## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Atrial fibrillation in patients with severe mental disorders and the risk of stroke, and fatal thromboembolic events, and bleeding: a nationwide cohort study |
| **AUTHORS** | Søgaard, Mette; Skjøth, Flemming; Kjældgaard, Jette; Larsen, Torben; Hjortshøj, Søren; Riahi, Sam |

## VERSION 1 – REVIEW

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| **REVIEWER** | Adam Rose<br>RAND Corporation, Boston, MA; Boston University School of Medicine, USA |
| **REVIEW RETURNED** | 29-Jun-2017 |

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| **GENERAL COMMENTS** | The authors use the Danish national health database to examine the care and outcomes of patients with AF who also have a serious mental disorder - depression, schizophrenia, or bipolar disorder. They use coarsened exact matching to find similar AF patients without those conditions for comparison. Patients with the mental disorders have more thromboembolic and bleeding complications, but this seems to be largely mediated by them not receiving oral anticoagulation at the same rate.<br><br>The manuscript and analyses are generally well-done. I do have a few questions about the methods that if clarified, could help improve the presentation or possibly improve the analyses - in some cases I am not sure if the details I'm asking for were not done or just not presented explicitly.<br><br>1. I am uncertain why control for confounding is necessary when coarsened exact matching was used. If differential stroke or bleeding risk exists between those with mental health conditions and the controls, why not match on those factors to begin with, to balance these risks? I would not match on OAT therapy, however, since this is hypothesized (and shown) to be a key mediator of excess risk. I suppose matching on these factors would also make it impossible to demonstrate that these factors are mediating the excess risk...but one could also show it by having an unmatched comparison group as well. The authors are encouraged to make their choices explicit and to justify them, although I do not wish to dictate how they choose to handle this.<br><br>2. I saw a lot of detail about how baseline variables and covariates were defined, but I did not see anything about the codes that were used to define the study outcomes - ischemic stroke, hemorrhagic stroke, and fatal thromboembolic events. |

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| | Ideally these codes would be listed and a source cited for the method chosen, or at least a justification. This can be done in an appendix, although the main text should contain at least a few lines.<br><br>3. I am uncertain why major hemorrhage is not included as a study outcome, only hemorrhagic stroke. If the authors consider major hemorrhage to be too much of a heterogeneous category, may I suggest looking at only GI bleeding in its various forms, which is more well-defined and represents a large percentage of non-intracranial bleeding. There are published methods for detecting GI bleeding or major bleeding using ICD codes.<br><br>4. It appears from the tables and the methods that the authors focused largely on examining whether patients were on anticoagulants or anti-platelet agents during the year prior to AF diagnosis. However, I do not see any explanation of the methods for determining whether patients received these medications during the 5 years of follow-up after the AF diagnosis, nor a definition of how much therapy was considered sufficient to say the patient received it as opposed to not. This appears to be a key covariate that mediates much of the between group differences in outcomes, namely that the mental health patients received OAT less often. Therefore, the methods for determining who received OAT need to be made explicit, and also the data on how many patients received OAT in each group should also be presented, whether in the main text or in an appendix. |

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| **REVIEWER** | Lars Frost, MD<br>Department of Medicine<br>Silkeborg Regional Hospital<br>Denmark |
| **REVIEW RETURNED** | 30-Jun-2017 |

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| **GENERAL COMMENTS** | The authors report on outcomes of atrial fibrillation (AF) in patients with severe mental disorders. The study is based on secondary data sources (administrative Danish data). The author conclude that severe mental disorders in AF patients were associated with increased risk of ischemic and in particular hemorrhagic stroke compared with matched comparisons. The excess rates were explained by more comorbidity and lower user rates of oral anticoagulation.<br><br>Comments<br>All major conclusions are based on non-significant findings. This is not a problem for me as a reviewer, but could potentially lead many readers to conclude that there are no problems associated with AF among patients with mental disorders. Please add more weight to arguments about the potential public health implications of these non-significant study findings.<br>Would it be possible to explore in more detail why oral anticoagulation was underused in AF patients with mental disorders. A problem in general practice, somatic hospitals, psychiatric hospitals, or patient reluctance?<br>Please define “severe” mental disorder. Why do you only count severe depression as a severe mental disorder? Can schizophrenia be mild? Can bipolar disorders be mild? |

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| | The ICD code F30 is the code for mania. Is mania always a bipolar disease?<br><br>What are the criteria for “severe” depression? Do psychiatrists always graduate in mild, moderate and severe depression, when reporting to the patient registry?<br>Why did you not include all types of depression and graduated into severe, moderate and mild? This approach would give much more statistical power and would also give an opportunity for studying a possible dose-response relation.<br><br>What were the ICD codes for intracranial bleed? Did intracranial bleed include epidural bleed caused by head injury?<br>Figure 2 does not support the conclusion that the risk of hemorrhagic stroke is increased among AF patients with mental disorders.<br><br>How did you determine whether a systemic embolism was fatal or not? Not all types of systemic embolism leads to death.<br>Should diagnostic bias be considered? Do patients with mental disorders more often have a CT scan of the head? Do alcohol drinking more often lead to a CT scan of the head? |

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| **REVIEWER** | Andrea Natale<br>Texas Cardiac Arrhythmia Institute, Austin, Texas, USA<br>No Competing Interest |
| **REVIEW RETURNED** | 12-Jul-2017 |

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| **GENERAL COMMENTS** | This is a well-written paper that has addressed a very important topic in clinical EP; risk of stroke and fatal thromboembolic events in AF patients with a prior diagnosis of severe mental disease. However, there are several flaws in this paper that need to be addressed point by point.<br><br>1. Please clarify why the patients were excluded, if they had not been residents in Denmark for at least 1 year before date of AF diagnosis<br><br>2. How many patients were excluded because they ‘died on the day of AF diagnosis’ as has been stated in the ‘methods’ section?<br><br>3. Please provide information on BMI, obstructive sleep apnea and thyroid dysfunction in the population, as that are known predictors of AF<br><br>4. As the stroke diagnosis was based on in-hospital ICD, there is a possibility of underestimation of stroke events that occurred outside the in-patient facility. Is there any historic data available to estimate what % of patients weren’t included because they either didn’t get hospitalized for the stroke or died of it?<br><br>5. Was Transient Ischemic Attack (TIA) also included in the thrombo-embolic events’ category? If not, please discuss why.<br><br>6. In the flow chart of the study population, it says that >15 years were considered as eligible adults. Is that a typographical mistake or it is so in Denmark? |

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| | 7. Several anti-psychotic medications are known to be associated with increased stroke-risk (Shin et al. PLoS One. 2015; 10(3): e0119931; Douglas et al. BMJ 2008;337:a1227). All patients with severe mental diseases must be receiving anti-psychotic medications. However, neither the stroke risk was adjusted for use of those drugs nor that topic was addressed in the 'discussion' section of the manuscript. Please provide the data and discuss it or add it as a major limitation.<br><br>8. In the 'results', it is mentioned that the AF patients with schizophrenia were substantially younger; please provide a p value to validate that. In fact, please provide p values for all parameters given in the baseline table, which would show if the clinical characteristics were comparable between the groups or not<br><br>9. In what proportion of cases, non-compliance was responsible for 'lower use of OAT'?<br><br>10. How many patients with CHADS2-VASc score of 2 or more, did not receive OAT because of contraindications? What was the thrombo-embolic event rate in that subpopulation?<br><br>11. The higher CHA2DS2-VASc score in patients with severe depression, was also possibly driven by highest number of females and a large proportion with hypertension and bleeding disorders, as reported in Table 1. Please discuss that in the manuscript.<br><br>12. In the 'discussion' it is said that the AF patients with mental disorders were substantially more likely to have highly supra-therapeutic International Normalized Ratio (INR) values than those without mental disorders. Please discuss what might be the plausible mechanism underlying this observation.<br><br>13. In this population, excess stroke risk was seen to be majorly due to lower use of OAT. Again, association of higher rates of hemorrhagic stroke was detected that emphasized the importance of cautious assessment of bleeding in this population. Please discuss, how a balance can be maintained between oral anticoagulation and bleeding risk in AF patients with severe mental diseases.<br><br>14. Patients with schizophrenia were observed to experience higher mortality following a thromboembolic event than matched comparisons. What can be a plausible explanation for that? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Adam Rose
Institution and Country: RAND Corporation, Boston, MA; Boston University School of Medicine, USA
Competing Interests: None declared

The authors use the Danish national health database to examine the care and outcomes of patients with AF who also have a serious mental disorder - depression, schizophrenia, or bipolar disorder. They use coarsened exact matching to find similar AF patients without those conditions for comparison. Patients with the mental disorders have more thromboembolic and bleeding complications, but this seems to be largely mediated by them not receiving oral anticoagulation at the same rate.

The manuscript and analyses are generally well-done. I do have a few questions about the methods that if clarified, could help improve the presentation or possibly improve the analyses - in some cases I am not sure if the details I'm asking for were not done or just not presented explicitly.

Comment 1. I am uncertain why control for confounding is necessary when coarsened exact matching was used. If differential stroke or bleeding risk exists between those with mental health conditions and the controls, why not match on those factors to begin with, to balance these risks? I would not match on OAT therapy, however, since this is hypothesized (and shown) to be a key mediator of excess risk. I suppose matching on these factors would also make it impossible to demonstrate that these factors are mediating the excess risk...but one could also show it by having an unmatched comparison group as well. The authors are encouraged to make their choices explicit and to justify them, although I do not wish to dictate how they choose to handle this.

Response: We thank the reviewer for the positive reception of our work. Before responding to the comments raised below, we would like to explain that we found a few minor coding errors in a couple of the covariates and in our algorithm for the CHA2DS2-VASc and HAS-BLED scores, which we corrected during the revision. As a consequence, we have abstracted a new data set from the registries. The number of patients are unchanged as are baseline covariates for the patients with severe mental disorders. However, because the 1:5 match with AF patients without mental disorders yielded slightly different comparison cohorts (as shown in the revised Table 1 and Supplementary Table 3), event rates in the matched comparisons were changed (evident from the revised Table 2). Due to this, the outcome estimates are slightly different but the conclusions are unchanged. Regarding the design and analysis of our study, we have carefully considered the reviewer's comment. The choice of analytic strategy depends on the question being addressed. Since the coarsened exact matching only took age, sex and year of diagnosis into account, the prevalence of other stroke risk factors still varied widely among exposure groups and matched comparisons (Supplementary Table 3). We aimed to address "the whole package of mental illness" including comorbidities and lifestyle risk factors. As pointed out by the reviewer, this could have been examined using unmatched comparison cohorts. However, as the patients differed substantially by age and sex according to type of mental illness (e.g., the mean age of patients with schizophrenia approximately 10 years lower than those with bipolar disease or depression), we chose to pre-process the data with CEM in order to reduce this imbalance and provided the unadjusted hazard ratio for the matched cohorts (Figure 2). In the subsequent, sequential adjustment we sought to describe whether severe mental illness remained associated with stroke when controlling for stroke risk factors and use of OAT during follow-up. This seemed not to be the case, as all estimates declined toward the null in the fully adjusted analyses.

Comment 2. I saw a lot of detail about how baseline variables and covariates were defined, but I did not see anything about the codes that were used to define the study outcomes - ischemic stroke, hemorrhagic stroke, and fatal thromboembolic events. Ideally these codes would be listed and a source cited for the method chosen, or at least a justification. This can be done in an appendix, although the main text should contain at least a few lines.

Response: We apologize for not making this clear. We have revised the revised Supplementary Table 1 to better identify all codes used to identify the study population, exposures, outcomes and baseline covariates.

Comment 3. I am uncertain why major hemorrhage is not included as a study outcome, only hemorrhagic stroke. If the authors consider major hemorrhage to be too much of a heterogeneous category, may I suggest looking at only GI bleeding in its various forms, which is more well-defined and represents a large percentage of non-intracranial bleeding. There are published methods for detecting GI bleeding or major bleeding using ICD codes.

Response: We have considered the reviewer's suggestion and agree that major bleeding is a more appropriate outcome instead of focussing solely on haemorrhagic stroke. We have therefore revised the analyses and manuscript accordingly and included major bleeding encompassing intracranial, gastrointestinal and major bleeding in various anatomical positions as study outcome (reported as "any bleeding"). We have therefore also changed the title of the manuscript in order to include the new outcome. In additions, we plan follow-up studies on treatment disparities and anticoagulation in AF patients with mental disorders which will address quality of treatment in more detail.

Comment 4. It appears from the tables and the methods that the authors focused largely on examining whether patients were on anticoagulants or anti-platelet agents during the year prior to AF diagnosis. However, I do not see any explanation of the methods for determining whether patients received these medications during the 5 years of follow-up after the AF diagnosis, nor a definition of how much therapy was considered sufficient to say the patient received it as opposed to not. This appears to be a key covariate that mediates much of the between group differences in outcomes, namely that the mental health patients received OAT less often. Therefore, the methods for determining who received OAT need to be made explicit, and also the data on how many patients received OAT in each group should also be presented, whether in the main text or in an appendix.

Response: It is correct that the baseline characteristics provided in Table 1 show medication usage, including OAT, within the year prior to AF diagnosis. However, as described in the statistical methods, the adjusted analyses also accounted for use of OAT following AF diagnosis modelled as a time-varying covariate that shifted according to treatment status once the patient had a prescription redemption that indicated treatment initiation. Furthermore, the Supplementary Figure 2 depicts the distributions of time to initiation of OAT following AF diagnosis for each type of mental illness.

**Reviewer: 2**
Reviewer Name: Lars Frost, MD
Institution and Country: Department of Medicine, Silkeborg Regional Hospital, Denmark Competing Interests: None declared

The authors report on outcomes of atrial fibrillation (AF) in patients with severe mental disorders. The study is based on secondary data sources (administrative Danish data). The author conclude that severe mental disorders in AF patients were associated with increased risk of ischemic and in particular hemorrhagic stroke compared with matched comparisons. The excess rates were explained by more comorbidity and lower user rates of oral anticoagulation.

Comment from the authors: During the revision of the analyses, we found a few minor coding errors in a couple of the covariates and in our algorithm for the CHA2DS2-VASc and HAS-BLED scores. As a consequence, we have abstracted a new data set. The number of patients are unchanged as are baseline covariates for the patients with severe mental disorders. However, because the 1:5 match with AF patients without mental disorders yielded slightly different comparison cohorts (as shown in the revised Table 1 and Supplementary Table 3), event rates in the matched comparisons were changed (evident from the revised Table 2). Due to this, the outcome estimates are slightly different. Moreover, in response to Reviewer 1's third comment we have changed the study outcome "hemorrhagic stroke" to "major bleeding". Please refer to our response to reviewer 1 for a more detailed description.

Comments

Comment 1. All major conclusions are based on non-significant findings. This is not a problem for me as a reviewer, but could potentially lead many readers to conclude that there are no problems associated with AF among patients with mental disorders. Please add more weight to arguments about the potential public health implications of these non-significant study findings.

Response: We agree with the reviewer that there is an unfortunate tendency to equate lack of significance with lack of effect in the medical community. Due to the relatively low number of AF patients with severe mental disorders, our study has less precision meaning that the effect estimates are subject to more random error as indicated by the width of the confidence interval. Regrettably, confidence intervals are too often used as a as a surrogate test of statistical significance. Using a confidence interval merely to determine "significance" ignores the potentially useful quantitative information about the magnitude of effect and precision. Notwithstanding, we have revised the conclusion of our paper to emphasize the importance of optimized coordination and integration of care for patients with mental disorders between general somatic and psychiatric care services.

Comment 2. Would it be possible to explore in more detail why oral anticoagulation was underused in AF patients with mental disorders. A problem in general practice, somatic hospitals, psychiatric hospitals, or patient reluctance?

Response: We agree with the reviewer that this is a very important issue and a number of previous studies have provided evidence for a systematic under-recognition and under-treatment of cardiovascular diseases in patients with severe mental disorders [1–5]. However, we find that this is beyond the scope of the present paper. In our opinion, this question is best addressed in a separate paper with this as the primary aim. As noted in our response to Reviewer 1's third comment, we are currently planning a follow-up study on treatment disparities in AF patients with mental disorders.

Comment 3. Please define "severe" mental disorder. Why do you only count severe depression as a severe mental disorder? Can schizophrenia be mild? Can bipolar disorders be mild?

Response: Unfortunately, there is little consistency in how severe mental illness is defined in practice and several definitions have been used in the previous literature [6]. Severe mental illness is often defined by the length of duration and the disability it produces. These illnesses include disorders that produce psychotic symptoms, such as schizophrenia and schizoaffective disorder, and severe forms of other disorders, such as severe depression and bipolar disorder. In most prior studies theses different disorders have been lumped together as one collective category of "severe mental illness". However, given the distinct clinical characteristics associated with each individual disease, we felt that it was more appropriate to analyze them separately. We therefore focused on three of the most common: Schizophrenia, severe depression and bipolar disease.

Comment 4. The ICD code F30 is the code for mania. Is mania always a bipolar disease?

Response: We acknowledge that a diagnosis of a single manic episode may not always translate into bipolar disease. Nonetheless, it usually occurs as part of bipolar disease. Accordingly, the ICD-10 code F30 (single manic episode) has been used to define bipolar disease in other Danish studies [7–9]. In our data, about 12% of the patients with bipolar disease were identified because of a F30 diagnosis. Since we only included first time diagnoses, these patients may subsequently have been diagnosed with a type of bipolar disorder.

Comment 5. What are the criteria for "severe" depression? Do psychiatrists always graduate in mild, moderate and severe depression, when reporting to the patient registry?

Response: In ICD-10 depression is categorized into mild, moderate, and severe. There is a code for unspecified depression but the validity of this code is low [10]. Since the duration and severity of the depression affects the diagnosis and choice of treatment, we suspect that Danish psychiatrist use the graduation defined by ICD-10. Moreover, the ICD-10 graduation has proven clinically useful by predicting the long-term clinical course and outcome [11]. Furthermore, all Danish specialists in psychiatry have completed courses in ICD-10 coding in order to improve the diagnostic reliability among the physicians.

Comment 6. Why did you not include all types of depression and graduated into severe, moderate and mild? This approach would give much more statistical power and would also give an opportunity for studying a possible dose-response relation.

Response: Although we understand the reviewer's line of thought, we did not use this strategy for several reasons. First, in a recent Danish validation study the diagnosis of depression was confirmed in 75.4% of the patients using a detailed questionnaire a reference. However, the validity was highest for patients with severe depression (PPV of 82.8%) and decreased with declining severity (PPV was 76.0% for moderate depression and as low as 65.2% for mild depression) [10]. Second, including patients with mild depression also runs the risk of exposure misclassification because an unknown proportion of patients with mild depression would be diagnosed and treated by their general practitioner without having an ICD-10 diagnosis. Finally, rather than striving to reach statistical significance (please also refer to our response to the reviewer's first comment), we were more concerned about the completeness and validity of the diagnostic codes, and therefore decided to focus on patients with severe mental disorders, which we suspect are more likely to be in contact with the psychiatric hospital system.

Comment 7. What were the ICD codes for intracranial bleed? Did intracranial bleed include epidural bleed caused by head injury?

Response: As described in the revised supplementary table 1 our definition of intracranial bleeding included non-traumatic subarachnoid hemorrhage (ICD-10 code I60), non-traumatic intracerebral hemorrhage (ICD-10 code I61), and other and unspecified non-traumatic intracranial hemorrhage (ICD-10 code I62). The reason for not including intracranial bleeding subsequent to head injury was because we inferred that risks of injury could differ for patients with mental disorders. As noted above and in more detail in our response to Reviewer 1's third comment we have included gastrointestinal bleeding and major bleeding in other anatomical positions in a combined outcome of "any bleeding" in the revised manuscript.

Comment 8. Figure 2 does not support the conclusion that the risk of hemorrhagic stroke is increased among AF patients with mental disorders.

Response: As noted above, the outcome "hemorrhagic stroke" has been changed to any major bleeding in response to the comment raised by reviewer 1.

Comment 9. How did you determine whether a systemic embolism was fatal or not? Not all types of systemic embolism leads to death.

Response: We characterized thromboembolic events (ischemic stroke, systemic embolism, pulmonary embolism or myocardial infection) as fatal if the patient died within the 30 days following the event as done previously [12].

Comment 10. Should diagnostic bias be considered? Do patients with mental disorders more often have a CT scan of the head? Do alcohol drinking more often lead to a CT scan of the head?

Response: The reviewer makes an important point. As noted above, several prior studies have indicated under-recognition and under-treatment of cardiovascular and other comorbid diseases in patients with severe mental disorders [1–5]. In the discussion of the revised manuscript, we added a comment stating that we cannot exclude misclassification of outcomes, which may be differential according to exposure status.

**Reviewer: 3**
Reviewer Name: Andrea Natale
Institution and Country: Texas Cardiac Arrhythmia Institute, Austin, Texas, USA Competing Interests: None

Comment: This is a well-written paper that has addressed a very important topic in clinical EP; risk of stroke and fatal thromboembolic events in AF patients with a prior diagnosis of severe mental disease. However, there are several flaws in this paper that need to be addressed point by point.

Response: We thank the reviewer for the positive reception of our work and the many insightful observations. Before responding to the comments raised below, we have to explain that the estimates have changed slightly during the revisions process. When revising the analyses, we found a few minor coding errors in a couple of the covariates and in our algorithm for the CHA2DS2-VASc and HAS-BLED scores, which led us to abstract a new data set. The number of patients are unchanged as are baseline covariates for the patients with severe mental disorders. However, the 1:5 match with AF patients without mental disorders yielded slightly different comparison cohorts (as shown in the revised Table 1 and Supplementary Table 3), event rates in the matched comparisons were changed (evident from the revised Table 2). Due to this, the outcome estimates are slightly different. Moreover, in response to Reviewer 1's third comment we have changed the study outcome "hemorrhagic stroke" to "major bleeding". Please refer to our response to reviewer 1 for a more detailed explanation.

Comment 1. Please clarify why the patients were excluded, if they had not been residents in Denmark for at least 1 year before date of AF diagnosis

Response: The reason for excluding patients, who had not been residents in Denmark for at least one year before AF diagnosis, was to ensure sufficient clinical record history for treatment and diagnoses. This has been clarified in the revised manuscript (please see the Methods section, page 6).

Comment 2. How many patients were excluded because they 'died on the day of AF diagnosis' as has been stated in the 'methods' section?

Response: As described in the supplementary Figure 1 describing the assembly of the study population, 631 patients died on the day of AF diagnosis.

Comment 3. Please provide information on BMI, obstructive sleep apnea and thyroid dysfunction in the population, as that are known predictors of AF

Response: We acknowledge that these conditions are known risk factors for AF and stroke. However, we do not know the completeness and validity of the coding of these conditions in the Danish patient registry, but suspect that it is poor (see for instance reference [13] regarding the coding of weight status in the Danish National Patient Registry). In addition, we lack laboratory data on thyroid hormone levels. Furthermore, as the hazard ratio of stroke declined toward the null, when adjusting for the more well described risk factors including the components of the CHA2DS2VASc and the HAS-BLED scores, we suspected that further adjustment for BMI, sleep apnea and thyroid dysfunction would have little additional effect. We are therefore reluctant to include further adjustment but kindly leave it to the Editor to decide whether this is required.

Comment 4. As the stroke diagnosis was based on in-hospital ICD, there is a possibility of underestimation of stroke events that occurred outside the in-patient facility. Is there any historic data available to estimate what % of patients weren't included because they either didn't get hospitalized for the stroke or died of it?

Response: The reviewer raises an important question. We relied on all patients with acute stroke being registered in the Danish National Patient Registry, although it is evident that there will be exemptions. We are unaware of studies on the proportion of patients with unrecognized stroke. However, other studies have shown that heart disease appear to be under-diagnosed in patients with mental illness [14,15]. We have therefore included a comment in the discussion of study limitations stating that we cannot exclude differential misclassification of study outcome according to exposure status. If stroke were under-diagnosed in patients with severe mental disorders, this would bias the estimates toward the null.

Comment 5. Was Transient Ischemic Attack (TIA) also included in the thrombo-embolic events' category? If not, please discuss why.

Response: We did not include TIA due to the documented low validity of the diagnosis in the Danish National Patient Registry (PPV around 60% depending on the setting [16]). In addition, we suspect that the completeness is probably lower for TIA compared with stroke due to the discrete or transitory symptoms.

Comment 6. In the flow chart of the study population, it says that >15 years were considered as eligible adults. Is that a typographical mistake or it is so in Denmark?

Response: In Denmark, children are under pediatric care until the age of 15. We decided to exclude these patients since physiology, pathogenesis, symptoms, and treatment may be widely different. In total, there were only 130 AF patients aged below 15 years.

Comment 7. Several anti-psychotic medications are known to be associated with increased stroke-risk (Shin et al. PLoS One. 2015; 10(3): e0119931; Douglas et al. BMJ 2008;337:a1227). All patients with severe mental diseases must be receiving anti-psychotic medications. However, neither the stroke risk was adjusted for use of those drugs nor that topic was addressed in the 'discussion' section of the manuscript. Please provide the data and discuss it or add it as a major limitation.

Response: We acknowledge the reviewers criticism and have included descriptive data on the use of antiepileptics, anticholinergics, antipsychotics, lithium and anxiolytics/hypnotics, and antidepressants in order to better characterize patients with severe mental disorders. Moreover, we have included a sentence in the section concerning study limitations concerning the anti-psychotic medications.

Comment 8. In the 'results', it is mentioned that the AF patients with schizophrenia were substantially younger; please provide a p value to validate that. In fact, please provide p values for all parameters given in the baseline table, which would show if the clinical characteristics were comparable between the groups or not

Response: Table 1 contains no inferential statistics (p-values), which is in line with the current recommendations for reporting of observational studies (STROBE statement) [17]. The data displayed in Table 1 represent variables that could potentially confound an association between the mental disorders and AF outcomes, and statistical significance (p-values) is not a suitable criterion to assess confounding (see for instance reference [18] for further discussion). Furthermore, in contrast to randomized trials, in which randomization provides a solid theoretical basis for the probability models from which p-values are derived, such a mechanism is missing in observational studies [19]. For valid interpretation of statistical significance testing in observational studies, several assumptions and requirements therefore have to be met. Importantly, the interpretability of the p-value depends on the absence of bias and confounding, because bias and confounding can influence the test size, power or both [20]. Because these theoretical requirements are seldom met in observational studies, we respectfully propose maintaining the current presentation of our data.

Comment 9. In what proportion of cases, non-compliance was responsible for 'lower use of OAT'?

Response: As described in our response to reviewer 1's fourth comment use of OAT was determined based on prescription redemption, which may be a limitation, as some patients may not take their medication. In the limitations section of revised manuscript, we have emphasized that we were unable to evaluate the quality and compliance with OAT (please see page 14).

Comment 10. How many patients with CHADS2-VASc score of 2 or more, did not receive OAT because of contraindications? What was the thrombo-embolic event rate in that subpopulation?

Response: As noted in our comments above, the primary focus of this paper was to describe stroke risk fatal thromboembolic events and major bleeding in AF patients with severe mental disorders. We acknowledge that quality of OAT is a major issue, but find that investigation of contraindications in subgroups is beyond the scope of this paper. We plan to investigate treatment disparities in a spate follow-up paper. Moreover, due to the overall low rate of thromboembolic events, we are reluctant to provide event rates in subgroups because we are concerned that there would be too few events to provide meaningful estimates.

Comment 11. The higher CHA2DS2-VASc score in patients with severe depression, was also possibly driven by highest number of females and a large proportion with hypertension and bleeding disorders, as reported in Table 1. Please discuss that in the manuscript.

Response: We thank the reviewer for pointing our attention to the gender differences. We have included a comment on this in the revised paper (please see page (10)). The prevalence of hypertension was virtually the same among patients with severe depression and AF patients without mental disorders. Bleeding disorders are not included in the CHA2DS2-VASc score.

Comment 12. In the 'discussion' it is said that the AF patients with mental disorders were substantially more likely to have highly supra-therapeutic International Normalized Ratio (INR) values than those without mental disorders. Please discuss what might be the plausible mechanism underlying this observation.

Response: Our comment about potential supra-therapeutic INRs were made in reference to the findings of Walker et al [21]. As we note in the discussion this should be interpreted with caution because the finding were made in a selected subgroup including few patients.

Comment 13. In this population, excess stroke risk was seen to be majorly due to lower use of OAT. Again, association of higher rates of hemorrhagic stroke was detected that emphasized the importance of cautious assessment of bleeding in this population. Please discuss, how a balance can be maintained between oral anticoagulation and bleeding risk in AF patients with severe mental diseases.

Response: As in other patient populations, maintaining a balance between risks of stroke and bleeding among patients with mental disorders require monitoring treatment quality (INR) of OAT. Moreover, as emphasized in the 2016 ESC Guidelines for the management of atrial fibrillation [22] bleeding risks during OAT should be minimized by identifying modifiable bleeding risk factors, e.g. hypertension should be well-controlled, concomitant antiplatelet or NSAID therapy should be as short in duration as possible and alcohol use moderated. These efforts may be complicated by suboptimal integration of general somatic and psychiatric care services. We might have to focus on psychiatrists (especially in AF patients with schizophrenia or bipolar disorder) since they are most competent to promote comprehensive medication in patients with mental disorders.

We have revised the conclusion in order to emphasize the importance of optimized coordination of care when managing these patients in order to optimize treatment and care.

Comment 14. Patients with schizophrenia were observed to experience higher mortality following a thromboembolic event than matched comparisons. What can be a plausible explanation for that?

Response: As discussed in our paper the underlying mechanisms are likely multifactorial. Plausible explanations may entail both severity of illness, comorbidity, quality of care, and factors beyond patient care. As noted in our response to reviewer 2's last comment prior studies have indicated that there may be disparities in the treatment of cardiovascular diseases in patients with severe mental disorders [1–5]. In our opinion, this call for further investigation.

References

1 Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med 2013; 11: 263.
2 Woodhead C, Ashworth M, Broadbent M, Callard F, Hotopf M, Schofield P, Soncul M, Stewart RJ, Henderson MJ, Henderson M, Hotopf M, Shah I, Laursen T, Olsen TM, Vestergaard M, Crump C, Winkleby M, Sundquist K, Sundquist J, Lawrence D, et al. Cardiovascular disease treatment among patients with severe mental illness: a data linkage study between primary and secondary care. Br J Gen Pract 2016; 11: 37–37.
3 Jakobsen L, Terkelsen CJ, Christiansen EH, Maeng M, Jensen LO, Veien K, Raungaard B, Jensen SE, Mehnert F, Johnsen SP. Severe Mental Illness and Clinical Outcome After Primary Percutaneous Coronary Intervention. Am J Cardiol 2017; 120: 550–5.
4 Schulman-Marcus J, Goyal P, Swaminathan R V, Feldman DN, Wong S-C, Singh HS, Minutello RM, Bergman G, Kim LK. Comparison of Trends in Incidence, Revascularization, and In-Hospital Mortality in ST-Elevation Myocardial Infarction in Patients With Versus Without Severe Mental Illness. Am J Cardiol 2016; 117: 1405–10.
5 Hippisley-Cox J, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. Heart 2007; 93: 1256–62.
6 Schinnar AP, Rothbard AB, Kanter R, Jung YS. An empirical literature review of definitions of severe and persistent mental illness. Am J Psychiatry 1990; 147: 1602–8.
7 Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Arch Gen Psychiatry 2009; 66: 713–20.
8 Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. PLoS One 2011; 6.
9 Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder - Changes in the danish population between 1994 and 2006. J Psychiatr Res Elsevier Ltd; 2011; 45: 29–35.
10 Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. Clin Pract Epidemiol Ment Health 2009; 5: 4.
11 Kessing LV. Severity of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. Br J Psychiatry 2004; 184: 153–6.
12 Nielsen PB, Larsen TB, Gorst-Rasmussen A, Skjøth F, Lip GYH. β-Blockers in Atrial Fibrillation Patients With or Without Heart Failure: Association With Mortality in a Nationwide Cohort Study. Circ Heart Fail 2016; 9: e002597.
13 Søgaard M, Heide-Jørgensen U, Nørgaard M, Johnsen SP, Thomsen RW. Evidence for the low recording of weight status and lifestyle risk factors in the Danish National Registry of Patients, 1999-2012. BMC Public Health 2015; 15: 1320.

14 Crump C, Winkleby M a, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013; 170: 324–33.
15 Nielsen J, Juel J, Al Zuhairi KSM, Friis R, Graff C, Kanters JK, Jensen SE. Unrecognised myocardial infarction in patients with schizophrenia. Acta Neuropsychiatr 2015; 27: 106–12.
16 Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. J Clin Epidemiol 2002; 55: 602–7.
17 Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007; 18: 805–35.
18 Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed. Lippincott Williams & Wilkins; 2008.
19 Poole C. Low P-values or narrow confidence intervals: which are more durable? Epidemiology 2001; 12: 291–4.
20 Stang A, Poole C, Kuss O. The ongoing tyranny of statistical significance testing in biomedical research. Eur J Epidemiol 2010; 25: 225–30.
21 Walker GA, Heidenreich PA, Phibbs CS, Go AS, Chiu VY, Schmitt SK, Ananth L, Frayne SM. Mental illness and warfarin use in atrial fibrillation. Am J Manag Care 2011; 17: 617–24.
22 Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893–962.

## VERSION 2 – REVIEW

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| **REVIEWER** | Adam Rose<br>RAND Corporation and Boston University School of Medicine |
| **REVIEW RETURNED** | 11-Sep-2017 |

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| **GENERAL COMMENTS** | I have no further comments. The authors have been responsive to the initial comments. |

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| **REVIEWER** | Lars Frost<br>Department of Medicine, Diagnostic Centre, Silkeborg and Aarhus University Hospital, Denmark. |
| **REVIEW RETURNED** | 20-Sep-2017 |

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| **GENERAL COMMENTS** | The manuscript has been clarified. Well balanced discussion. |

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| **REVIEWER** | Andrea Natale<br>Texas Cardiac Arrhythmia Institute, Austin, TX, USA<br>No Competing Interest |
| **REVIEW RETURNED** | 12-Sep-2017 |

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| **GENERAL COMMENTS** | The authors have answered all my questions.<br>Comments:<br>There are few grammatical errors in the manuscript; please correct those in the final revision.<br>Also, the conclusion is too long and descriptive; please make it brief but comprehensive. |

## VERSION 2 – AUTHOR RESPONSE

**Reviewer: 3**
Reviewer Name: Andrea Natale
Institution and Country: Texas Cardiac Arrhythmia Institute, Austin, TX, USA Competing Interests: None

The authors have answered all my questions.

Comments:
There are few grammatical errors in the manuscript; please correct those in the final revision.

Response: We agree that linguistic acuity is important and have carefully proofread the revised manuscript

Comment: Also, the conclusion is too long and descriptive; please make it brief but comprehensive.

Response: we agree and have revised the conclusion as suggested.