; 1999–2004) did not show significant differences, although a decreasing trend in the mortality rate was observed”.

2. When the present study was finished (in 2004), treatment with statins was only indicated in patients with hypercholesterolemia. From the results of SPARCL study in 2006, the indication of statin therapy was expanded. We have added this sentences in the Discussion: “Presumably, baseline cholesterol levels of the statin-treated patients in this study were higher than those of non-statin treated patients. Unfortunately, cholesterol levels were not considered in the study.”

3. The measure of stroke severity was the modified Rankin scale.

4. In accordance with your suggestion “spontaneous neurological recovery” is substituted by “favourable outcome”, which includes spontaneous neurological recovery and minimal stroke associated disability at discharge” in the tables and throughout the text. In the Methods section it is clarified: “The outcome of patients was classified as favourable outcome (spontaneous neurological recovery or stroke-associated minimal disability at discharge) (mRS grades 0–2), and unfavourable outcome (not improved, mRS grades 3–5 or in-hospital death).”

5. All variables that were considered in the modeling phase are now added in Table 1.

Table 3. Frequency of favourable outcome and in-hospital mortality in statin users during the study period

<table>
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<tbody>
<tr>
<td>Favourable outcome (n = 84)</td>
<td>33 (22.6)</td>
<td>24 (22.4)</td>
<td>27 (21.1)</td>
<td>0.950</td>
</tr>
<tr>
<td>In-hospital mortality (n = 23)</td>
<td>18 (8.2)</td>
<td>6 (5.6)</td>
<td>5 (3.9)</td>
<td>0.319</td>
</tr>
</tbody>
</table>

*Statin use or hypercholesterolemia.
6. This comment of the SPARCL study is also included: “The Stroke Prevention with Aggressive Reduction in Cholesterol (SPARCL) study found that –as compared to placebo- the use of high-dose atorvastatin in accurately selected patients who had a stroke or TIA was associated with a non-significant 13% risk reduction of non-fatal stroke during a 5-year follow-up without improving survival [30].” The reference is also added.

**Discretionary Revisions**

1. As previously indicated we have changed “spontaneous neurological recovery” is substituted by “favourable outcome”, which includes spontaneous neurological recovery and minimal stroke associated disability at discharge” in the tables and throughout the text.

2. In the Methods section, we have clarified: “The outcome of patients was classified as favourable outcome (spontaneous neurological recovery or minimal stroke associated disability at discharge (mRS grades 0–2), and unfavourable outcome (not improved, mRS grades 3–5 or in-hospital death).”

3. We have clarified the procedure of the multivariate analysis. This new information is added: “data from patients with and without favourable outcome (mRS grades 0–2) were compared with the Student’s t test, χ² test and the analysis of variance (ANOVA) when appropriate. Statistical significance for inclusion in the multivariate analysis was set at P < 0.02. Variables related to either in-hospital death or favourable outcome in the univariate analyses plus sex and age were subjected to multivariate analysis with a logistic regression procedure. All variables selected were included in the initial model. Criteria for variables to remain in the model were based on the statistical significance of the Wald’s test (P < 0.05) and on the comparison of the estimated coefficient of each variable with the coefficient of the model containing only this variable. Variables that did not contribute to the model according to these criteria were removed and the model readjusted. The new model after removing a variable was compared with the former model with the likelihood ratio test. Age was used in multivariate analysis as a continuous variable with a constant odds ratio for each year.”

4. In the Discussion section, it is added that “Unfortunately, cholesterol levels were not considered in the study.”