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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AUTHORS’ COMMENTS TO SUGGESTIONS OF DR. LUCA MASCITELLI

Major Compulsory Revisions

The potential role of hypercholesterolemia is now mentioned in the Abstract’s conclusions. The sentence reads: “Use of statins or hypercholesterolemia before first-ever ischaemic stroke was associated with better early outcome with a reduced mortality during hospitalization and neurological disability at hospital discharge.”

In the Results section of the Abstract we have added: “Early outcome was better in the presence of statin therapy or hypercholesterolemia (cholesterol levels were not measured) with significant …”

In the Conclusion of the Abstract, we have added this sentence: “However, statin therapy may increase the risk of intracerebral haemorrhage, particularly in the setting of thrombolysis.”

In the Discussion section we have included these comments regarding thrombolytic therapy: “The present findings should be interpreted taking into account some limitations of the study. Cholesterol levels were not measured in the study and it should be mentioned that thrombolytic therapy was introduced in our hospital after the collection of the studied patients. Therefore, is not possible to generalize the results in a population of patients with stroke who undergo thrombolytic therapy. Although statin therapy may increase the risk of intracerebral haemorrhage, it has been shown that patients treated with statins before stroke had a better response to thrombolytic therapy [38]. On the other hand, in a study of gene expression of cerebral endothelial cells in rat brain tissue, atorvastatin reduced exogenous tPA-aggravated cerebral endothelial genes that mediate thrombosis and blood-brain barrier permeability. This could contribute to the beneficial effects of statins on thrombolytic treatment of acute stroke [39].” References #38 and #39 are added to the reference list.

In the Conclusion of the paper, it is also mentioned: “However, statin therapy may increase the risk of intracerebral haemorrhage, particularly in the setting of thrombolysis.”
AUTHORS’ COMMENTS TO SUGGESTIONS OF DR. DANIEL BERECZKI

We have shortened the Discussion and the large paragraph discussing the possible mechanisms of the beneficial effects of statins is almost deleted. We have rewritten and condensed this information as follows: “Statin drugs improve the outcome of ischaemic stroke patients through different mechanisms, including better cerebral collateral supply, a direct neuroprotective effect, plaque stabilizing effects, and induction of angiogenesis, neurogenesis and synaptogenesis [21–29]. The Stroke Prevention with Aggressive Reduction in Cholesterol (SPARCL) study found that the use of high-dose atorvastatin as compared to placebo 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].”

We have checked all percentages in Table 2 and errors corrected. In the footnote, it is clarified “Percentages in parenthesis unless otherwise stated. Percentages are calculated for the total number in each column.”