Author’s response to reviews

Title: Risk Factors for Medication Non-Adherence among Atrial Fibrillation Patients

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Author’s response to reviews:

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Inmaculada Hernandez, Pharm.D., Ph.D.
Associate Editor, Non-Coronary Artery Cardiac Disease
BMC Cardiovascular Disorders

RE: Manuscript BCAR-D-18-00718 entitled “Risk Factors for Medication Non-Adherence among Atrial Fibrillation Patients”
Dear Dr. Hernandez,

On behalf of myself and my co-authors, I wish to sincerely thank the reviewers for their time and effort in evaluating our manuscript and providing constructive feedback. We have carefully considered each of the provided comments and revised our manuscript accordingly. An annotated list of each of the comments and our responses are provided below.

Thank you again for your consideration of our manuscript for publication in BMC Cardiovascular Disorders.

Sincerely,

Corresponding Author:
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RESPONSE TO REVIEWERS:

Editor Comments:

1. I agree with the reviewers comments and particularly worry about the lack of medication data. It would be important to make sure that all patients actually receive medications, as well as to which medications the questionnaire refers.
Response: Thank you for your comment. The questionnaire solicits information on non-specific medication adherence or, in our population, general medication adherence not specific to treatment for atrial fibrillation. We modified our manuscript text to reflect this point throughout, namely the introduction and discussion sections. As for the inclusion of medication data, given our large sample size (n=12,159) and the lack of medication questions within the questionnaire we were unable to account for specific medication usage from the patients within our cohort. However, even for those patients who may not have received medications specific to their atrial fibrillation (only 16% had a CHADS2 Score of 0), 79% of our sample had hypertension and at least 39% used aspirin. Therefore, the likelihood that someone in our sample was not taking at least one medication is unlikely.

Reviewer Reports:

Supriya Shore (Reviewer 1):

Major comments

2. Which medications are the authors assessing adherence to? Were these questions assessing adherence specifically to medications related to atrial fibrillation or were they generic questions enquiring about all medications prescribed? This is important to clarify since if these questions were not with regards to atrial fibrillation medications (Anticoagulants/anti-arrhythmics/rate control medications), could the authors please clarify how this manuscript differs from prior work related to predictors of medication adherence among patients with cardiovascular disease.

Response: Thank you for your question. As stated above, we are assessing general medication adherence in a population of patients with atrial fibrillation. We are not assessing adherence to one specific medication (e.g. adherence to anticoagulants). We believe that in examining a specific cardiovascular disease subpopulation, in this case atrial fibrillation, we may be able to shed light on a unique experience exclusive to this population. For example, according to the American Heart Association, more than 65% of people with atrial fibrillation do not recognize the seriousness of their illness and may be less adherent to their atrial fibrillation-specific medications compared to those in the general cardiovascular disease population. Additionally, patients with atrial fibrillation may not experience symptoms, leading to potentially lower adherence to their medication. Although these instances are specific to treatments for atrial
fibrillation, these behaviors may carry over into adherence to their other medication regimens. Thus, we were interested in understanding the adherence experience specifically in those with diagnosed atrial fibrillation. We have added this information to the introduction. Please see page 5, lines 49-55.

3. In their definition of non-adherence, cut offs based on answers to questions 1 to 3 are not consistent. Not taking medications once per week would still imply an adherence rate >85%.

Response: Thank you for your comment. Our three-question assessment of medication adherence and the respective scoring cut-off for defining non-adherence is based on a previously validated assessment adapted from the Coronary Artery Risk Development in Young Adults (CARDIA) study. As this assessment is not specific to a certain medication, and patients with atrial fibrillation may be on multiple medications, we cannot attribute a certain adherence rate to our scoring method (e.g., some medications are prescribed for daily use while others are prescribed for weekly or monthly use). Thus, this scoring method is best suited to measure general non-specific medication adherence and is the reason why we used it in our study.

4. Since the dataset used is within an integrated healthcare system, is it possible to calculate adherence based on prescription refill data? The reported non-adherence rates are extremely low suggesting lack of sensitivity in identifying non-adherent patients.

Response: This is a good suggestion and a great point. Unfortunately, given the large sample size (n=12,159) and the likelihood that each patient is taking multiple medications (both prescription and over the counter -- which would not have prescription refill data within our integrated healthcare system), we do not have the ability to calculate adherence for each patient and each medication. Additionally, we recognize that some patients may be misclassified due to the self-reported nature of our medication adherence assessment, however, we do believe that those individuals who we did capture are truly non-adherent and help to address our primary aim of identifying risk factors for non-adherence in an atrial fibrillation population.
5. How do the authors explain hypertension as a risk factor for better medication adherence?

Response: This is a great question. In 2000, Kaiser Permanente Northern California (KPNC) implemented a highly successful hypertension control program. From 2001 to 2013, hypertension control within KPNC increased from 44 percent to 90 percent. One aspect of this program encouraged single pill combination therapy — combining multiple drugs into one pill. This strategy improved adherence, lowered patient costs and improved blood pressure control. This program was also implemented in Kaiser Permanente Southern California (KPSC). Thus, many, if not all, patients included in our study were recipients of this program. We have added this information to our discussion section. Please see page 12, lines 215-223.

6. Patients with a CHADS2 score of 0 were more likely to be non-adherent. However, these patients are unlikely to be on anticoagulants for atrial fibrillation implying this refers to adherence to other medications related to coexisting medical comorbidities. This again would not be specific to patients with atrial fibrillation. Also, instead of CHADS2 score can the authors provide more commonly used CHADSVASc score?

Response: You are correct. Our assessment of medication adherence is general and broadly applies in a population of patients with atrial fibrillation. It is not specific to only those patients on anticoagulants. As for the CHADS2 score, we recognize that the newer CHA2DS2-VASc score is now the preferred assessment to evaluate risk for stroke. However, we do not have vascular disease data to allow us to calculate that measure. Thus, we reported the CHADS2 score which was the measure of choice at the time of the questionnaire distribution.

7. Can time from diagnosis of atrial fibrillation be included in the model? Most literature suggests that adherence rates decline with time.

Response: This is another great point. Unfortunately, we do not have access to that level of individual data in our current cohort database. We do know that patients had to be newly diagnosed with atrial fibrillation to enter into the cohort (could not have a prevalent diagnosis of atrial fibrillation in the four years prior to cohort entry) and the median length of time between
cohort entry and questionnaire completion was 2.65 years. However, since we do not have the time from atrial fibrillation diagnosis to questionnaire completion, we cannot include that variable in the model. We have noted this point in our discussion section limitations. Please see page 13, lines 233-237.

8. Do the authors have data on how many medications were prescribed per patient? Polypharmacy is another proposed risk factor for non-adherence and should be included in the model if possible.

Response: This is a great point. Unfortunately, we do not have data on how many medications were prescribed per patient and cannot include that data in the model. We have noted this point in our discussion section limitations. Please see page 13, lines 231-233.

Minor comments

9. In introduction, para 2 line 45 - the authors state "complexity of dosing may increase or decrease adherence." How does complex medication dosing increasing adherence?

Response: Thank you for pointing out this error. We have changed the text in the introduction to indicate that dosing regimen complexity has been found to decrease medication adherence in patients with atrial fibrillation. Please see page 5, lines 59-60.

Josh Niznik, PharmD (Reviewer 2):

Abstract
10. Please include a brief description of how medication non-adherence was defined, if possible.

Response: Thank you for your suggestion. We have included a sentence in the abstract to indicate how medication adherence was measured, as well as, a sentence that describes how medication non-adherence was defined. Please see page 3, lines 11-14.

11. In results, please include the reference categories were in the comparisons that you present to help with interpretation.

Response: Thank you for this suggestion. We have updated the abstract results with each of the appropriate reference categories. Please see pages 3-4, lines 19-25.

12. In conclusions section, I would avoid saying that "potentially modifiable" factors were associated with non-adherence as many of the factors presented are actually non-modifiable, or if they were, would not necessarily result in improved adherence.

Response: Thank you for your comment. We have included the term “potentially modifiable” as it relates to select risk factors. For example, physical inactivity and alcohol use are modifiable behaviors. Although most likely not directly related to medication non-adherence, they can contribute to poor physical and/or mental health along with sleep quality. These later three factors have all been shown to be related to medication non-adherence. To your point, however, we have included a line in the abstract to note that some of the identified risk factors are not modifiable (e.g., race/ethnicity). We have also added the word “preventable”, as that may be clearer for risk factors such as health literacy and/or type 2 diabetes mellitus. Please see page 4, lines 27-28.
Introduction

13. Page 4, line 37 - The authors reference a study reporting rates of anticoagulation discontinuation to justify the significance of non-adherence in this population. However, discontinuation and non-adherence are two distinct concepts. I would suggest the authors acknowledge this distinction and refer to non-adherence consistently throughout the introduction and discussion.

Response: Thank you for pointing out this distinction and error. We have removed the references and text that discuss discontinuation and persistence. We have included only the language and references that specifically discuss medication adherence. This can be seen throughout the manuscript, namely the introduction and discussion.

14. In the introduction, the authors spend significant effort trying to justify why medication adherence is so important in AFib, yet this analysis addresses medication adherence generally, rather than focusing specifically on adherence to medications used to treat AFib. This seems to be a disconnect and puts into question the significance of these findings in this population. This should be addressed in the discussion.

Response: This is a good point. We have modified the introduction to decrease the focus on atrial fibrillation specific medication adherence and broaden the focus to include overall medication adherence in a population of patients with atrial fibrillation. Please see pages 4-5, lines 42-55.

Methods

15. Study Population - Were patients required to be on treatment for AFib in order to be included in your sample? If not, why? This requires justification and discussion in the paper. In the results (Table 2), the distribution of CHADS2 scores falls below the threshold that usually warrants treatment for AFib, indicating there were probably a number of untreated patients in your sample. This again puts into question the significance of these findings since for some patients, medication adherence cannot be extrapolated to the medications used to treat AFib.
Response: Thank you for your comment. Patients were not required to be on treatment for atrial fibrillation. This was because our research question was to look at general medication adherence among patients who had been diagnosed with atrial fibrillation. We recognize that this means some atrial fibrillation patients may not be on atrial fibrillation specific medication, but we expect due to likelihood of comorbidities (see question 1 response) that every patient will be on at least one medication.

Results

16. Please explicitly state the relationship between age categories and adherence in the results section. In the discussion section, the authors state that age 65-84 was associated with a lower likelihood of non-adherence, but they fail to mention this in the results. Please be consistent.

Response: We apologize for the confusion. In the results section we stated that patients who self-reported non-adherence to prescribed medications were younger, but did not specify age categories. We have added “<65 years of age” to clarify our meaning of younger. We used the same method in the discussion section. Please see section page 9, line 151 and page 10, line 175.

17. Tables are nice, however, please make columns left justified for reading.

Response: Thank you for your suggestion. We have made all of the tables left justified, with a slight indent in the response options for clarity.

Discussion

18. Page 9-10, lines 162-180 - The authors discuss the low prevalence of non-adherence in their sample, compared to prior studies. Per my comment above, the authors need to address the fact that medication adherence in this study was not specific to anticoagulants or antiarrhythmic
medications. This is important to consider when interpreting the overall rate of non-adherence as well as the implications of the findings presented in this analysis. Essentially, this analysis presents factors associated with medication adherence in a population with AFib, rather than factors associated with non-adherence in the treatment of AFib. The discussion section needs to reflect this. Again, please be consistent with discontinuation vs. non-adherence. The studies referenced here are the same as what was referenced in the introduction and carry the same problem.

Response: Thank you for the suggestion. We have broadened the comparisons with our medication non-adherence estimate in the discussion section. We present literature non-adherence estimates, removing those previously reported from discontinuation and persistence studies, specific to atrial fibrillation medications, general cardiovascular disease medications and also more broadly from an elderly population with a range of comorbidities. We have also updated the citations accordingly. Please see page 10, lines 178-184.

19. Page 10, lines 171-175 "Nonetheless, using a brief self-reported measure of medication adherence, such as the 3-question instrument used in this investigation may be advantageous in a clinical setting…” - This statement should be removed. Justifying whether a medication adherence tool is advantageous in a clinical setting is irrelevant to whether or not its use was appropriate in this investigation or whether it impacted results.

Response: Thank you for the opportunity to clarify. We made note of the advantages of using this type of self-report assessment in a clinical setting (the setting for this study), as we wanted to point out why this method was most appropriate. Namely, that the ease and cost-effectiveness allow for a broader capture of information from a large patient population. We have rephrased this sentence to allow for that specification. Please see page 11, lines 191-194.

20. Page 10-11, lines 181-194 - These two paragraphs should be re-worked so that there is more discussion of the results and potential explanations for the findings of the analysis, rather than just listing them.
Response: Thank you for the suggestion. We have updated the discussion section to reflect a greater amount of results interpretation. Please see pages 11-12, lines 207-213 and 215-223.

21. Page 11, lines 200-203 - This statement regarding the time of data collection and new anticoagulants entering the market is somewhat irrelevant as assessments of adherence were not limited specifically to anticoagulants or antiarrhythmics.

Response: This is a good point. We have removed that sentence.

Conclusions

22. Page 12, lines 214-215 - The authors mention risk factors for non-adherence that may be potentially modifiable but fail to address in the discussion section. This should be included in the discussion and identify which are modifiable and which are not.

Response: Thank you for the suggestion. We have added this information into the discussion section. Please see page 11, lines 207-213.