Author’s response to reviews

Title: Gender and thrombolysis therapy in stroke patients with incidence dyslipidemia

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Author’s response to reviews:

We thank the reviewer for insightful and constructive criticism of our manuscript “Gender and exclusion from thrombolysis therapy in stroke patients with incidence dyslipidemia.” We have significantly revised the manuscript based on the comments raised on the earlier version of the manuscript by the reviewers. The response on our own part is provided, each comment is copied and addressed below as in the new version of the manuscript.

Reviewer 1

Comments

Although questions have been raised on the use of recombinant tissue plasminogen activator (rtPA) for the treatment of Ischemic stroke, the risk it presents to patients has led the exclusion of some patients from the therapy. This study aimed at examining the gendered differences in the inclusion and exclusion of patients from the therapy. This may be the first study to examine such differences and provides sufficient evidence to determine the risk factors that can be targeted to eliminate gender differences and improve the use of rtPA in the management of acute ischemic stroke patients. There are a few minor comments that need to be addressed before the paper goes for publication.
Response. We appreciate the comments of the reviewer. The reviewer is right, the goal is to determine the risk factors that can be targeted to eliminate gender differences and improve the use of rtPA in the management of acute ischemic stroke patients.

Comments.

1. The introduction of the paper was well written and is logically coherent. However, I will ask that the authors indicate the questions or hypothesis guiding the study in the concluding paragraph of the introduction.

Response. We thank the reviewer for this comment. We have clearly articulated the rationale and the hypothesis that was tested in this study. Briefly, when untreated, dyslipidemia is a higher risk factor for stroke and stroke-related mortality in men than in women. However, when dyslipidemia is treated the risk reduction is the same, but men benefited from mortality reduction more than women. Whether there is a gender difference in exclusion criteria for the use of thrombolysis therapy in an acute ischemic stroke subpopulation with dyslipidemia is yet to be investigated. If a greater benefit of thrombolytic therapy continues to persist in women within the stroke population with dyslipidemia, one possibility is that there is a disproportionate distribution of demographic and clinical risk factors between male and female acute ischemic stroke with incidence dyslipidemia, such that more male or female or vice versa maybe excluded from thrombolysis therapy. We tested this hypothesis in a population of female dyslipidemic acute ischemic stroke patients and compared our results with male dyslipidemic acute ischemic stroke patients. Secondly, we determined the effect of demographic and clinical risk factors that influence the exclusion or inclusion of acute ischemic stroke patients with incidence of dyslipidemia from thrombolysis therapy.

Comments.

2. It will add depth to the paper if the authors provide statistical evidence for the number of men and women who are at risk of stroke and those who died from stroke to show for the gender differences (e.g. reference could be made to the past year).

Response. We thank the reviewer for prompting us to provide additional information to strengthen the manuscript. Briefly, female stroke patients are known to present with more severe symptoms, less likely to recover all functions, poor outcomes, and a general reduction in quality of life when compared to men stroke patients[15-18]. Moreover, women are more likely to present with atrial fibrillation[19], and hypertension[20], whereas men are more likely to present congestive heart disease and diabetes[21]. These studies reveal evidence of a gender difference in stroke symptoms and past clinical history. The current study determined the effect of demographic and clinical risk factors that influence the exclusion or inclusion of acute ischemic stroke patients with incidence of dyslipidemia from thrombolysis therapy.

Comments
3. The authors excellently provided a general overview of the data collection process and do refer to the description of the GHS registry in previous studies. However, it will be beneficial to readers if the authors briefly provided a description of the GHS registry highlighting how data on each of the variables was previously collected and coded for the analysis.

Response. We thank the reviewer for this comment. We have added that all data including neuroimaging data were reviewed by a clinician, who determined whether the patient met the clinical case description of acute stroke. The events were categorized as ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage according to descriptions of stroke from the Classification of Cerebrovascular Diseases III. A stroke nurse identified and abstracted data for the patient’s demographics, clinical variables that were used for the study. Stroke risk factors were determined through evaluation of the documented patient medical history retrieved during admission to the stroke unit.

Comments.

4. The authors make an important statement regarding data collection as being scrutinized under quality control checks. The statement will be more complete if the authors indicated who embarked on the quality control checks and how it was done (could refer to the protocol).

Response. We have clarified the statement further in the revised version of the manuscript. The quality control check was done by the stroke program director using established protocol. This was done to ascertain the quality of the data and to insure against several types of errors, including errors in interpretation or coding, and errors in data entry. An important quality control check is the data cleaning to ameliorate data problems, including missing values, incorrect or out-of-range values, responses that are logically inconsistent with other responses in the database, and duplicate patient records. This was done with automated data checks that were preprogrammed into the database.

Comments.

5. The current statement of the authors on ethics committee approval of the study does not state which institution approved the study and when it was approved. The authors should kindly add such details for clarity. I see this at the end of the manuscript but could be repeated within the manuscript (Kindly refer to the journal author guidelines).

Response. We have added the statement on ethics committee approval in the manuscript. Our study was approved by the ethics committee of the Greenville Health system in 2017. This study is a retrospective data analysis and all data were de-identified.

Comments.
6. The authors should clarify whether rtPA in this study is used as a form of thrombolysis therapy for clarity. Its current application in the study is a bit confusing. The authors should consistently refer to rtPA or thrombolysis therapy to eliminate any confusion.

Response. We clarified that rtPA in this study is used as a form of thrombolysis therapy in the revised version of the manuscript.

comments

7. The paragraphs in the discussion are well developed; however, there seems to be a missing piece. The implications for the treatment of men and women with dyslipidemia. Currently, the paper does not address factors that increase the likelihood of being excluded from a thrombolysis therapy and how that can be checked.

Response. We thank the reviewer for prompting us to discuss more on the implications of our findings in the treatment of men and women stroke patients with dyslipidemia. In an adjusted analysis, elderly female patients with increased age, with a history of carotid artery stenosis, and previous stroke were more likely to be excluded from rtPA. Male patients with atrial fibrillation, carotid artery stenosis, and previous stroke were more likely to be excluded from rtPA. In our findings, elderly female stroke patients with incidence of dyslipidemia are more likely to be excluded from rtPA, even after adjustment for the effect of confounding variables, indicating a pattern towards a higher exclusion of older women than men. Understanding pre-treatment demographic and clinical variables that contribute to a gender difference could help eliminate any gender treatment disparities and improve treatment outcome in dyslipidemic stroke patients irrespective of gender. A better management of stroke patients with incidence of dyslipidemia irrespective of gender could improve the use of rtPA and stroke treatment outcomes. Investigating therapies targeting dyslipidemia may thus be useful to improve rtPA outcomes in patients with acute ischemic stroke.

(Reviewer 2):

In this paper the question the authors wanted to clarify is how dyslipidemia may interfere with the usual risk factors for exclusion from the thrombolysis therapy, knowing that women are more often excluded than men.

Comments.

The 3 multifactorial analyses show that women are more excluded from the treatment than men even though carotid artery stenosis and previous stroke are important risk factors for both. On the other hand, NIH stroke scale is for both a risk factor for inclusion to the thrombolysis therapy. Two other factors differentiate men and women for inclusion, one is clinical, antiplatelet medication for men and antihypertensive medication for women, and last but not least age for women.
Response. We appreciate the comment of the reviewer. The current study provides a significant addition to understanding the gender-related exclusion from rtPA associated with acute ischemic stroke with incidence of dyslipidemia. The importance of gender and age as risk factors in dyslipidemic stroke cannot be underestimated.

comments

I see an important weakness in the demonstration. The studied population has been selected retrospectively; so we cannot ignored that selection bias had been present probably in the acute ischemic stroke population and that this selection bias was associated with gender.

The scientific approach would be improved by two aspects; firstly, prospective selection of patients and not a retrospective study in a single institution, and secondly, analysis by stratified population of men and women by age. I want to say to analyse the different risk factors including sex among the stroke patients with dyslipidemia being at the same age.

Response.

We thank the reviewer for this comment, and we agree with the reviewer that preselection bias is a limitation in a retrospective study. We have included this in the limitation section of the revised manuscript. We also appreciate the suggestion of the reviewer for a prospective study with a selection of patients with an analysis in a stratified population of men and women of the same age. We really appreciate this suggestion for our prospective study.