

Author's response to reviews

Title: Effect of Pre-Stroke Use of ACE Inhibitors On Ischemic Stroke Severity

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Author's response to reviews: see over

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Peter Newmark
Editor-in-Chief
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RE: Revised Manuscript (MS 1513106270594539)

Dear Dr Newmark,

Please find our revised manuscript, "Effect of Pre-Stroke Use of ACE Inhibitors On Ischemic Stroke Severity". We have substantially modified our manuscript based upon the comments of the reviewers. A major change was based on a suggestion by Dr. Joan Marti-Fabregas to include all consecutive patients with acute stroke in our statistical calculations and to report MRI data as a sub-study. As a result, we report different numbers and results in this revised version. However, the main conclusion/finding remained unchanged.

We thank the reviewers for taking the time to review our work and for their thoughtful criticism and suggestions to improve our study. Below is a point-by-point response to their comments and suggestions.

Reviewer 1 (Dr. Majaz Moonis)

"Can the authors comment about the difference amongst groups between ACEI and non ACEI with respect to moderate stroke (NIHSS 7-14). It is not clear from the abstract or the results. While the abstract suggests that strokes were categorized as mild, moderate and severe, the methods suggest that the results were dichotomized into mid and severe stroke based on the NIHSS unless the NIHSS was used as a continuous variable. Please clarify."

Response:

Dr. Moonis' initial impression is correct. We did categorize stroke severity into mild, moderate or severe based on pre-determined NIHSS score cut-offs. Although, we did not directly report the differences in moderate strokes in the results section of our original submission, we did include the percentages of mild, moderate and severe strokes in Figure 1 of our earlier submission. We have eliminated Figure 1 from the current submission per reviewer 2 suggestions. We have re-organized our results section and now report the percentages of patients with mild (NIHSS ≤ 7), moderate (NIHSS 8-13) or severe (NIHSS ≥ 14) strokes in both ACEI and non-ACEI groups within the text.

Reviewer 2 (Dr. Joan Marti-Fabregas)

“This is an interesting study in which the authors suggest that patients with ischemic stroke pre-treated with any ACE inhibitor (ACEI) suffer less severe strokes, as measured by the NIHSS score. Patients were divided in 2 groups (ACEI vs. non-ACEI) and their mean NIHSS scores were compared. However, before accepting the results, there are some methodological problems that should be solved:”

“1) NIHSS scores should be provided as median values, and the authors should compare median NIHSS scores between groups (Mann Whitney U test) instead of mean values”.

Response:

We did follow Dr. Marti-Fabregas' suggestion and now report the median values, instead of means, for baseline NIHSS scores. The median NIHSS score is 5.5 (range 2-21) among ACEI-treated patients vs. 9 (range 1-36) in non-ACEI patients ($p=0.036$, Mann Whitney U test).

“2) Some studies showed that people with less severe strokes are admitted later and patients with more severe strokes are admitted earlier at the Emergency Room. Therefore, the authors should provide and compare the time from stroke onset to admission NIHSS between both groups.”

Response:

We thank Dr. Fabregas for bringing up this point. Indeed, we took a second look at our cohort and found that the median NIHSS score was 14 among patients who presented within 3h of stroke onset, 9 among those who presented between 3-6h, and 6 in patients presenting after 6h. We added the mean time from stroke-symptom onset to evaluation in each group to our results. The mean time from stroke-symptom onset to evaluation was 10.9 ± 5.2 h in ACEI-treated patients vs. 11.3 ± 6.4 h in non-ACEI group ($p= 0.62$). We found that 61% of patients in the ACEI group were evaluated within 6h of stroke onset vs. 63% in non-ACEI users. We added a paragraph to the discussion stating that “*Some epidemiological studies show that greater stroke severity at onset is associated with a shorter interval between symptom onset and time to emergency department arrival [12], suggesting that the observed difference in baseline NIHSS could be attributed to dissimilar distribution of patients' arrival time to the hospital. However, a roughly identical proportion of patients in both groups presented to our hospital within 6 hours of stroke-symptom onset.*” It is important to point out that our stroke team routinely evaluated all stroke patients within minutes of their arrival to our emergency department & that members of our stroke team, themselves, performed imaging studies (mostly MRI with DWI/PWI) within minutes of their evaluation during the time frame of this study.

“3) One explanation for the results is that lacunar infarcts are over-represented in the ACEI group. This is consistent with the idea that arterial hypertension is a risk factor for lacunar infarct and therefore more patients with lacunar infarct are treated with antihypertensive drugs. However, lacunar infarcts are a subtype of cerebral infarcts with a relative good prognosis, and lacunar infarcts will usually have a lower NIHSS score than total or partial non-lacunar cerebral infarcts. The authors should therefore re-analyze the results after controlling for stroke etiology.”

Response:

We did adjust for stroke mechanism/etiology, and other potential confounding variables by using the Cochran-Mantel-Haenszel row mean score test using ranks adjusted for stroke mechanism, time from stroke onset to evaluation, risk factors and other concomitant medications. The difference in baseline NIHSS score remained statistically significant ($p= 0.042$) after controlling for these co-variables. We re-wrote the section on statistical analysis and detailed the covariates included in the Cochran-Mantel-Haenszel row mean score test in the results section.

Furthermore, we re-analyzed our data after excluding patients with lacunar strokes. The median NIHSS score at admission was still lower in the ACEI group when the analysis was limited to patients with non-lacunar strokes (8.5 vs. 12; $p= 0.03$). We now include this information in the results section. We also added the following statements to the discussion *“We found a greater preponderance of lacunar strokes among ACEI-treated patients and cardioembolic strokes among non-ACEI patients. However, these differences were not significant and the difference in baseline NIHSS remained significant even after excluding patients with non-lacunar strokes from analysis” and “ Finally, it is noteworthy that the difference in baseline stroke severity between ACEI and non-ACEI groups remained statistically significant after adjusting for the above confounding variables”.*

“4) All consecutive patients with a diagnosis of ischemic stroke must be included in calculations. There is no reason to exclude those patients in whom a MRI was not obtained or was of poor quality. If they had an ischemic stroke, they must be included. The MRI sub-study can be done with a subset of patients.”

Response:

It is a routine practice at our institution to perform MRI on acute stroke patients, especially if they present within 24h of stroke symptom onset. We only perform CT on a minority of patients, often those with stroke > 24h, those with severe pre-morbid functional impairment, or those who have contraindications to MRI. Therefore, we decided not to include patients who had CT in this study given the obvious inherent selection bias outlined above. We re-analyzed our data after including all 126 patients who had MRI (regardless of its technical quality) and

presented within 24h of stroke onset during the study's period. We limited our MRI data analysis to a subset of 110 patients, after excluding 16 patients in whom MRI was of poor quality, as Dr. Fabregas suggested.

“5) As it has been demonstrated that previous Transient Ischemic Attacks elicit ischemic tolerance of the brain and patients with previous TIA have less severe strokes than patients without previous TIA, it would be useful to know the frequency of TIA in this study, and to calculate this variable in the 2 groups of patients (ACEI and non-ACEI).”

Response:

We thank Dr. Fabregas for this thoughtful criticism. We now report the percentages of patients with prior “TIA” in each group. We also added a paragraph to the discussion stating “*Recent studies have shown that TIAs before stroke can induce tolerance (ischemic preconditioning) to subsequent strokes by raising the threshold of brain tissue vulnerability, which results in smaller infarct volumes, and better recovery [9-11]. We found no significant differences in the frequency of prior history of TIAs, as reported by the patient or his/her family, between the ACEI and non-ACEI treated patients. In fact, a slightly higher percentage of patients in the non-ACEI group reported history of TIAs prior to their presenting stroke.*”

“6) The authors must explain whether they checked for compliance. It is frequent that patients with high blood pressure are non-compliant. Patients or their relatives should be asked about the last time that the patient received the treatment before the stroke.”

Response:

Unfortunately, we did not ask for compliance and we are unable to retrieve this information given the retrospective nature of our study. We added a sentence to the methods section stating “*We did not collect information about the duration of medication(s) use, daily use or compliance. Patients and families were only questioned about patient’s use of medication(s), including ACEI, in the week before stroke*”. We also added the following statement “*Similarly, we cannot be certain of the duration of treatment or compliance with daily use of ACEI in our patients*” to the discussion to highlight this limitation.

“7) The authors classified the stroke severity in mild, moderate and severe. This classification is arbitrary and not useful. Figure 1 is therefore unnecessary”.

Response:

We agree with Dr. Fabregas that our classification of stroke severity is based on arbitrary NIHSS cut-off points. However, we respectfully disagree that it is not useful. Several other studies have used similar cut-off points to categorize stroke severity. We believe this categorization provides an easy-to-follow overview of

the distribution of stroke severity/deficits among ACEI and non-ACEI groups. We deleted figure 1, and added the following statement “*We also used an arbitrary cut-off for NIHSS scores to categorize stroke severity. It is possible that different cut-off values could lead to different results*” to the discussion, in response to Dr. Fabregas’ comments.

“8) Although there were no differences in blood glucose and body temperature at admission, the values should be provided”.

Response:

We added these values to the results section.

“9) In Table 1, the p values of non-significant differences should be provided”.

Response:

We added all p-values to table 1.

“10) It is conceivable that if ACEI have some effect in provoking less severe strokes, the higher the dose of the drug the higher this effect. Therefore, it would be useful to analyze if there is an inverse relationship between the ACEI dose and the NIHSS score. Such dose-effect would reinforce the results of the study.”

Response:

While this concept seems appealing, establishing a dose-effect relationship is difficult given the retrospective, non-randomized nature of our study, and the use of four different classes of ACEIs. It is unclear how the different dose-regimens compare among various agents. Additionally, our sample size is too small to allow us to conduct any meaningful statistical subgroup analysis regarding differences among the various ACEIs or dose regimens within the same class. We added the dose-range used by our patients for each ACEI to the results section, given Dr. Fabregas’s concerns.

“11) The abstract should state that the study is retrospective”.

Response:

The first sentence in the methods section of the abstract now reads, “*We retrospectively studied 126 consecutive patients presenting within 24 hours of ischemic stroke onset*”.

“12) It would be interesting to analyze the results in patients admitted within the first 6 hours after the onset of symptoms.”

Response:

We now report the difference in baseline NIHSS between ACEI and non-ACEI patients who were evaluated and imaged within 6h from stroke onset.

“13) It would be interesting to have the 3-month follow-up of the patients included in the study. If patients pre-treated with ACEI have an increased probability of favourable outcomes, this would reinforce the suggested protective role of ACEI. However, as the authors state, this is not possible because some patients were treated with thrombolysis, endovascular treatments and neuroprotectants”.

Response:

Unfortunately, we do not have 3-month follow-up data for all of our patients. Furthermore, as we point out in the discussion and as Dr. Fabregas acknowledges, it is not possible to attribute favorable outcome to ACEI use alone since a large number of our patients were treated with t-PA or other experimental therapies upon presentation.

“14) Recent papers stress the effect of ACEI on cerebral autoregulation and cerebrovascular reactivity. This point should be included in the Discussion”.

Response:

We did allude to this effect of ACEI in our earlier submission by stating that *“ACEI may help maintain homeostatic balance of fibrinolytic and procoagulant factors and increase cerebral blood flow”*. We added the following statement to the discussion to highlight this effect of ACEI *“Recent studies using transcranial Doppler ultrasonography have shown that perindopril can improve the cerebral vasomotor reactivity in patients with lacunar infarcts beyond any effect on BP [22], and that treatment with quinapril can ameliorate cerebrovascular reactivity caused by methionine-induced hyperhomocysteinemia in healthy volunteers [23]”*.

Reviewer 3 (Dr. Janet L Wilterdink)

“1) There are a few typos - which will probably get corrected in the prepublishing edit. - eg on the abstract "Patients on ACE-inhibitors prior to [their stroke] had more milder stroke [more mild strokes would be better], and...”

Response:

We thank Dr. Wilterdink for pointing out these errors. We corrected this particular error/omission and performed a spelling and grammar check on the entire manuscript to minimize these mishaps.

“2) The only question I had was whether it might be reasonable in the statistical analysis to control for stroke subtype and other medication use. Even though these were not statistically different between the two groups, it is my understanding that they might still have significant confounding or modifying effects.”

Response:

We did adjust for stroke mechanism/etiology, and other potential confounding variables, including concomitant medications, by using the Cochran-Mantel-Haenszel row mean score test using ranks adjusted for these co-variables. The difference in baseline NIHSS score remained statistically significant ($p= 0.042$) after controlling for these co-variables. This was vaguely, and admittedly poorly, described within the text in our earlier submission. We re-wrote the section on statistical analysis and detailed the covariates included in the Cochran-Mantel-Haenszel row mean score test in the results section. We also re-analyzed our data after excluding patients with lacunar strokes. The difference in NIHSS score at admission remained statistically significant even when the analysis was limited to patients with non-lacunar strokes (8.5 in ACEI-treated patients vs. 12 in non-ACEI group; $p= 0.03$). We added this recent analysis to our results section.

Thank you again for considering our manuscript. We look forward to your response.

Regards,

Magdy Selim, MD, PhD