

Author's response to reviews

Title: Effect of pre-stroke use of ACE inhibitors on ischemic stroke severity

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Peter Newmark
Editor-in-Chief
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RE: MS 1513106270594539

Dear Dr. Newmark,

We would like to thank you, the editorial staff, and the reviewers for your thoughtful comments to improve the quality of the above referenced manuscript, and for accepting it for publication in BMC Neurology. We are submitting the final version for publication. We have made all the formatting changes that were requested by the senior assistant editor. We added a sentence to the "Authors' Contribution" to truly reflect Dr. Louis Caplan's contribution to this study. He does indeed meet the criteria for authorship.

We also made a few changes in response to the editorial board member's comments, as follows.

Comment: "The opening statement about the effect of ACE inhibitors on stroke being out of proportion to their effects on blood pressure is hotly disputed"

Change: We deleted the sentences stating that ACEI effect was likely unrelated to their blood pressure lowering action. This part now reads "In this trial, the use of the ACEI, ramipril, resulted in a 32% reduction in ischemic stroke risk despite minimal reduction in blood pressure (BP) [1], leading some to suggest that ACEI may also exert direct neuroprotective effects".

Comment: "The parent association of reduced severity with prior ACEI may be due to confounding factors (confounding by indication); with such a small sample size, it is difficult to adjust reliably for confounders"

Change: we added the following sentence to the discussion "It is possible that ACEI use reflected a greater degree of medical attention and more aggressive risk factor reduction in these patients, which subsequently lessened stroke severity.

Comment: "With the need for a large sample size to allow for better adjustments, it is unclear why they restricted themselves to a sample with MRI (which may have introduced some selection biases)"

Response: Dr. Fabregas raised similar concerns in the past. As stated in our earlier response, we routinely obtained MRI on all stroke patients who presented within 24h of stroke onset to our institution during the period covering data collection. CAT scan was reserved for patients who presented after 24h or who had contraindication to MRI. These indications for the latter group, in themselves, represent inherent selection biases. We, therefore, excluded them from our study.

Comment: "The prior hypothesis was very strong, so it would have been helpful if the authors could have taken steps to ensure that the people doing the data extraction/MR scan reading were blinded to the hypothesis, and the people looking at the clinical data were blinded to the MRI data and vice versa".

Response & change: The person who analyzed MRI data was indeed blinded to clinical data & patient's identity. We added a sentence to the methods section stating "An experienced researcher, blinded to clinical data and patient's identity, performed MRI measurements".

We thank you again for your time and support.

Regards,

Magdy Selim, MD, PhD