Author’s response to reviews

Title: Interatrial block in prediction of all-cause mortality after first-ever ischemic stroke

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Author’s response to reviews:

Dear Editor! Thank you very much for the possibility to revise our manuscript. We tried to reply for all comments. All changes made in the manuscript are marked (red).

Editor Comments:

Dear Professor Baturova

Many thanks for submitting your manuscript 'Intra-arterial block in prediction of all cause mortality after first-ever ischemic stroke' to BMC Cardiovascular disorders. After considering the comments of the reviewers and assessing the document myself, I believe that this may be of potential interest to our readers. However, the reviewers and I have raised some points which require revision. In addition to the comments below, I would also like to see you address the following points:

1) I think that the layout and transparency of the paper could be improved in general. There are large sections where data are reported in text, but are not shown in context in figures or Tables. For example, the OAC section contains significant data, but are only included in the text. I would
like to see a detailed data supplement detailing all of these findings for transparency and reference for the readers.

Response: Dear editor, thank you very much for your valuable comments. We have added detailed data concerning OAC and presented additional Figure 4 with Kaplan-Meier curves indicating survival in patients with and without IAB treated and not treated with OAC. The changes were made in the section Statistical Methods (lines 139-147) and Results (lines 217-234).

Of note, it would be very interesting to see the odds/hazards ratios for all included parameters in your multivariable analyses.

Response: We have added the hazards ratios of all parameters included in the multivariate analysis in the Table 4 showing the association of advanced IAB and partial IAB with all-cause mortality for the whole sample and included in the manuscript Table 5 with the results of multivariate Cox regression analysis separately in the group of patients with intermediate cardiovascular risk and in the group of patients with high cardiovascular risk.

2) For Cox regression models - was the proportional hazards assumption checked and adhered to?

Response: Yes, we have checked the proportional hazards assumption by graphical method generating log minus log plot. We have edited the Section Methods (line 123) by including this information.

3) Table 2 details Odds ratios for age (which is the only significant predictor), however units are not specified. I assume that the odds relates to a per-year increase in age? If so, perhaps consider providing this as a per 5 or 10 year increase as ORs generated for single years are very small, difficult to interpret, and possibly not clinically implementable.
Response: Table 2 reflects the logistic regression analysis showing the association of IAB with demographic and clinical characteristics of patients at the time of inclusion in the Stroke Register/admission with ischemic stroke. We included age of patients at stroke admission as a continuous variable and in the revised version of the manuscript dichotomized age at 65 years and 75 years, which we believe would make it easier to interpret for a reader. The changes are made in the Table 2.

4) Table 3 and Figure 3 concern me slightly, as you are trying to make firm conclusions based on a very small sample size (n=4 for patients with intermediate risk and partial IAB, with only 1 death). I would suggest that it is not appropriate to include the partial IAB, intermediate risk group in the Kaplan Meier analysis for this reason. In addition, this limitation should be clearly discussed in the appropriate section of the manuscript.

Response: We agree with this observation. In the revised version of the manuscript, we have changed the Figure 3, in which we have chosen to avoid separate presentation of survival for the small groups of patients with partial IAB and instead presented the two-group comparison of patients with advanced IAB vs patients without advanced IAB as our main message concerns mostly those this advanced IAB. In the text the changes were made in the Section Statistical methods (lines 134-138), in the Section Results (lines 197-201) and in the Section Limitation (lines 337-340).

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Reviewer reports:

Adrian Esterman (Reviewer 1): This is a well-written paper, on a topic with scarce literature. The methods are well described, however, I do have a couple of suggested modifications:

1. The authors should provide at least some justification for the sample size.
Response: Thank you very much for the evaluation of our paper. The sample size was limited to the number of ischemic stroke patients included in the Lund Stroke Register during the first year of the Register existence who had available ECG with sinus rhythm at stroke admission. We have further edited the description of the study sample in the section Material and methods, Study cohort on the page 3-4.

2. I would prefer the level of statistical significance to be set at (say) $p\leq 0.025$ to allow for the multiple comparisons.

Response: We have changed the level of significance in the Section Statistical methods. However, in our study all significant results on which we based our conclusions were at $p<0.02$.

3. There is no need to spell out IQR (line 82) - it is a widely accepted abbreviation

Response: We have removed the spelling.

4. In Table 4, with three categories of IAB there should only be two comparisons, eg Partial vs None, Advanced versus None

Response: Thank you for your advise. We have left two comparisons and have added parameters included in the multivariate analysis (see also editor comment #1 above).

Erik Biros (Reviewer 2): The authors "aimed to assess the association of IAB with all-cause mortality in first-ever ischemic stroke survivors during 10 years after stroke". The authors found that hazard ratio of death for whatever reason within 10 years after stroke is 4.99 ($p=0.008$). However, to achieve this, the patients have to be completely healthy except having the history of IAB and stroke. The IAB patients with stroke and comorbidities have hazard ratio of dying for whatever reason within 10 years after stroke approximately 1.0 ($p=0.966$). Anything that causes death is considered a cause of death. In this context, since advanced IAB could be a risk for embolic stroke, a potentially deadly cardiovascular event, the assessment of a cause specific mortality in IAB patients would be of higher information value for statistics in Sweden.
Response: Thank you very much for the evaluation of our manuscript. We fully agree that a cause specific mortality in patients with advanced IAB is very important as advanced IAB is a potential risk factor for embolic stroke. In our study we defined the only end point as all-cause mortality and did not perform the detailed data as number of died patients with advanced IAB in our study was not large (n=30). However, following the Reviewer’s advice, we have assessed the prevalence of the cerebral infarction as the cause of death in patients with and without advanced IAB. Of the 30 deaths in the advanced IAB group, 6 patients died from cerebral infarction (20%) while among those who did not have advanced IAB, it was the cause of death in 20 of 96 (21%, \( p=1.000 \)).

We included these data in the manuscript in the Section Results (lines 235-240) and edited Section Discussion (lines 319-331).