PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Dabigatran initiation in patients with non-valvular AF and first acute ischemic stroke: a retrospective observational study from the SITS registry
AUTHORS	Escudero-Martinez, Irene; Mazya, Michael; Teutsch, Christine; Lesko, Norbert; Gdovinova, Zuzana; Barbarini, Leonardo; Fryze, Waldemar; Karlinski, Michal; Kobayashi, Adam; Krastev, Georgi; Paiva Nunes, Ana; Pasztoova, Katarina; Peeters, André; Sobolewski, Piotr; Vilionskis, Aleksandras; Toni, Danilo; Ahmed, Niaz

VERSION 1 – REVIEW

REVIEWER	Ole-Christian Walter Rutherford Sykehuset Østfold, Sarpsborg, Norway. University of Oslo, Oslo, Norway
REVIEW RETURNED	06-Feb-2020

GENERAL COMMENTS	Escudero-Martinez and collaborators have investigated timing of initiation of dabigatran among patients with atrial fibrillation after experiencing quite severe ischaemic strokes; treated with thrombolysis, thrombectomy or both. The topic is highly relevant: the timing of initiation of oral anticoagulation in this patient group is an important issue, with great consequence, where evidence is lacking. I also applaud the authors especially for chosing to study patients with more severe strokes. The manuscript is well written, and includes all important elements. My comments are the following: 1. The definition of outcomes could be clerarer. Either categorised as primary and secondary; or as clinical or non-clinical, or in some other manner. 2.Although used in the pivotal RCTs, the term "non-valvular" AF is now abandoned, and should largely be avoided. Instead one might refer to the specific reason a NOAC may not be used (e.g. mechanical heart valves). 3. On page 9, in the chapter on material and Methods, the authors state that they collected information about which patients that died. Although not listed as an outcome, I miss information about number of deaths in the results section, preferentially with cause of death included. I may have missed this, but it seems relevant, as haemorrhagic transformation is the main fear in this instance, and any deaths caused by ICH in the follow-up period are highly relevant. (I notice that only one case of ICH is registered, but does that mean that no patients died from ICH?) 4. Perhaps it should be made clearer in the text or in the flow-chart that although information about clinical events within 90 days was

	available for 926 patients, information about the primary outcome (timing of dabigatran initiation) was only available for 702 patients. 5. In the statistics section: Which potential confounders were adjusted for and how were these confounders identified?

REVIEWER	Suodi Zhai Department of Pharmacy, Peking University Third Hospital, Beijing, China
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	The study shows interesting and potentially useful results. However, a few points could be improved: 1. Please complete the abstract (methods). 2. The relationship between initiation time and clinical event is of more interest to readers. However, little was shown and discussed in this manuscript. 3. The description of statistical method is poor. Actually, I can't figure out what model was used in this study to assess the influence of initiation time on outcomes of interest. Besides, the calculation of incidence rate was also problematic. Methods should be specified for the calculation of 95% CI for incidence rate. 4. The study period is only three months, which is too short to observe outcome, for example, stroke and so on. 5. The discussion section should focus more on practical insights to clinical decision makings based on current guideline recommendation.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Ole-Christian Walter Rutherford

Institution and Country: Sykehuset Østfold, Sarpsborg, Norway. University of Oslo, Oslo, Norway

Please state any competing interests or state 'None declared': None declared

Escudero-Martinez and collaborators have investigated timing of initiation of dabigatran among patients with atrial fibrillation after experiencing quite severe ischaemic strokes; treated with thrombolysis, thrombectomy or both.

The topic is highly relevant: the timing of initiation of oral anticoagulation in this patient group is an important issue, with great consequence, where evidence is lacking. I also applaud the authors especially for chosing to study patients with more severe strokes.

The manuscript is well written, and includes all important elements. My comments are the following:

1. The definition of outcomes could be clearer. Either categorised as primary and secondary; or as clinical or non-clinical, or in some other manner.

Response: We have rewritten this part to make it clearer.

2.Although used in the pivotal RCTs, the term "non-valvular" AF is now abandoned, and should largely be avoided. Instead one might refer to the specific reason a NOAC may not be used (e.g. mechanical heart valves).

Response: We agree with the reviewer that nowadays NVAF is not the best term to describe specific reasons to use NOAC. However, we used it in this manuscript because it is still used in clinical practice and AF type classification.

3. On page 9, in the chapter on material and Methods, the authors state that they collected information about which patients that died. Although not listed as an outcome, I miss information about number of deaths in the results section, preferentially with cause of death included. I may have missed this, but it seems relevant, as haemorrhagic transformation is the main fear in this instance, and any deaths caused by ICH in the follow-up period are highly relevant. (I notice that only one case of ICH is registered, but does that mean that no patients died from ICH?)

Response: We reported number of deaths in the results section (page 9, at the end of 2nd last paragraph) and we have added a sentence with the relevant causes of the dead according to the purpose of the study.

4. Perhaps it should be made clearer in the text or in the flow-chart that although information about clinical events within 90 days was available for 926 patients, information about the primary outcome (timing of dabigatran initiation) was only available for 702 patients.

Response: We have added a new sentence to make it clearer and we have modified the flow-chart.

5. In the statistics section: Which potential confounders were adjusted for and how were these confounders identified?

Response: We have added a sentence in the statistics section and explained it in the results section.

Reviewer: 2

Reviewer Name: Suodi Zhai

Institution and Country: Department of Pharmacy, Peking University Third Hospital, Beijing, China

Please state any competing interests or state 'None declared': None declared

The study shows interesting and potentially useful results. However, a few points could be improved:

1. Please complete the abstract (methods)

Response: we have completed it.

2. The relationship between initiation time and clinical event is of more interest to readers. However, little was shown and discussed in this manuscript. Response: We agree with the reviewer, however, as we refer in the methods section, due to the low number of events, no inferential analysis was performed.

3. The description of statistical method is poor. Actually, I can't figure out what model was used in this study to assess the influence of initiation time on outcomes of interest. Besides, the calculation of incidence rate was also problematic. Methods should be specified for the calculation of 95% CI for incidence rate.

Response: In our study we have not made any inferential analysis regarding initiation time and events of interest. We have added a paragraph in the Methods section regarding calculation of incidence rate and 95% CI.

4. The study period is only three months, which is too short to observe outcome, for example, stroke and so on.

Response: We agree with the reviewer that the follow up time point may be too short to observe new events. Our primary aim of the study was to describe timing of initiation of dabigatran and clinical outcome was additional outcome. We have used IV thrombolysis and or endovascular thrombectomy data entry protocol for this study and 3 months follow up is final follow in the SITS registry.

5. The discussion section should focus more on practical insights to clinical decision makings based on current guideline recommendation

Response: we have added a paragraph in the discussion section. However, as our study is descriptive and observational we can’t make strong statements regarding decision making.

VERSION 2 – REVIEW

REVIEWER	Ole-Christian W. Rutherford Østfold Hospital Trust, Cardiology
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	My previous comments have been answered and dealt with adequately satisfactorily

REVIEWER	Suodi Zhai Department of Pharmacy, Peking University Third Hospital
REVIEW RETURNED	09-Apr-2020

GENERAL COMMENTS	I agree the publication since it was imporved according to the previous comments.