Author's response to reviews

Title: Management of oral anticoagulation after cardioembolic stroke and stroke survival Data from a population based stroke registry (LuSSt)

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Author's response to reviews: see over
Reviewer 1:

1. I suggest to better explain why having considered only patient with a first ever stroke/TIA (I guess, to better evaluate the "recurrence rate" in naive patients?).

We focused on FEIS as LuSSt is a population-based registry. Mortality rates can be compared to those of other population based registries. Recurrent ischemic stroke (especially cardioembolic stroke) cause higher mortality rates possibly confounding the analysis.

2. Was NIHSS assessed by trained personnel? Were all of the Ludwigshafen Klinikum patients admitted to the stroke unit or to other department? How many stroke units are cooperating in the Registry? Are there other treating specialists besides neurologists?

Presenting study methodology is a very important issue. We made changes to the subjects and methods section. According to remarks by reviewer three, we did not respond to all of these important issues. A more detailed description of LuSSt has recently been published (Palm et al. Stroke 2010).

3. Why had you considered old lacunar infarction or SAE in the same item?

We really thank the reviewer for this remark. Mixing up two different neuroradiological findings will lead to confusion. In order to reduce unimportant presented data (see reviewer 3) this item was deleted.

4. In table 1 some "old lesions" have been reported, while the sample has been defined as made of "first ever stroke" patients. Did you meant first ever "symptomatic cerebrovascular event"? If yes, this has to be acknowledged at some point. If no, you should explain the finding or exclude those patients from further analyses.

We apologize for lack of clarity. LuSSt is a population-based registry using epidemiological definitions of stroke (see Palm et al. Stroke 2010). We added further information in the text (p.6 l.5).

5. Why a CT/MRI has been repeated only within 5 days after the event? If a symptomatic bleeding occurred after this period, would it be recorded or not?

We are sorry for causing confusion. Hemorrhagic transformation, hemorrhagic infarction, parenchymal haematoma or subarachnoid hemorrhage in any CT/MRI were registered.

6. Could you provide the rate of early (=in hospital) ischemic stroke recurrence?

Rate of early stroke recurrence (7 days and 14 days) is provided in the results section (p.9 l.13).

7. From Table n° 2, I can see that also antiplatelet treatment before stroke and thrombolysis have been recorded: insert this in the Methods section text. For OAC-implementation, do you mean that patients finally received an OAC or an antithrombotic?

We apologize for causing confusion. Methodes section has been updated (p.7 l.9-11). We used OAC as synonym for VKA treatment. OAC implementation means finally VKA treatment.

8. Antiplatelets post stroke is an important, but missing, data. I think that patients that receive antiplatelets cannot be equalized to the ones that do not receive an antithrombotic at all. If this info cannot be regained, you should specify the design of the study as investigating the adherence in prescription of the recommended therapy for CES secondary prevention, not considering the other antithrombotics. The same consideration for LMW heparin, that often is used as a bridging therapy.

We thank the reviewer for this remark. As treatment with antiplatelets post stroke has been registered, we modified the results section (p. 8 l. 25 to p.9 l 2). The majority of patients (22/27) that received no antithrombotic treatment (neither OAC nor antiplatelets) died during hospital stay. Hence, this represents the result of very bad clinical condition. We therefore (also see 7.) excluded antiplatelet treatment from multivariate analysis.

9. Why having excluded patients who died early after stroke? Describe this subgroup of patient: number, causes of death, age, stroke severity... Have they been excluded because of an extreme clinical condition or comorbidity that would have influenced the whole statistics? In any case, this has to be explained and acknowledged.

It is our main objective to investigate the impact of OAC initiation (in hospital vs. post discharge) on mid-term mortality. As stroke severity is the main contributor to short-term mortality, we excluded all patients that died within the first week. We updated the results section (p.8 l.14). However, according to reviewer the comments by reviewer three, we avoided to provide additional information.

10. Please report the range of length-of-stay.

These data are now presented in the results section (p. 8 l.11).

11. About recurrences within 500 days: specify the rate of recurrence in the subgroups of patients received OAC during vs after hospitalization, and compare the finding.
These data are provided in the results section (p. 9 l.9). However, these small numbers do not justify statistical analysis.

12. “OAC management post stroke” is not a precise interpretation of data in the text: No-OAC after discharge (not recommended or recommended but not given) is independently associated with stroke mortality, while OAC started after discharge does not reach the statistical significance.

We really appreciate the reviewers remark and made the changes in the text.

13. Patient receiving OAC during hospitalization seem to be "healthier" than the other (lower NIHSS and mRS, younger, lower HAS-BLED, ...): this point could be discussed.

This is a really important remark. However, these differences between boths groups are included in multivariate analysis increasing the gap between both groups. We added in the text that it is the result of multivariate analysis which includes adjustment for stroke severity and age (p.10 l. 10).

14. "Increased risk of bleeding under (insert: early) treatment with OAC in more severe strokes might be"...

We thank the reviewer for his remark and made changes to the text (p.10 l. 11).

15. Study limitations: Consider my previous statements if the required missing data are in fact unavailable, and report the lacks in this section.

Study limitations were updated according to point 18.

16. I think the Authors should better explain and highlight, both in the Abstract and in the main text, the main finding of their work: "OAC non-treatment after CES is the main predictor of stroke mortality".

We thank the reviewer to remind us of this really important issue. Abstract, discussion and conclusion were updated.

17. In the Abstract: what do you mean for "eligible" patient? The previously called "healthier"? Perhaps "selected" patient would be more precise.

In the main text: Later initiation= post discharge?, and Early initiation= during in-hospital stay? The adjectives are intuitive, but in fact you do not report the exact timing (i.e., in days) of starting therapy.

We gratefully thank the reviewer for this suggestion which was implemented in the abstract (p.3 l.3).

18. Background: Contributing to a similar project in my country setting, I am aware of the fact that studying anticoagulants management by means of a registry is very difficult, because many clinical variables affect doses, timing and need of therapeutic shifts, with a huge body of information that has somehow to enter in a scheme. I think you should report in the Introduction this critical methodological issue.

According to this very important issue, we made changes to the limitations section. However, despite of all these disadvantages, population-based stroke registries represent real-life data including all challenges outside RCTs.

19. Almost the whole sample has a brain lesion on imaging. Can you provide the proportion of CT and MRI/DWI that were performed?

These data are now presented in the results section (p. 8 l.15).

20. Reasons of non-OAC implementation after discharge have been recorded?

Unfortunately, we are not able to provide these very interesting data.

Reviewer 2:

1. Suffered is not a synonym for parts of the verb to have. one can have a stroke without suffering

We apologize for this mistake. Changes have been made in the text.

2. is there any information about echocardiography results. these can be used as guide to the need for early anticoagulation

This is a very important issue. Competitive sources of cardiac embolism (such as endocarditis, ventricular thrombus) have been ruled out prior to study inclusion. We only report on patients with AF as the only cardiac source of embolism (p.7 l.2).
Reviewer 3:

Authors have provided lot of data without a clear objective. Multiple issues being addressed at the same time. It appears that primary objective is to compare early initiation versus late start of anticoagulation then it switches to compare started versus recommended versus not recommended. Tables are only comparing survived versus not survived out of 479 patients.

1. This paper needs to be re written with one or two primary objectives and only presenting data related to that objective. All other data related to registry should be written as a separate paper.

We gratefully thank the reviewer for his very important comment. As presented in the introduction, we do now primarily focus on two objectives.

2. Patients are divided into five groups based on management. It is too many. Just divide them in two groups: OAC started in hospital and OAC started post discharge and then compare these groups. Rest of data is confusing for readers.

We are sorry for causing confusion. With regards to our primary objective we do now only compare OAC non-treatment with OAC initiation in hospital and OAC initiation after discharge.

3. Methodology needs to be shortened and tailored for objective.
   Tables and figure needs revision. There is duplication of information in text and tables/figures.

We critically revised tables and figures. Considering the methodology we had to deal with questions raised by reviewer 1.

4. References are too many which again represent lack of focus

References were critically reviewed and reduced where possible.