PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of anticoagulation status for atrial fibrillation on early ischaemic stroke outcomes: a registry-based, prospective cohort study of acute stroke care in Surrey, United Kingdom
AUTHORS	Han, Thang; Fry, Christopher; Fluck, David; Affley, Brendan; Gulli, Giosue; Barrett, Christopher; Kakar, Puneet; Patel, Tasmin; Sharma, Sapna; Sharma, Pankaj

VERSION 1 – REVIEW

REVIEWER	Ying Xian Duke University, USA No Competing Interest
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	The authors reported a study of patients with ischemic stroke or hemorrhagic stroke and the association between AF, anticoagulation status and early outcomes. The key findings are that patient with AF, particularly those without anticoagulation, are at increased risk of severe stroke, longer LOS, increased risk of infection, disability, and mortality. 1. My main suggestion is for the authors to emphasize more on gaps in knowledge (introduction) and the new findings (discussion). E.g. the relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature. Hylek EM et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003;349(11):1019-1026. O'Donnell M et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol. 2006;5(9):749-754. Xian Y et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. JAMA. 2017;317:1057-1067 However, none of the previous research have reported the relationship of AF/anticoagulation therapies with pneumonia, UTI, and LOS. 2. My second suggestion is to exclude hemorrhagic stroke in the study population because anticoagulation therapy is supposed to reduce stroke/embolic event and potentially increase the risk of hemorrhagic stroke. The latter seems to beyond the scope of the current analysis. In addition, it is well-known that OAC-related hemorrhagic stroke are more severe than non-OAC-related ones. 3. Abstract/Results: Please report event rates along with the OR e.g. Compared with stroke patients free from AF, those with AF without anticoagulation had an increased risk of more severe stroke (##%

	vs. ##%, OR 2.3, 95% CI) 4. It appears that severe disability doesn't not include death. If so, I'd recommend better defining as mRS of 4 or 5 instead of mRS≥4 because the latter includes death (mRS=6). Alternatively, the authors can report better functional outcomes such as mRS≤1 or mRS≤2. 5. Page 6 categorisation of variables. The AF and anticoagulation status were catergorised into four groups: free from AF, AF with anticoagulation, AF without anticoagulation; and AF unsuitable for anticoagulation. It is well-documented in the literature that cardioembolic stroke due to AF are larger. As such, it would be more reasonable to exclude non-AF patients from the study population and focus on the anticoagulation status and its relationship with outcomes. Please define unsuitability, are these patients contraindicated or has a CHA2DS2-VASc<2? Did the authors have information on OAC and INR. If so, it might be helpful to focus on those with CHA2DS2-VASc≥2 and categorize into the following groups: no OAC, warfarin with INR<2, warfarin with INR>=2, and NOACs. 6. Results. Please report the event rates along with the ORs e.g. severe stroke ##% vs. ##%, OR (95% CI). Longer stay in HASU median ## days (IQR) vs. ## days (IQR), adjusted differences 4.6 days (IQR), etc. 7. Discussion, 2nd paragraph. "We found a high proportion (95%) of AF were not on anticoagulation in the community were anticoagulated on discharge after admission for acute stroke (Han et al, 2017 unpublished). Please present these unpublished data in the result section. 8. Page 12, line 14. Please change "weighted" to "after risk adjustment" because "weighted" has a different meaning from a statistical perspective. 9. Table 1. Please present the baseline characteristics by study groups. e.g. no AF, AF with anticoagulation, AF without anticoagulation, along with the ## and % for categorical variables and mean (SD) or median (IQR) for continuous variables. In addition, please move the distribution of age and sex from the title to the table. 10. Table 2. Association of AF and anticoagulation status with outcomes. I'd recommend presenting the these results as numerator/denominator (event rate), unadjusted OR (95% CI), and adjusted OR (95% CI). 11. Table 3. It is well-known that severe stroke results in worse outcomes. As such, table 3 and the examination between stroke severity and outcomes can be removed from the manuscript. 12. Table 4. In general, LOS doesn't follow a normal distribution. As such, it might be more appropriate to report the median (IQR) in each group and then the adjusted differences in the table.

REVIEWER	Bassand University of Bourgogne-Franche-Comté, Besançon France Thrombosis Research Institute, London No Competing Interest
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	This study confirms that stroke in atrial fibrillation patients leads to more severe outcomes, whichever is considered, compared with no atrial fibrillation patients. It's an already known fact linked to several factors, comorbidities, but also size of the emboli, greater in atrial fibrillation compared to no atrial fibrillation. It also confirms that the more severe the stroke at admission, the more prone the patients are to suffer from a deteriorated outcome compared to less severe stroke. It also confirms that the outcome of non-anticoagulated patients is worse than anticoagulated atrial fibrillation pts and non-atrial fibrillation patients. Nothing new under the sun. The authors also show that haemorrhagic strokes have a more deleterious impact on outcome particularly about risk of death than ischemic stroke, an already known fact as well. The conclusions of this manuscript as given in the abstract and in the last lines of the body of the manuscript are valid. But this manuscript suffers from serious limitations that are not envisaged by the authors, both about presentation and interpretation of the data: -atrial fibrillation patients w or w/o anticoagulation are compared with no-atrial fibrillation patients. This latter population is not described at all. Who are these patients, baseline characteristics …. -table 1 gives partial information about baseline characteristics of the cohort of patients. For example the median age is not indicated in the table…... -there is no information about the rates and types of strokes in the 2 anticoagulation and no-anticoagulation atrial fibrillation patients groups. To the best of my knowledge, there is no internet supplementary figures or tables where to find this information. -which types of anticoagulants were prescribed to the anticoagulated patients, VKA or NOACs ? This makes a big deal of difference. -what about VKAs control before stroke. No information about a key element. Poor control leads to more frequent haemorrhages particularly haemorrhagic stroke and more death. -lines 48 to 54, page 11. Strange statement referring to an unpublished paper. 90% of atrial fibrillation patients are not anticoagulated? How could it be? The most recent prospective registry in atrial fibrillation, run all over the planet shows that ~50% of atrial fibrillation patients are not anticoagulated at inclusion (Garfield-AF). There are also zillions of references about registries that report the same figures. The references quoted in this manuscript are outdated or incomplete. -lines 34 to 41, page 12, the authors refer to the higher risk of death in anticoagulated patients linked to haemorrhagic stroke. They should not leave the reader with the impression that anticoagulation has a detrimental effect on outcome in atrial fibrillation patients. Haemorrhagic stroke has a detrimental effect, but not anticoagulation. It should be reminded that anticoagulation leads to a significant risk reduction for stroke and death in AF patients compared with no anticoagulation. -the rather high rate of haemorrhagic stroke in this study, may well be the reflect of poor VKA treatment

	-in addition, assessing outcomes in anticoagulated patients with ischemic stroke only as shown in model 2 is irrelevant. It is known that haemorrhagic stroke carries a higher risk of poor outcomes than ischemic stroke. -formulation line 14, page 11 should be revisited. Do the authors mean that patients consciously and voluntarily changed their outcome?!? - Lastly, there is no information about approval of the study by any IRB or Ethics committee, informed consent ....One may assume that this is described in the Sentinel Stroke National Audit Programme (SSNAP)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Ying Xian

Institution and Country
Duke University, USA

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

Please leave your comments for the authors below

The authors reported a study of patients with ischemic stroke or hemorrhagic stroke and the association between AF, anticoagulation status and early outcomes. The key findings are that patient with AF, particularly those without anticoagulation, are at increased risk of severe stroke, longer LOS, increased risk of infection, disability, and mortality.

1. My main suggestion is for the authors to emphasize more on gaps in knowledge (introduction) and the new findings (discussion). E.g. the relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature.
Hylek EM et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003;349(11):1019-1026.
O'Donnell M et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol. 2006;5(9):749-754.
Xian Y et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. JAMA. 2017;317:1057-1067
However, none of the previous research have reported the relationship of AF/anticoagulation therapies with pneumonia, UTI, and LOS.

Authors' response:
We are grateful for this reviewer's suggestion and have now added this comment into text and references (page 4, para 2).

2. My second suggestion is to exclude hemorrhagic stroke in the study population because anticoagulation therapy is supposed to reduce stroke/embolic event and potentially increase the risk of hemorrhagic stroke. The latter seems to beyond the scope of the current analysis. In addition, it is well-known that OAC-related hemorrhagic stroke are more severe than non-OAC-related ones.

Authors' response:
We agree with this suggestion and have now omitted patients with haemorrhagic stroke from analysis.

3. Abstract/Results: Please report event rates along with the OR e.g. Compared with stroke patients free from AF, those with AF without anticoagulation had an increased risk of more severe stroke (##% vs. ##%, OR 2.3, 95% CI)

Authors' response:
We have now added event rates to Abstract and Results (page 9, para 2).

4. It appears that severe disability doesn't not include death. If so, I'd recommend better defining as mRS of 4 or 5 instead of mRS≥4 because the latter includes death (mRS=6). Alternatively, the authors can report better functional outcomes such as mRS≤1 or mRS≤2.

Authors' response:
We have now clarified the definition of disability (mRS of 4 or 5) throughout the text.

5. Page 6 categorisation of variables. The AF and anticoagulation status were catergorised into four groups: free from AF, AF with anticoagulation, AF without anticoagulation; and AF unsuitable for anticoagulation. It is well-documented in the literature that cardioembolic stroke due to AF are larger. As such, it would be more reasonable to exclude non-AF patients from the study population and focus on the anticoagulation status and its relationship with outcomes.

Please define unsuitability, are these patients contraindicated or has a CHA2DS2-VASc<2? Did the authors have information on OAC and INR. If so, it might be helpful to focus on those with CHA2DS2-VASc≥2 and categorize into the following groups: no OAC, warfarin with INR<2, warfarin with INR>=2, and NOACs.

Authors' response:
Our objective was to examine the degree of adverse outcome from different AF treatment status has on patients relative to those who did not AF. We therefore wish to keep this group as a reference category.

We do not have information on OAC or INR. We emphasised that among those recorded as "not suitable for anticoagulation" before admission, most of them (75%) were anticoagulated on discharge, thus most of these patients were not contraindicated, and more likely to be undertreated. We have now added the results in Results section (page 10, para 2) and further emphasised this point in the Discussion (page 11, first para).

6. Results. Please report the event rates along with the ORs e.g. severe stroke ##% vs. ##%, OR (95% CI). Longer stay in HASU median ## days (IQR) vs. ## days (IQR), adjusted differences 4.6 days (IQR), etc.

Authors' response:
We have now added event rates to Results and reported median LOS in HASU (page 9, para 2-3).

7. Discussion, 2nd paragraph. “We found a high proportion (95%) of AF were not on anticoagulation in the community were anticoagulated on discharge after admission for acute stroke (Han et al, 2017 unpublished). Please present these unpublished data in the result section.

Authors’ response:
We have now presented these data in Results (page 10, para 2).

8. Page 12, line 14. Please change “weighted” to “after risk adjustment” because “weighted” has a different meaning from a statistical perspective.

Authors’ response:
We have now corrected this term as suggested (page 12, para 2, line 3).

9. Table 1. Please present the baseline characteristics by study groups. e.g. no AF, AF with anticoagulation, AF without anticoagulation, along with the ## and % for categorical variables and mean (SD) or median (IQR) for continuous variables. In addition, please move the distribution of age and sex from the title to the table.

Authors’ response:
Characteristics of subgroups have now been added to the new Table 2.

10. Table 2. Association of AF and anticoagulation status with outcomes. I’d recommend presenting the these results as numerator/denominator (event rate), unadjusted OR (95% CI), and adjusted OR (95% CI).

Authors’ response:
We have now added event rates to the original Table 2 (now changed to Table 3).

11. Table 3. It is well-known that severe stroke results in worse outcomes. As such, table 3 and the examination between stroke severity and outcomes can be removed from the manuscript.

Authors’ response:
We agree and have removed the original Table 3 and results from the manuscript.

12. Table 4. In general, LOS doesn’t follow a normal distribution. As such, it might be more appropriate to report the median (IQR) in each group and then the adjusted differences in the table.

Authors’ response:
We agree and have now reported median and IQR (page 9, para 3).

Reviewer: 2
Reviewer Name
Bassand

Institution and Country
University of Bourgogne-Franche-Comté, Besançon France

Thrombosis Research Institute, London

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

Please leave your comments for the authors below

1. This study confirms that stroke in atrial fibrillation patients leads to more severe outcomes, whichever is considered, compared with no atrial fibrillation patients. It's an already known fact linked to several factors, comorbidities, but also size of the emboli, greater in atrial fibrillation compared to no atrial fibrillation. It also confirms that the more severe the stroke at admission, the more prone the patients are to suffer from a deteriorated outcome compared to less severe stroke. It also confirms that the outcome of non-anticoagulated patients is worse than anticoagulated atrial fibrillation pts and non-atrial fibrillation patients. Nothing new under the sun.

The authors also show that haemorrhagic strokes have a more deleterious impact on outcome particularly about risk of death than ischemic stroke, an already known fact as well.
The conclusions of this manuscript as given in the abstract and in the last lines of the body of the manuscript are valid. But this manuscript suffers from serious limitations that are not envisaged by the authors, both about presentation and interpretation of the data:
-atrial fibrillation patients w or w/o anticoagulation are compared with no-atrial fibrillation patients. This latter population is not described at all. Who are these patients, baseline characteristics ….

Authors' response:
We agree with this reviewer's comments which are in line with Reviewer 1. We have therefore omitted haemorrhagic stroke group from analysis, focusing on ischaemic stroke patients only. We have now added Table 2 to include subject characteristics of subgroups according to AF and treatment status.

2. table 1 gives partial information about baseline characteristics of the cohort of patients. For example the median age is not indicated in the table…...

Authors' response:
We have now added more baseline characteristics to Table 1 and the new Table 2 which includes information for patient groups according to AF and anticoagulation status.

3. there is no information about the rates and types of strokes in the 2 anticoagulation and no-anticoagulation atrial fibrillation patients groups. To the best of my knowledge, there is no internet supplementary figures or tables where to find this information.

Authors' response:
We agree that rates of stroke subtype should have been provided. The proportions of ischaemic stroke amongst those with AF is in Table 1. The proportions with haemorrhagic stroke is no longer needed as we have excluded this group from analysis in this revised MS.

4. which types of anticoagulants were prescribed to the anticoagulated patients, VKA or NOACs ? This makes a big deal of difference.

Authors' response:
We appreciate this reviewer's comments. The objective of this paper is to compare differences in outcomes between non-anticoagulation against anticoagulation. Information on individual anticoagulants such as VKA or NOACs is not available in this study and beyond the scope of our

study. We have now added this point to the Discussion, which requires further studies in the future (page 12, para 2).

5. what about VKAs control before stroke. No information about a key element. Poor control leads to more frequent haemorrhages particularly haemorrhagic stroke and more death.

Authors' response:
This is possibility. However, it would be impossible to accurately quantify VKA's control for any patient as the levels of INR fluctuate constantly. A complex method would require to make any sense of control such as a defined period of time and the summation of INR levels etc. To do this on thousands of patients would require a different study design (page 12, para 2).

6. lines 48 to 54, page 11. Strange statement referring to an unpublished paper. 90% of atrial fibrillation patients are not anticoagulated? How could it be? The most recent prospective registry in atrial fibrillation, run all over the planet shows that ~50% of atrial fibrillation patients are not anticoagulated at inclusion (Garfield-AF). There are also zillions of references about registries that report the same figures. The references quoted in this manuscript are outdated or incomplete.

Authors' response:
This sentence was ambiguously written. We meant to say that "Of those not anticoagulated in the community (which are 46.1% of patients with AF), over 90% of this group were eventually anticoagulated on discharge." Our figure of 46.1% of AF patients not anticoagulated in the community is consistent with data from Garfield-AF and other authors. We have now clarified this sentence (page 10, last para to page 11, first para) and added a paragraph in Results section (page 10, para 2) in line with Review 1.

7. lines 34 to 41, page 12, the authors refer to the higher risk of death in anticoagulated patients linked to haemorrhagic stroke. They should not leave the reader with the impression that anticoagulation has a detrimental effect on outcome in atrial fibrillation patients. Haemorrhagic stroke has a detrimental effect, but not anticoagulation. It should be reminded that anticoagulation leads to a significant risk reduction for stroke and death in AF patients compared with no anticoagulation.

Authors' response:
We appreciate this point and would not purposefully leave the impression that anticoagulation has a detrimental effect on outcome in atrial fibrillation patients. We have included the importance of anticoagulation in the Discussion section (page 12, para 1). Regardless, we have now omitted haemorrhagic stroke from analysis as suggested by Reviewer 1 therefore this point no longer applies.

8. the rather high rate of haemorrhagic stroke in this study, may well be the reflect of poor VKA treatment

Authors' response:
We agree that it is a possibility and further prospective studies are required as in our response above.

9. in addition, assessing outcomes in anticoagulated patients with ischemic stroke only as shown in model 2 is irrelevant. It is known that haemorrhagic stroke carries a higher risk of poor outcomes than ischemic stroke.

Authors' response:
We agree with this reviewer that it is known that haemorrhagic stroke carries a higher risk of poor outcomes than ischaemic stroke. However, we feel that this reviewer's point that "assessing outcomes in anticoagulated patients with ischemic stroke only as shown in model 2 is irrelevant" is

unfair. The focus of this paper is not to look for differences in stroke subtypes. Our objective is to assess the risk of poor outcomes in those with AF but not anticoagulated. As pointed out earlier, we have taken the advice from Reviewer 1 to omit haemorrhagic stroke patients which has strengthened the focus of our paper.

10. formulation line 14, page 11 should be revisited. Do the authors mean that patients consciously and voluntarily changed their outcome?!? - Lastly, there is no information about approval of the study by any IRB or Ethics committee, informed consent ....One may assume that this is described in the Sentinel Stroke
National Audit Programme (SSNAP)

Authors' response:
We have now clarified then sentence on page 11, para 2.
This reviewer is correct that data collection is part of SSNAP registry and we have now mentioned this in our MS (page 5, para 2).

VERSION 2 – REVIEW

REVIEWER	Bassand Université de Besançon, France & Thrombosis Research Institute, London, UK No Competing Interest
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	The manuscript is substantially improved compared with initial version. Two minor remaining issues: -spelling mistake in one last name quoted in the discussion, Passand instead of Bassand, page 11 line 5 -inversion of the reference numbers Bassand 22 vs Perez 21. page 11 lines 5 and 6 -still I believe that stating that a patient cannot decide to reduce its risk. Improper formulation page 10, lines 32 to 34. ....'AF patients who were anticoagulated reduced their risk' .... 'had a reduced risk ' ... would be better formulation

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name
Bassand

Institution and Country
Université de Besançon, France & Thrombosis Research Institute, London, UK

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

Please leave your comments for the authors below

1. The manuscript is substantially improved compared with initial version.

Authors' response:
We appreciate Professor Bassand's comment.

Two minor remaining issues:
-spelling mistake in one last name quoted in the discussion, Passand instead of Bassand, page 11 line 5

Authors' response:
We apologise to Professor Bassand for typographical error which has now been corrected.

-inversion of the reference numbers Bassand 22 vs Perez 21. page 11 lines 5 and 6

Authors' response:
We have now corrected the order of citation in References section to match the reference numbers in text.

-still I believe that stating that a patient cannot decide to reduce its risk. Improper formulation page 10, lines 32 to 34. ....'AF patients who were anticoagulated reduced their risk' .... 'had a reduced risk ' ... would be better formulation

Authors' response:
We have now amended this sentence. We apologise for misunderstanding this suggestion originally.