

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Adherence to oral anticoagulants among patients with atrial fibrillation: A systematic review and meta-analysis of observational studies
<b>AUTHORS</b>	Salmasi, Shahrzad; Loewen, Peter; Tandun, Rachel; Andrade, Jason; De Vera, MA

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Marc Saez University of Girona, Spain
<b>REVIEW RETURNED</b>	20-Oct-2019

<b>GENERAL COMMENTS</b>	<p>The authors tried to summarize the evidence on atrial fibrillation (AF) patients' observational adherence to oral anticoagulants. However, the authors have had only partial success in achieving their objective. In fact, I have both major and minor comments.</p> <p>Major comments</p> <p>1.- The introduction is too short. The authors should include and explain in detail, in the introduction, all the systematic reviews on the subject and the results of any of the studies with a high level of evidence. Without knowing the keywords, in a Medline search, entering the keywords non-adherence, atrial fibrillation, oral anticoagulants, I found 5 reviews (from 2015 to 2017), 2 clinical trials and 11 cohorts.</p> <p>2.- The authors have forgotten to contrast the publication bias. It is very important to contrast it, since the authors point out, as a limitation, 'The high number of studies from a few developed countries (...)' (page 12)</p> <p>3.- In the discussion they do not compare their findings with those of other reviews or with other studies that provide great evidence.</p> <p>Minor comments</p> <p>1.- The authors do not include the search period</p> <p>2.- They also don't include the keywords</p>
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<b>REVIEWER</b>	Dr Leanne Chalmers Curtin University, Australia I have received consultancy funding from Aspen Pharmacare Australia, the Australian manufacturers of warfarin (2011-12).
<b>REVIEW RETURNED</b>	12-Nov-2019

<p><b>GENERAL COMMENTS</b></p>	<p>Thank you for the opportunity to review this systematic review and meta-analysis of observational studies of adherence to oral anticoagulants among patients with AF. This study is particularly timely with the significant uptake of the DOACs into clinical practice for this indication over recent years, given that the shorter half-lives of these agents makes adherence to DOACs perhaps even more important than with the vitamin K antagonists.</p> <p>1. It is a matter of personal preference but, in this era of person-centred care (which has been widely promoted in international guidelines for the management of AF),[1,2] I tend to avoid the term 'AF patients' (where patients are defined by their disease), in favour of 'patients (or people) with AF'. I would therefore suggest revising the title of the manuscript to 'Adherence to oral anticoagulants among patients with atrial fibrillation: A systematic review and meta-analysis of observational studies', and consequently amending all references within the paper from 'AF patients' to 'patients with AF'.</p> <p>2. Abstract</p> <ul style="list-style-type: none"> <li>- Please clarify that the pooled mean adherence results referred to in the Results section are out of 100.</li> <li>- Please review the use of the term 'six-month'; this would read better as 'six months' here and in a number of points throughout the manuscript. Also please consider using the term 'post index date' in the first sentence rather than the second sentence for clarity.</li> <li>- Conclusions: Please consider rewording the first sentence to, 'Our findings show that up to 30% of patients with AF are non-adherent to their OAC therapy...' as it is the non-adherence that truly represents the clinical challenge in this population.</li> </ul> <p>3. Strengths and limitations</p> <ul style="list-style-type: none"> <li>- The second point relating to 'initiation, implementation and discontinuation' should be addressed in the Methods section of the paper, as it is an important consideration in the interpretation of the results.</li> <li>- Limitations associated with the use of MPR and PDC for patients taking warfarin (who may be undergoing regular dose changes in response to their INR results) should be mentioned here too (as in the Discussion).</li> </ul> <p>4. Introduction</p> <ul style="list-style-type: none"> <li>- The Introduction provides a brief, though appropriate context for the work. I think that it would be worthwhile highlighting that OACs are the only pharmacological therapy that reduces mortality in AF (to reinforce its importance) and to also include some details regarding the particular importance of adherence with the short half-life DOACs (as above), which will strengthen the rationale for the current study.</li> <li>- Please review the references in lines 9 (2-45) and 11 (6-12). I think that the first might be a typographical error, while I do not think that 7 references are required regarding the seriousness of strokes in people with AF.</li> </ul> <p>5. Methods</p> <ul style="list-style-type: none"> <li>- Overall, the Methods are comprehensive and would permit repetition of the study.</li> </ul>
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	<p>- Please define 'secondary adherence (also known as "implementation")' (p5, line 30) – this is currently unclear and, as mentioned previously, is crucial to the interpretation of the results.</p> <p>- Please specify what was excluded as 'self-reported adherence' (p5, line 39). I assume that this includes all self-reported measures, including validated adherence scales (e.g. MMAS)?</p> <p>- Please clarify that the primary adherence measure refers to six or twelve months 'post index date' (as per the Abstract) and define what this means.</p> <p>- Please clarify whether the 'pooled proportion of adherent patients' (p6, line 40) was defined as those with a mean score <math>\geq</math> or <math>&gt;</math> 80 (it states <math>&gt;</math> here but the text above [line 3] refers to <math>\geq</math>).</p> <p><b>6. Results</b></p> <p>- Please indicate what proportion of the studies included in this analysis utilised data from administrative databases (as this type of research is not the norm worldwide).</p> <p>- Please provide further details regarding why 'There was insufficient information on warfarin for inclusion in meta-analysis...' (p9, line 22). What is meant by 'insufficient'?</p> <p>- Determinants of adherence: I believe that the manuscript would benefit overall from increasing the relevance of this section of the paper to the reader. Given that the primary data were not obtained from the authors of the observational studies, it was not possible to conduct a large scale multivariate regression analysis which may have clarified some of the inconsistencies in the findings of different studies. As it is, the findings in this section are potentially influenced by the significant heterogeneity among the studies, including the study populations. Little is made of these findings within the Discussion of the paper – value could be added to these results by discussing, perhaps, the relative predictive value of the identified predictors of non-adherence (i.e. how clinically relevant are these various factors?), reasons behind the inconsistent findings, etc. Furthermore, please review the presentation of these findings in the Results section. The apparent relevance to the WHO dimensions is currently limited.</p> <p>- Impacts of adherence: p10, line 56: Please specify – increased hazard of what?</p> <p>- Table 1: To what does 'Both' refer in the 'Indication for OAC' column; and 'NA' in the 'Adherence reported to index OAC or current OAC'? The footnote appears to be missing.</p> <p><b>7. Discussion</b></p> <p>- Please revise the first paragraph of the Discussion to provide a strong summary of the main findings of the study and/or the novelty of what it adds to the literature, rather than merely re-stating its aims and objectives.</p> <p>- The discussion of the findings of the outcomes is very limited. Can anything be added here (e.g. comparison to other studies) to support the clinical relevance of these findings?</p> <p>- The limitations of the study and future directions are well described, and the Conclusion is sound. Please provide appropriate references for the statement, 'While the association between taking <math>&gt;</math>80% of medications and improved clinical outcomes has been shown in three AF studies,' (p13, line 30).</p> <p><b>8. Overall</b></p> <p>- The English expression is very good but there are a number of typographical errors that require review, for example: Introduction (p4, line 9): 'responsible for a with'; Search strategy (p5, line 15):</p>
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	<p>replace 'On March 2019' with 'In March 2019'; Results: please be consistent in spacing between '95% CI' (p6, line 52); Figure 1.0: please check the spacing in the exclusions box. This is not an exhaustive list. Please proofread thoroughly.</p> <ul style="list-style-type: none"> <li>- Please ensure consistency in the use of the terms 'DOAC' and 'NOAC'. They are currently used interchangeably throughout the paper.</li> <li>- There are multiple inconsistencies in the formatting and capitalisation of the references in the References list, including some references with the journal titles missing (e.g. Ref 14, 28, 30). Please proofread thoroughly and ensure that the Journal's formatting requirements are met.</li> </ul> <p>1. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. <i>Heart Lung Circ.</i> 2018; 27(10):1209-66. doi:10.1016/j.hlc.2018.06.1043.</p> <p>2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. <i>Eur Heart J.</i> 2016; 37(38):2893-2962. doi:10.1093/eurheartj/ehw210.</p>
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## VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

### Major comments

#### 1.- The introduction is too short.

**The authors should include and explain in detail, in the introduction, all the systematic reviews on the subject and the results of any of the studies with a high level of evidence. Without knowing the keywords, in a Medline search, entering the keywords non-adherence, atrial fibrillation, oral anticoagulants, I found 5 reviews (from 2015 to 2017), 2 clinical trials and 11 cohorts.**

The following paragraph has been added to introduction to explain the current evidence on the topic:

*“Studies have previously attempted to summarize the medication taking behavior of AF patients. These reviews however focus on discontinuation of therapy (not implementation or execution of dosing), or when looking at implementation, only focus on DOACs, summarize evidence from randomized controlled trials (which do not reflect the day to day behaviors of patients), and provide a narrative summary of results with no meta-analysis.<sup>2-4</sup> Further, no studies have summarized the evidence on determinants of adherence in this patient population and the association between adherence and outcomes (clinical or economical).”*

#### 2.- The authors have forgotten to contrast the publication bias.

**It is very important to contrast it, since the authors point out, as a limitation, 'The high number of studies from a few developed countries (...)' (page 12)**

We have assessed the potential for publication bias using funnel plots which can be found in supplementary file 3 (Pages 30,31,32). Given the descriptive nature of results of included studies, we could only conduct these tests for results based on measures of association (e.g., odds ratios). This

can be found in Supplementary file 3 (pages 30,31,32). We revised the methods section to make this more clear.

*“Forest plots and funnel plots were constructed using OpenMeta-Analyst (Microsoft Corporation, Redmond, WA)<sup>5</sup> or RevMan5 (version 5.3, Copenhagen, Denmark) software to illustrate the results and assess publication bias using funnel plots where relevant, that is, where studies reported measures of association (e.g., OR).”*

We also revised the limitations to highlight the potential for publication bias.

*“Furthermore, there may be potential for publication bias or under-representation from studies from developing countries. As described in the methods, we attempted to assess publication bias using funnel plots but were limited with few studies reporting measures of association. Nonetheless, for these meta-analyses, findings do not suggest presence of publication bias (Supplementary 3).”*

### **3.- In the discussion they do not compare their findings with those of other reviews or with other studies that provide great evidence.**

Discussion has gone through major revision. This section has been strengthened with evidence from other systematic reviews, and relevant studies to place our findings in context of the current evidence.

#### **Minor comments**

##### **1.- The authors do not include the search period**

This information can be found under the search strategy section of the manuscript (under the “Methods” section)

*“In March 2019 we systematically searched PubMed/Medline, Embase, CINAHL and PsycINFO (from inception) using the relevant keywords and MeSH terms”.*

##### **2.- They also don't include the keywords**

Relevant keywords and MeSH terms have been provided in detail in Supplementary 2. Reference has been made to this supplementary file in the manuscript:

*“In March 2019 we systematically searched PubMed/Medline, Embase, CINAHL and PsycINFO (from inception) using the relevant keywords and MeSH terms (Supplementary 2).”*

#### **Reviewer: 2**

**1. It is a matter of personal preference but, in this era of person-centred care (which has been widely promoted in international guidelines for the management of AF),<sup>[1,2]</sup> I tend to avoid the term ‘AF patients’ (where patients are defined by their disease), in favour of ‘patients (or people) with AF’. I would therefore suggest revising the title of the manuscript to ‘Adherence to oral anticoagulants among patients with atrial fibrillation: A systematic review and meta-analysis of observational studies’, and consequently amending all references within the paper from ‘AF patients’ to ‘patients with AF’.**

We agree with the reviewer. This has been revised throughout the manuscript, including the title and running head.

#### **2. Abstract**

**- Please clarify that the pooled mean adherence results referred to in the Results section are out of 100.**

This has been clarified in the abstract.

- Please review the use of the term 'six-month'; this would read better as 'six months' here and in a number of points throughout the manuscript. Also please consider using the term 'post index date' in the first sentence rather than the second sentence for clarity.

We thank the reviewer for this observation. This has been revised throughout the manuscript.

- **Conclusions:** Please consider rewording the first sentence to, 'Our findings show that up to 30% of patients with AF are non-adherent to their OAC therapy...' as it is the non-adherence that truly represents the clinical challenge in this population.

We agree with the reviewer. This sentence has been revised in the abstract.

### 3. Strengths and limitations

- The second point relating to 'initiation, implementation and discontinuation' should be addressed in the Methods section of the paper, as it is an important consideration in the interpretation of the results.

This has been clarified under "*inclusion criteria and study selection*" of the manuscript "Methods" section as follows:

*"Studies were included if they utilized a prospective or retrospective observational study design, and quantitatively measured secondary adherence, (also known as the "implementation" phase) which looks at medication dose omissions, additions, or delays and does not involve those who did not initiate their therapy"*

- **Limitations associated with the use of MPR and PDC for patients taking warfarin (who may be undergoing regular dose changes in response to their INR results) should be mentioned here too (as in the Discussion).**

The lack of data on warfarin as a result of its changing dose was the limitation of data not a methodological limitation of the systematic review. This limitation was revealed to us during data synthesis and analysis. It was therefore the result of this systematic review.

According to BMJ Open instructions, the strengths and limitation bullet points should contain five short bullet points, that relate specifically to the methods and cannot include results. We have therefore, respectfully not added this information to the strengths and limitation bullets.

### 4. Introduction

- **The Introduction provides a brief, though appropriate context for the work. I think that it would be worthwhile highlighting that OACs are the only pharmacological therapy that reduces mortality in AF (to reinforce its importance) and to also include some details regarding the particular importance of adherence with the short half-life DOACs (as above), which will strengthen the rationale for the current study.**

Due to lack of comparative data between DOACs and warfarin, it is not known if the shorter half-lives of DOACs truly translate into worse outcomes in the context of poor adherence. Pharmacokinetically, however, the hypothesis seems plausible.

Introduction has been revised as follows to emphasize the importance of OAC therapy and discuss the possibility of nonadherence having more serious negative consequences among DOAC users.

*"Oral anticoagulants (OACs), which include vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), are the only effective agents thus far in preventing stroke in patient with AF, showing approximately 66% relative risk reduction in clinical trials.<sup>6-10</sup> When used outside the controlled environment of clinical trials, however, the effectiveness of these drugs is impacted by*

patients' adherence.<sup>11,12</sup> The clinical consequences of non-adherence can potentially be more significant for DOACs, given their short half-lives.<sup>13-15</sup>

**- Please review the references in lines 9 (2-45) and 11 (6-12). I think that the first might be a typographical error, while I do not think that 7 references are required regarding the seriousness of strokes in people with AF.**

We apologize for this mistake. The first references (2-45) was a typographical error. The reference meant to say (2-5). This has been corrected.

References for seriousness of stroke in AF have been reduced from 7 to 3.

## 5. Methods

**- Overall, the Methods are comprehensive and would permit repetition of the study.  
- Please define 'secondary adherence (also known as "implementation")' (p5, line 30) – this is currently unclear and, as mentioned previously, is crucial to the interpretation of the results.**

Methods has been revised to provide information on "secondary adherence" and how it differs from primary adherence:

*"Studies were included if they utilized a prospective or retrospective observational study design, and quantitatively measured secondary adherence, (also known as the "implementation" phase) which looks at medication dose omissions, additions, or delays and does not involve those who did not initiate their therapy."*

**- Please specify what was excluded as 'self-reported adherence' (p5, line 39). I assume that this includes all self-reported measures, including validated adherence scales (e.g. MMAS)?**

The reviewer is correct. All self-reported measures, including validated scales (e.g. MMAS) were excluded. This has now been clarified in the manuscript.

*"Studies of self-reported adherence were excluded (including those using validated scales such as MMAS) as they are prone to overestimation of adherence (social desirability bias)."*

**- Please clarify that the primary adherence measure refers to six or twelve months 'post index date' (as per the Abstract) and define what this means.**

We thank the reviewer for their suggestion. The term "post index-date" and its definition have been added under "data extraction and synthesis".

**- Please clarify whether the 'pooled proportion of adherent patients' (p6, line 40) was defined as those with a mean score  $\geq$  or  $>$  80 (it states  $>$  here but the text above [line 3] refers to  $\geq$ ). As illustrated in Table 2, under the "Adherence measure (threshold)" column, the included studies varied in their definition of thresholds ( $>80$  vs  $\geq 80$ ) for good adherence. We have therefore revised methods section as follows:**

*"Secondary adherence measure included proportions of adherent patients, that is proportion of patients reported in each study to have mean adherence score more than 80 (this could be  $>$  or  $\geq$  depending on how the study defined "adherent")."*

## 6. Results

**- Please indicate what proportion of the studies included in this analysis utilised data from administrative databases (as this type of research is not the norm worldwide).**

Except for McCormick 2001 that used Medical records of 21 community-based long-term care facilities located throughout the state of Connecticut, all retrospective studies (n=28) used administrative data. This makes up 93.33% of all the included studies. We agree with the reviewer that this type of study is not the norm worldwide (due to lack of infrastructure) however, all of the included studies in this systematic review have been conducted in developed countries where such infrastructure is available.

**- Please provide further details regarding why ‘There was insufficient information on warfarin for inclusion in meta-analysis...’ (p9, line 22). What is meant by ‘insufficient’?**

Majority of the included studies measured and reported adherence to newer agents (DOACs) and did not report any adherence data on warfarin. Overall only 4 observational studies measured and reported adherence to warfarin (two over 6 months and 2 over one year). This is probably because warfarin dose variations complicate adherence measurement from administrative data, an issue we have discussed under the “future directions” section.

A minimum of two studies are needed for meta-analysis to be conducted. As illustrated in Table 2, focusing on mean adherence scores, there was no mean adherence data reported for warfarin over 6 months and one year. No meta-analysis could therefore be performed to calculate pooled mean adherence scores for warfarin [denoted as “No data available” in Table of pooled adherence results (table3)].

Looking at proportion of adherent patients, this data was only reported for warfarin by two studies over 6 months and 2 studies over one year. Meta-analysis was therefore performed for reported proportion of adherent patients; however, their results were marked by ++ to denote that results are pooled from two studies only.

We have added the following sentence to the first paragraph of results:

*“Majority of the included studies focused on adherence to DOACs with only 4 observational studies measuring and reporting adherence to warfarin.”*

We agree with the reviewer that our statement in results was not very informative. The paragraph has therefore been revised as follows:

*“No meta-analysis could be conducted for mean adherence to warfarin since this was not reported by the included studies. Pooled estimates of proportion of adherent patients for warfarin were resulted from meta-analysis of 2 studies only (as illustrated in tables 2 and 3). Due to the limited data in warfarin, no drug class comparison could be made.”*

**- Determinants of adherence: I believe that the manuscript would benefit overall from increasing the relevance of this section of the paper to the reader. Given that the primary data were not obtained from the authors of the observational studies, it was not possible to conduct a large scale multivariate regression analysis which may have clarified some of the inconsistencies in the findings of different studies. As it is, the findings in this section are potentially influenced by the significant heterogeneity among the studies, including the study populations. Little is made of these findings within the Discussion of the paper – value could be added to these results by discussing, perhaps, the relative predictive value of the identified predictors of non-adherence (i.e. how clinically relevant are these various factors?), reasons behind the inconsistent findings, etc. Furthermore, please review the presentation of these findings in the Results section. The apparent relevance to the WHO dimensions is currently limited.**

Discussion around determinants of adherence has been revised extensively. Reasons behind the inconsistent findings is now discussed with connections made to findings of other relevant studies:

The following has been added under discussion: *“Further, questions remain about the role of sex, age, risk of stroke, presence of multiple comorbidities, and number of concomitant medications on adherence. One explanation for the inconsistencies we observed could be differences in how these factors were defined in our included studies. A 2019 systematic review of 34 systematic reviews on determinants of adherence to cardiovascular medications (beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics) also reported inconsistent results for the role of gender in adherence.<sup>16</sup> These authors also found that the effects of concomitant medications and comorbidities seem to be drug-specific and condition-specific, which could explain some of the inter-study variability with this factor.<sup>16</sup> A multivariate patient-level meta-regression analysis could provide more clarity to these issues with OACs in patients with AF.”*

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The clinical relevance of the identified factors can only be ascertained if we know the following: 1) the strength of the impact of these factors on adherence and 2) the direct relationship between adherence and clinical outcomes. We do not know either one of these.

- 1) The strength of the impact of these factors on adherence: Determinants were defined quite differently in each of the studies. Further, each of the listed determinants were reported to have a significant impact on adherence by one or maximum of two studies, impeding our ability to perform meta-analysis. We therefore did not feel we had adequate data to make comments on the strength of impact of the identified factors on adherence.
- 2) The direct relationship between adherence and clinical outcomes: Ascertaining such relationship requires meta-analysis of patient-level data which was not available to us and was beyond the scope of our study. Further, the threshold below which adherence becomes problematic is not known.

We therefore believe that discussion of the predictive value and clinical relevance of the identified determinants of adherence is beyond the scope of this study and only possible with more research.

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Following other adherence systematic reviews, we used the WHO classification of determinants of adherence as a way of summarize the results around adherence determinants, and identifying areas in need for more research.<sup>16</sup> Methods and results have been revised to clarify the relevance of the WHO dimensions.

**- Impacts of adherence: p10, line 56: Please specify – increased hazard of what?**

We apologize for the vague sentence. The term “ischemic stroke” has been added to this sentence to clarify.

**- Table 1: To what does ‘Both’ refer in the ‘Indication for OAC’ column; and ‘NA’ in the ‘Adherence reported to index OAC or current OAC’? The footnote appears to be missing.**

We thank the reviewer for catching this mistake. The table should have said “AF” in that cell, which is the general term we used to refer to both valvular and non-valvular AF when inclusion criteria of the study was not clear.

Further, a footnote has been added to this table, spelling out abbreviations used.

**7. Discussion**

**- Please revise the first paragraph of the Discussion to provide a strong summary of the main findings of the study and/or the novelty of what it adds to the literature, rather than merely re-stating its aims and objectives.**

The first paragraph of discussion has been revised as follows:

*“In this systematic review, we synthesized observational data of over half a million patients with AF to reveal that up to 30% of patients are non-adherent to OACs, and that nonadherent patients were more likely to experience bleeds and stroke and incurred higher medical costs compared to adherent patients. We also found that older age, higher stroke risk, once-daily regimen, history of hypertension, diabetes, or stroke, concomitant cardiovascular medications, living in rural areas, and being an experienced OAC user could be associated with better adherence.*

**- The discussion of the findings of the outcomes is very limited. Can anything be added here (e.g. comparison to other studies) to support the clinical relevance of these findings?**

This paragraph has been strengthened with data from two other major systematic reviews:

*“Lastly, we looked at outcomes of adherence. Our review found evidence of association between lower adherence and strokes, bleeds, death, healthcare utilization and costs. Our findings confirm the results of a 2017 systematic review of 79 studies across 14 disease groups which reported that \$3347-19472 are attributed to nonadherence per patient per year among those with cardiovascular conditions (hypertension, hypercholesterolaemia, and chronic heart failure).<sup>17</sup> As for clinical outcomes, our findings are in line with results of meta-analyses of a large body of research showing that poor adherence across a range of conditions was associated with a 26% increased risk of poor treatment outcomes.<sup>18</sup> The adherence-outcome relationship is, however, very complex, and dependant on many factors, including the nature of the disease.<sup>18</sup> This is why it was important to summarize the strength of this relationship specifically in AF. Our findings, while based on only four studies, reveal the relationship between lower adherence and poor clinical outcomes in patients with AF, and support the potential of interventions aimed at increasing adherence in patients with AF.”*

**- The limitations of the study and future directions are well described, and the Conclusion is sound. Please provide appropriate references for the statement, ‘While the association between taking >80% of medications and improved clinical outcomes has been shown in three AF studies,’ (p13, line 30).**

This sentence is referring to the four studies which looked at the association between adherence and clinical outcomes, whose results were presented under “impacts of adherence”. We agree with the reviewer that this sentence needs referencing. The reference for the four studies have been added.

## 8. Overall

**- The English expression is very good but there are a number of typographical errors that require review, for example: Introduction (p4, line 9): ‘responsible for a with’; Search strategy (p5, line 15): replace ‘On March 2019’ with ‘In March 2019’; Results: please be consistent in spacing between ‘95% CI’ (p6, line 52); Figure 1.0: please check the spacing in the exclusions box. This is not an exhaustive list. Please proofread thoroughly.**

We thank the reviewer for their careful examination of our manuscript and the suggestions. The recommended editorial changes have been reflected in the manuscript.

**- Please ensure consistency in the use of the terms ‘DOAC’ and ‘NOAC’. They are currently used interchangeably throughout the paper.**

Changed to “DOAC” throughout the manuscript for consistency.

**- There are multiple inconsistencies in the formatting and capitalisation of the references in the References list, including some references with the journal titles missing (e.g. Ref 14, 28,**

**30). Please proofread thoroughly and ensure that the Journal’s formatting requirements are met.**

All references have been changed to the BMJ format. Capitalization has been standardized throughout by using sentence style capitalization for all titles. All journal names have been changed to their abbreviated version and italicized. Missing journal names have been added.

Intext references: multiple references have been separated by comma. For sequences of consecutive numbers, we have give the first and last number of the sequence separated by a hyphen.

We have listed the names and initials of all authors if there were 3 or fewer; otherwise listed the first 3 and added ‘et al.’

**1. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ. 2018; 27(10):1209-66.**

doi:10.1016/j.hlc.2018.06.1043.

**2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38):2893-2962.**

doi:10.1093/eurheartj/ehw210.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Marc Saez University of Girona, Spain
<b>REVIEW RETURNED</b>	29-Dec-2019

<b>GENERAL COMMENTS</b>	The authors have answered quite well not only to my comments, but also those of the other reviewers. In addition, they have incorporated much of them in the new version of the manuscript. I have no further comments.
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<b>REVIEWER</b>	Dr Leanne Chalmers Curtin University, Australia I have received consultancy funding from Aspen Pharmacare Australia, who were the Australian sponsors of warfarin at the time.
<b>REVIEW RETURNED</b>	08-Jan-2020

<b>GENERAL COMMENTS</b>	<p>Thank you to the authors for the comprehensive review of their manuscript. I am satisfied that the issues from my previous review have been adequately addressed. My remaining suggestions are minor and largely editorial.</p> <ol style="list-style-type: none"> <li>1. While the term ‘AF patients’ has been replaced with ‘patients with AF’ in the majority of cases, the former term is still used in several places – Abstract line 10, Introduction (page 4, line 24), Methods (page 5, line 37), Discussion (page 13, line 3). Please revise for consistency.</li> <li>2. Please also review the remaining references to ‘six-month’ and ‘one-year’ to remove hyphens, also for consistency.</li> <li>3. Please consider defining MMAS as ‘Morisky Medication Adherence Scale’ for the naïve reader.</li> </ol>
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	<p>4. Results, page 10, line 23: Please reword ‘Pooled estimates of proportion of adherent patients for warfarin were resulted from meta-analysis of 2 studies only...’ – maybe omit the ‘were’?</p> <p>5. Discussion, page 13, line 5: Please consider rewording for clarity - e.g. ‘In our study, the pooled proportions of adherent patients at six months and one year were 63% and 70%, respectively, which are higher than those found for other chronic cardiovascular medications such as statins (54%) and antihypertensives (59%).65’</p> <p>6. There remain some additional minor typographical errors:</p> <ul style="list-style-type: none"> <li>- Please correct the spelling of “INTRODUCTION” in the Abstract.</li> <li>- Please use a hyphen in the 95% CI for apixaban at one year in the Abstract, as per the other CIs.</li> <li>- Introduction, page 4, line 15: please correct to ‘patients with AF’.</li> <li>- Methods, page 6, line 8: ‘Secondary adherence measure included...’. Should this read, ‘The secondary adherence measure was...’?</li> <li>- Results, page 9, line 20: please change to ‘The majority of...’.</li> </ul> <p>Similarly, page 10, line 11 should read: ‘A wide range...’</p> <ul style="list-style-type: none"> <li>- Please be consistent with hyphenation of ‘non-adherence’ and ‘non-adherent’.</li> <li>- Discussion, page 14, line 7: Please reword – e.g. ‘Our findings in relation to clinical outcomes are...’</li> <li>- The references look much better but there are some words/abbreviations in the journal article titles in the Reference list that should ideally be capitalised (e.g. SPAF, Framingham, ESC, United States). See also the journal title in reference 18.</li> </ul>
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## VERSION 2 – AUTHOR RESPONSE

### Reviewer(s)' Comments to Author:

**Reviewer: 1**

**Reviewer Name**

**Marc Saez**

**Institution and Country**

**University of Girona, Spain**

**Please state any competing interests or state ‘None declared’:**

**None declared**

**Please leave your comments for the authors below**

**The authors have answered quite well not only to my comments, but also those of the other reviewers. In addition, they have incorporated much of them in the new version of the manuscript. I have no further comments.**

We thank the reviewer for taking the time to read the revised version.

**Reviewer: 2**

**Reviewer Name**

**Dr Leanne Chalmers**

**Institution and Country**

Curtin University, Australia

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

I have received consultancy funding from Aspen Pharmacare Australia, who were the Australian sponsors of warfarin at the time.

**Please leave your comments for the authors below**

**Thank you to the authors for the comprehensive review of their manuscript. I am satisfied that the issues from my previous review have been adequately addressed. My remaining suggestions are minor and largely editorial.**

We thank the reviewer for their time and careful assessment of the revised manuscript.

**1. While the term 'AF patients' has been replaced with 'patients with AF' in the majority of cases, the former term is still used in several places – Abstract line 10, Introduction (page 4, line 24), Methods (page 5, line 37), Discussion (page 13, line 3). Please revise for consistency.**  
We thank the reviewer for their careful review of our revised manuscript. "AF patient" has been replaced with "patients with AF" throughout the manuscript.

**2. Please also review the remaining references to 'six-month' and 'one-year' to remove hyphens, also for consistency.**

Revised.

**3. Please consider defining MMAS as 'Morisky Medication Adherence Scale' for the naïve reader.**

MMAS has been defined.

**4. Results, page 10, line 23: Please reword 'Pooled estimates of proportion of adherent patients for warfarin were resulted from meta-analysis of 2 studies only...' – maybe omit the 'were'?**

"were" has been removed.

**5. Discussion, page 13, line 5: Please consider rewording for clarity - e.g. 'In our study, the pooled proportions of adherent patients at six months and one year were 63% and 70%, respectively, which are higher than those found for other chronic cardiovascular medications such as statins (54%) and antihypertensives (59%).65'**

We appreciate the suggested edits. This sentence has been reworded as suggested by the reviewer.

**6. There remain some additional minor typographical errors:**

**- Please correct the spelling of "INTRODUCTION" in the Abstract.**

Corrected.

**- Please use a hyphen in the 95% CI for apixaban at one year in the Abstract, as per the other CIs.**

Comma has been replaced with hyphen for consistency.

**- Introduction, page 4, line 15: please correct to 'patients with AF'.**

Revised.

**- Methods, page 6, line 8: 'Secondary adherence measure included...'. Should this read, 'The secondary adherence measure was...'?**

The sentence has been revised.

**- Results, page 9, line 20: please change to 'The majority of...'. Similarly, page 10, line 11 should read: 'A wide range...'**

Revised.

**- Please be consistent with hyphenation of 'non-adherence' and 'non-adherent'.**

Hyphen added throughout.

**- Discussion, page 14, line 7: Please reword – e.g. 'Our findings in relation to clinical outcomes are...'**

Reworded.

**- The references look much better but there are some words/abbreviations in the journal article titles in the Reference list that should ideally be capitalised (e.g. SPAF, Framingham, ESC, United States). See also the journal title in reference 18.**

Revised.