Author's response to reviews

Title: Ethnicity and thrombolysis in ischemic stroke: a hospital based study in Amsterdam

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Author's response to reviews: see over
To: the Editorial Board of BMC Neurology

Amsterdam, 31-05-2011

Dear Editor,

We are pleased to submit the revised version of our manuscript ‘Ethnicity and thrombolysis in ischemic stroke: a hospital based study in Amsterdam’.

We have revised the manuscript according to the comments of the reviewers. Below you will find a point-by-point response to the concerns. We hope you will consider our manuscript in its current form suitable for publication in BMC Neurology.

Sincerely yours,

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Response to reviewers

Reviewer 1


We added the suggested reference to the introduction.

Reviewer 2

1. Ethnicity and race have been used interchangeably in the medical literature. However, I would suggest the authors to be consistent. For example on page 4 (last sentence of first paragraph of ‘Methods’- the two commonest ethnicities were ‘black’ and ‘hindustani’. However, in the 2nd paragraph of ‘Methods’- the ethnicities are different.

To remain consistent, we only use the word ‘ethnicity’ and not ‘race’. The term Hindustani has been replaced by Asian.

2. Since authors have lumped various ethnicities into 2 broad group of race (white and non-white), the word ‘ethnicity’ becomes redundant.

We agree that the word ethnicity was redundant at several points in the text and removed the term or changed it to “white vs. non-white”.

3. Some simple questions might come in the minds of the readers. How many patients could not be thrombolysed due to the failure of bringing blood pressure to acceptable range? Were there any patients who were not thrombolysed due to low NIHSS on presentation? Both the factors could have contributed towards lesser rates of thrombolysis among ‘non-whites’. I understand that some of the questions may not be easy to answer in a retrospective study. However, these are valid questions and the possibilities need to be mentioned.

In our hospital we never pharmacologically reduce the blood pressure before thrombolysis, so this cannot have been a factor. We now mention this specifically in the methods (page 5, under “thrombolysis protocol”). A low score on the NIHSS is indeed a potential confounder and therefore we examined this variable in the logistic regression analysis (NIHSS 4 or lower). The variable had no significant effect on the relation between thrombolysis and ethnicity (<5% change in OR) and was therefore not used in the multivariate analysis.
4. Table 2 and 3 produce confusion in the minds of the reader. Table 2 shows that there were no significant differences in 'onset-to-treatment' or 'door-to-needle' times. That means, there were no differences in 'the time elapsed outside the hospital' and the 'time elapsed inside the hospital'. However, the rates of thrombolysis were significantly different between the two groups. Now, in table 3, authors show that significantly larger number of patients presented to the hospital beyond 2.5 hours (150 minutes). I would advise the authors to present these numbers more clearly.

We agree that our manner of presentation on this subject was confusing. The numbers regarding the onset-to-treatment and door-to-needle times are derived from thrombolysed patients only, not the whole cohort. The numbers in table 3 are based on the entire cohort. We changed table 2 to address this and hope that it is clearer to the reader now.

Reviewer 3

1. The authors contacted patients via telephone to acquire missing data and a considerable proportion of cases had missing data as reported in the results. More detail is needed regarding the nature of this missing data. For example, it is not clear what data elements were missing and to what extent. It is also of interest to note whether missing data varied by ethnicity which could impact the validity of the study findings.

We believe that our manner of describing this aspect was somewhat confusing in the first draft of the manuscript. In the cases where patients were contacted by telephone, this was done to assess ethnicity, since this variable was often not available in the patients chart or stroke database. Sometimes other missing values such as smoking status and medication use were collected. However, this occurred only sporadically and therefore we cannot perform a sensitivity analysis to investigate whether this influenced the validity of the findings. We clarified the nature of the missing values in the first paragraph of the results (page 6).

2. The authors combined data from various ethnic minorities into a single group because of sample size issues. Presumably the black and Asian subgroups could vary considerably with respect to the potential confounding factors. The authors should at least provide the descriptive data regarding treatment rates by the ethnic subgroups.

We added the thrombolysis rates for Asian and black ethnicities to the results section, which are similar (both 7%).

3. The authors state that a 5% rule for determining confounding was used. Based on the data presented in table 4 it seems several other factors like gender and mild stroke fit the author’s criteria of
confounding but were not described as such and therefore were not included in the multivariable model. This requires clarification.

The numbers presented in table 4 are rounded off to 2 decimals, but to calculate the change in OR in the bivariate models, we obviously used the raw numbers. The actual OR for ethnicity and thrombolysis was 0.343. For instance, adding gender to the model changed the OR to 0.358. This constitutes a change in OR of 4.4%. Hence, gender was not used in the multivariate analysis. Similarly, previous stroke and diabetes, NIHSS<5 and NIHSS>25 resulted in changes in the OR of less than 5%.

4. An important aspect of confounding is the nature of the relationship between the confounding factor and the outcome of interest. In this regard it would be of interest to include a table of the associations between the various confounders and tPA treatment. We calculated the different OR's of the confounding factors and thrombolysis and added this information to table 4.

5. In the methods the author state that they used “stepwise” logistic regression but from the way the results are presented it does not appear to be the case - i.e., variables were selected for inclusion based on their confounding of the main association of interest. The approach utilized seems correct. I would recommend that the language regarding the stepwise approach be modified to reflect the actual analysis. This is indeed a mistake. We removed the term “stepwise” and just describe the method of logistic regression.

6. The authors provide an interesting analysis of potential explanations regarding the observed ethnicity association. If sample size permits it would be of interest to see what happens to the ethnic association among the tPA eligible population. This would speak to other potential causes to ethnic differences in tPA treatment. If we understand the reviewer correctly, she would like to see the association between ethnicity and thrombolysis among the ‘tPA eligible patients’. For some variables it is difficult to say in general whether it precludes a patient from being thrombolysed. For instance, a patient with a NIHSS score of less than 5 may still be treated with tPA if the neurological deficit is considered disabling. Therefore, we chose to perform a subgroup analysis wherein only patients with an unconditional contraindication for thrombolysis were removed (arrival hospital after 2.5 hours from symptom onset, blood pressure above 185/110 and oral anticoagulation use). In this subgroup, which constitutes approximately one-third of the original cohort, non-whites were still less often treated with thrombolysis, although the difference was no longer significant (45 vs. 29%, p=0.12). This information was added to the results section (end of paragraph 2 of the results, page 7).
7. The authors state that their results are not impacted by insurance status. These statements are not clear. If insurance status varies by ethnicity then their is the potential for this factor to play a role. According to Dutch law, hospitals and doctors are obliged to provide emergency medical care (which includes thrombolysis) to any person, regardless of insurance status. Therefore, even if there were a difference in insurance status between ethnicities (we did not measure this), this cannot have influenced the decision to treat a patient with thrombolysis. Of course, insurance status could have an effect on whether a patient decides to come to the hospital, and how fast. This was not properly addressed in the first draft, so we adapted the discussion to clarify this (page 9).

8. Several aspects of the abstract require further detail including: 1) explanation of what constitutes "non-white", 2) a few sentences regarding the statistical analysis methods, 3) clarification of the data presented in the results - are these means or medians, 4) what confounders were adjusted for in the multivariable model. We added the suggested information to the abstract.

9. In the discussion, the authors raise the issue of ethnic differences in stroke awareness. There is a considerable body of literature on this topics that could be cited to support this line of discussion. Thank you for the suggestion. We added a number of references.

10. Do the authors have data on patient refusals or consent issues for tPA treatment? This data could provide an alternative angle to ethnic differences in treatment. If they do not this would be worth mentioning in the discussion. We do not have data on patient refusals or consent issues. However, in our experience it is extremely rare that patients do not receive thrombolysis due to lack of consent. According to national law, we inform patients and/or their relatives about the potential benefits and risks of thrombolysis and explain that the benefits generally outweigh the risks. Consent only needs to be given verbally. If the patient cannot provide consent, and there are no relatives present, thrombolysis is given without consent.