Author's response to reviews

Title: Admission C - reactive protein after Acute Ischemic Stroke is associated with Stroke Severity and Mortality: The Bergen Stroke Study.

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Author's response to reviews: see over
Dear Editor,

We thank you very much for reviewing our article. We greatly appreciate the valuable comments and criticisms of the referees which enabled us to improve the quality of the article. We have made substantial changes to the article as suggested by the referees. Below, please find our point by point response to your comments.

Your's faithfully,

Dr. Titto Idicula (for authors)

Response to the comments of Referee 1 (Luca Masotti)

1. High CRP in acute phase of stroke is associated to stroke severity, probably related to infarct size. You should evaluate the relation between CRP and infarct size (for example < 1.5 cm vs >1.5 cm) for each stroke subtype.

We do agree that the relationship between high CRP and stroke severity is probably related to infarct size. We don't have volume measurement for all our patients. Therefore, we cannot evaluate infarct size for each subgroup of stroke.

2. Functional disability, acute phase mortality, long term mortality are all associated to CRP values and these were well described by meta-analyses not cited and discussed from You (see Di Napoli M et al Stroke 2005).

The article by Di Napoli et al was an important basic element in our discussion during the preparation of the manuscript. Regrettably, we failed to include it in the manuscript. We have, of course, included this reference in the revision. The pivotal paper by Di Napoli et
al concluded that there is uncertainty on the role of CRP in stroke patients. Therefore, we believe that our paper adds to the present knowledge basis and provide some future orientation.

3. *You should evaluate the relation between functional disability and treatment, for example thrombolysis; good outcomes could be the effect of treatment.*

Nineteen percent of our patients received thrombolysis. As you suggested, we did a further analysis by including thrombolysis. The result was essentially the same. The revised version is based on this new analysis.

4. *Introduction is too focused on ischemic heart disease: You should focused on CRP in cerebrovascular disease.*

Introduction is re-written with more emphasis on cerebrovascular disease and less emphasis on ischemic heart disease.

5. *The study is not well documented. You have omitted many important studies referred to this topic.*

More studies are included in the revision.

6. *In discussion You say that CRP is associated to cardioembolic stroke: it is not true.*

*This is probably the effect of major severity of cardioembolic stroke*
previously demonstrated.

We do agree. We have edited the discussion part and this argument is highlighted in the revision.

7. Table 3 and 4 are not present in supplementary materials.

We apologize for the mistake. We have corrected the mistake.

8. The important size and long follow-up of Your study don't justify the clinical implication of Your results compared to other studies.

We made changes in the 'conclusion' so that the implications are under-stressed.

9. English should be revised

We have gone through the language part thoroughly and necessary revisions are made.

10. in References You write Di NM...: do You mean Di Napoli M.? Please modify.

We modified it, thanks.

Response to the comments of referee 2 (Tunde T Magyar)
1. There is a tendency to overinterpretation of the results in "Abstract" in "Conclusion" part, when authors wrote that "admission CRP is associated with short term functional outcome". This sentence contradicts the "Results", where "High CRP was not associated with short term functional outcome after adjusting for confounding factors". It should be discussed more circumspectly.

   We agree. ‘Conclusion’ part in the ‘abstract’ is modified and we have discussed it in details under ‘discussion’.

2. In "Background" part there is a typing error: in JUPITER trial not rovustatin effect, but rosvastatin effect was examined.

   Thanks, corrections are made.

3. Methods:

   What do authors mean "pre-existing illnesses"? Hypertension, diabetes mellitus, smoking habit and previous CV disease, what they used for statistical analysis, or did they consider the other factors what may have influence on CRP level?

   How did authors work with the patients with infections, malignancies, autoimmune diseases, surgery in recent past, generalized atherosclerosis, or lipid lowering therapy etc.? Exclusion criteria should be redefined.

   By 'pre-existing illness' we meant past medical history such as diabetes and hypertension.

   We did include them in the statistical analysis. Factors that were found to have a
significant association with outcome were included in the multivariate logistic regression analysis. These factors (pre-existing illness) along with age, gender and thrombolysis were included in the final analysis. However, we did not have sufficient data on infection and malignancies and therefore they were not included in the analysis.

4. Results:

Table 3 and 4 were the same tables, what I could download. I did not find OR, HR, Beta, * and ** on Table 3, what authors denoted on Table 3 legends. The article - tables - should be compiled more precisely.

We apologize for the mistake. They have been uploaded correctly in the revision.

5. Discussion:

TOAST criteria, stroke etiology, Table 3. Most part of stroke etiology is unknown based on Table 3, only in high CRP level group was the highest part of the cardioembolic origin. It should be discussed more circumspectly.

Yes, we do agree. We have included a detailed discussion in the revision.


Authors wrote in Methods, that acute vascular events were collected from the hospital registry, and mortality was collected from the National Population Registry of Norway. They don't know the reason of death of the patients. Is there any data about the hospitalization rate of the acute cardiovascular events from this area? I mean, is it possible that patients did not admit to the hospital because of the second acute
cardiovascular event, or the most part of the stroke patients died because of other reasons (pneumonia, pulmonary embolism, malignancy)?

Unfortunately we do not have data on hospitalization rate of cardiovascular events in our area. However, we do have data on vascular events for the study population. We found that CRP was not related with vascular events. Therefore it is very well possible that patients might have died of other reasons, as you commented. This is mentioned in the discussion part.