Author's response to reviews

Title: Stroke with atrial fibrillation or atrial flutter: descriptive population-based study from the Brest Stroke Registry.

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Author's response to reviews: see over
MAJOR COMPULSORY REVISIONS:

1. “General” The abstract states the aim of the manuscript is to look at the prevalence of cardiac arrhythmias in stroke patients, however from the body of the manuscript the aim is look at the prevalence of AF and flutter. It seems the term “CA” is used in two different contexts throughout the manuscript; firstly to describe cardiac arrhythmias in general, and secondly to specifically and solely refer to AF and flutter. I would suggest consideration of using “AF and flutter” (or choose a different abbreviation) instead of CA, as there are many other arrhythmias that fall into the category of CA, that are not included in the analysis.

The term “Cardiac arrhythmia” is replaced by “atrial arrhythmia” and refers to atrial flutter/fibrillation.

2. “Background section”: There are some statements in the background that need to be referenced (eg: first paragraph, sentences 7 and 9).

For sentence 7, a new reference was added (SPAF) and we clarified the reference for the sentence 9.

3. “Methods, statistical analysis section”: The statistical analysis methods and tests used should be described in some detail, rather than stating the analyses were performed by a statistician.

The median and the mean age were calculated with quartiles and standard deviation respectively. Frequencies were calculated for gender, prior stroke, prior TIA, myocardial
infarction, hypertension, and diabetes mellitus. Missing data were also calculated, and variables with more than 10% missing data were not analysed.

Prevalence of atrial arrhythmia was calculated according to age and gender.
The above lines were added to the ‘statistical analysis’ section (lines 141-145).

4. “Results”: The results section is quite lengthy and a little difficult to extract the information from. I would suggest that many of the results could be condensed into a table, especially the final three paragraphs that describe medication prescription. Therefore figure 3 may not be required in its current form.

We have compiled the most important results in the Table 2 and we have removed the initial Figure 3.

5. “Figure 3 »

It is of interest to readers to be able to see the proportion of patients in each CHADS2 category that were prescribed appropriate VKA and were within the therapeutic range. At present the total figure of VKA prescription is presented, incorporating both therapeutic and non-therapeutic ranges together. Additionally are the patients on both aspirin and VKA included in the VKA group too?

Finally, we represented the antithrombotic therapy according to the CHADS2 score in the Table 2. In order to view the proportion of patients in each CHADS2 category that were prescribed VKA in the therapeutic range, we represented the INR according to the CHADS2 score in the Table 3.

Yes, in the patients on both aspirin and VKA included in the VKA group too because it concern few patients: only 3 patients were receiving both aspirin and VKA. These 3 patients
had a CHADS2 score $\geq 2$. This information were added to the ‘results’ section (lines 170-171).

6. “Results”: I understand the authors chose to present CHADS breakdowns based on the fact that the CHADS score was being used by the guidelines in 2008. To make the data presented in the manuscript of more interest to the readers, it would be good to also know what the breakdown was for stroke according to the CHADS-VASc score (advocated by the current guidelines). This information may be available from the Brest database and could be discussed in the results or discussion section.

We calculated the CHA2DS2Vasc score for the patients with atrial arrhythmia known prior to stroke. With this score, more patients are at high risk of thrombo embolism and requiring anticoagulation, as shown in Figure 3. These results were added in the “results” section (lines 176-179) and in the discussion (lines 235-239).

7. “Discussion section”: The discussion felt like a repeat of the results only. I think the discussion would benefit from some rewriting and exploration/interpretation of the results. The discussion could also include discussing the results in the light of the new AF guidelines, the use of CHADS-VASc and the move away from aspirin prescription.

We revised the discussion by adding the new guidelines (lines 259-260), the CHA2DS2Vasc score and the limitations of our study (lines 255-256).

8. “Limitations” Limitations were not listed. One limitation is that it is possible some people with paroxysmal AF were not identified/diagnosed at the time of stroke as long term monitoring did not appear to be performed, only a single ECG.
We have identified the limitations including the possible underestimation of paroxysmal AF. The limitations were added to the “Discussion section” (lines 255-256).

MINOR ESSENTIAL REVISIONS:

9. In some places the quality of written English detracted from the manuscript. I found some sentences were difficult to understand and therefore I needed to read them a few times to understand what the authors were trying to convey (for example, the second sentence of the background in the abstract). The manuscript would be improved by some rewording and grammar corrections (for example: Abstract, results section, second sentence: “the prevalence of CA was of 31.0%” – “of” should be removed)

Thank you for bringing up this issue. The manuscript was revised by a Medical Writer.

10. I would suggest limiting the use of abbreviations when the term is only used once in the manuscript, as it detracts the reader when there are so many abbreviations. For example, I would remove the abbreviations TEE, CHF and WHO from the manuscript, and from the list of abbreviations.

The abbreviations that are used only once in the manuscript are deleted.
Response to the report of Ben Lacey, release of 21 January 2015:

Major Compulsory Revisions:

1. Abstract: the results section needs to be rewritten to improve clarity. For example, line 39 - the ‘78.4%’ in parentheses uses those stroke patients with atrial fibrillation as the denominator, rather than all stroke patients, but this is not made clear; likewise, the denominator of the ‘35.5%’ in line 40 is patients with CHADS2 scores #2 rather than those with know AF at the time of stroke, but this is also not clearly expressed; it might help if the percentages were reserved for the key findings only (i.e. the overall and age-specific prevalences, the proportion previously diagnosed with AF and proportion being treated with vitamin K antagonist).

We have reviewed the results section in the abstract and we have reserved the percentages only for the key findings.

2. Methods: The methods needs a more lucid explanation of the second definition for stroke (lines 94-96): what constitutes an abnormal brain image, what is a clinically relevant picture, and does the abnormal brain imaging associated with a clinically relevant picture refer to both focal deficits lasting more and less than one hour? This is important for comparison with other studies as the definition may include events classified elsewhere as transient ischaemic attacks.

An abnormal imaging is an image visible on CT or MRI scan showing a stroke (ischemic or haemorrhagic) which may explain by its location the clinical picture. The above lines were added to the ‘methods’ section (lines 97-98).
3. Results: Even though it is reasonable to report the overall proportion of strokes in which patients had AF, the strong association with age means that reliable comparisons which other studies cannot be made unless this proportion is standardised to the age distribution of standard population, or at least the age-specific results are reported in the appendix.

In the others population-based studies referenced in the discussion, the authors have calculated the prevalence of atrial arrhythmia by age +/- by gender.

Given the differences in age and gender distribution among AA-associated strokes, the comparison of AA prevalence between studies was difficult. Using prevalence analysis by age interval and gender, we compared our results with those by Marini et al. and the North Dublin Stroke Study. In such comparison with Marini et al. our results showed a higher prevalence in men for all age intervals and for women < 60 years and those > 80 years. Prevalence analyses by age intervals showed that in our study, the prevalence for patients under 84 years was lower than that in Dublin registry. However, the prevalence for patients aged 85 years and older was moderately higher than that in Dublin registry.

We have clarified this in the discussion (lines 189-199).

Minor revisions:

1. Abstract: line 35 - CHADS2 score needs to be described, however briefly.

The CHADS2 is now described briefly in the abstract (lines 35-36).


The term “epidemiologic” is now replaced by epidemiological.
3. Background: The background needs to make it clear in what population(s) the incidence and prevalence are calculated.

The incidence and the prevalence are calculated in a population-based study. We have clarified this in the “Background” section (lines 52-53).

4. Methods: I could not find the definition for haemorrhagic stroke in the paper referenced on line 101, as purported.


5. Results: the proportion given on line 146 is among all stroke rather than among the 835 strokes reported.

The proportion on line 146 was modified: 31.7%, now line 156.

Discretionary revisions 1.

The paper refers to cardiac arrhythmias but it is perhaps better to described these throughout the paper as atrial fibrillation (as in the title) and just make it clear that a very small proportion of events are atrial flutter.

The term “Cardiac arrhythmia” is replaced by “atrial arrhythmia” and refers to atrial flutter/fibrillation.
Response to the report of Peter L Thompson, release of 1 February 2015:

Major compulsory revisions

1. The authors do not comment on why the study presents data collected in 2008. As this was nearly 7 years ago, there is the possibility that the information is out of date, particularly as the arrival of the NOAC’s have been accompanied by new guidelines and extensive education programmes driven by the pharmaceutical industry to alert physicians to the need for recognising and anticoagulating patients with atrial fibrillation. A comment clarifying the gap between the conduct of the study and its presentation and whether this affects current relevance should be included.

The Brest stroke registry was set up in 2008. The high completeness and reliability of Brest Stroke Registry were established in our previous study. Today’s results presentation is the step after the preliminary validation of the Registry in 2014. We added a comment in the “discussion” section (lines 252-254).

2. The Conclusion in the last sentence of the Abstract that there is a higher prevalence of AF in stroke than 20 years ago is not justified by the data. Firstly, there is reference to only one study from 1992 to support this statement, and it is unclear how representative was that study. Secondly, the methods of ascertaining AF prevalence were very complete in the current study and there is no data presented to confirm that the same extensive methods of checking for AF were used in the 1992 Oxfordshire study. The Discussion also refers to other studies in which the prevalence of AF was much higher (refs 14, 29, 30), and the discrepancy between these reports, the current report and the 1992 Oxfordshire study need clarification.
We think that the prevalence in our study is higher because: 1/ perhaps because the population has aged in developed countries, and 2/ the methods of checking for atrial arrhythmia have developed. In fact, ambulatory monitoring of electrocardiograms was not routinely performed in the 1992 Oxfordshire study. We clarified this in the “discussion” section (lines 200-212).

Minor Essential revisions

3. The authors appear to have decided to include the AF prevalence for all types of strokes in the overall data, Discussion, and Abstract. It is confusing why this has been done as there is clearly enough detail presented in the Methods and in Figure 2 to distinguish thrombotic from haemorrhagic and undetermined stroke. Obviously the prevalence for thrombotic stroke is of far more relevance than the prevalence in haemorrhagic stroke, and the reasons for including all strokes in the conclusions and Abstract needs to be clarified.

We aimed to evaluate the prevalence of AA among all types of stroke (ischemic, hemorrhage and “undetermined”) for several reasons. First of all, the patients with “undetermined strokes” a) died before either arriving at hospital or having a brain imaging, b) were either at home or institutionalised, with serious comorbidities. The category “undetermined stroke” included severe and fatal strokes. It is known that strokes associated with AF are more serious due to a high 30-day case-fatality rate, than strokes without AF [26]. The above fact led us to include patients with “undetermined strokes”. Secondly, our inclusion of patients with hemorrhage strokes was aimed to estimate the proportion of hemorrhage strokes associated with AA among strokes in general, and determine the impact of oral anticoagulants in these patients. We clarified this in the “discussion” section (lines 240-248).
4. While the term “cardiac arrhythmias” is well defined in the Methods and text of the manuscript, the choice of the term may lead the casual reader to conclude that the study covers all cardiac arrhythmias including ventricular arrhythmias. For clarity, the title and references in the manuscript could be rewritten as “atrial arrhythmias” or “atrial flutter/fibrillation”, but of course this remains the prerogative of the authors. At the least, the selective use of the term “cardiac arrhythmias (CA)” should be explained in the last line of the “Background” in the Abstract.

The term “Cardiac arrhythmia” is replaced by “atrial arrhythmia” and refer to atrial flutter/fibrillation.

5. The data on under-treatment with anticoagulants and the adverse consequences of this are concerning and in line with many other studies. (Nieuwlaat R, et al the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2005;2622:2422-2434). The relevance of this 2008 data to current treatment patterns needs a comment.

We added a comment for these data in the discussion (lines 219-221 ).