PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	ECG risk markers for atrial fibrillation and sudden cardiac death in minimally symptomatic obstructive sleep apnoea: The MOSAIC randomized trial.
AUTHORS	Schlatzer, Christian; Bratton, Daniel; Craig, Sonya; Kohler, Malcolm; Stradling, John

VERSION 1 - REVIEW

REVIEWER	Younghoon Kwon University of Virginia, VA USA
REVIEW RETURNED	09-Nov-2015

GENERAL COMMENTS	This paper by Schlatzer et al. explores whether CPAP has impact on ECG measures that have been described as markers for arrhythmia. This is a sub-study of MOSAIC trial in which minimally symptomatic OSA patients were randomized to receive CPAP or standard care. Strength comes from the fact that there was a control group. However I find many issues with the study. Positive study may have made a case but it's hard to interpret negative results as in this study. I don't think we have good evidence of any relationship between OSA (presence or absence) or severity (regardless of symptomatology) and daytime awake 10 sec 12 lead ECG to begin with. As illustrated in this study, there was no such relationship at baseline. Therefore it's very hard to make a case what the effect of CPAP would be and if so, what to really make out of. Additionally authors need to be very careful in generalizing the validity of ECG markers being used in the study in terms of their clinical/ epidemiological utility. Some are very controversial. In the abstract, "Effective treatment of OSA with continuous positive airway pressure (CPAP) could prevent the development of AF and SCD."- This is an overstatement. May be acceptable to say AF recurrence but not AF development. Reference 3 and 4 did limit their studies to only symptomatic OSA. We know that majority of patients with OSA included in clinical studies are largely without excessive daytime sleepiness. "While there is good evidence for this relationship in patients with moderate to severe OSA, no data from randomized controlled trials (RCT) on this association is available in patients with minimally symptomatic OSA." - I am not sure if we have good evidence for the relationship particularly in moderate to severe OSA necessarily. In addition authors continue to use a term "minimally symptomatic OSA" in contrast to moderate to severe OSA. What is the definition of this? Those without excessive daytime sleepiness or daytime symptoms of OSA as they stated? What is daytime symptoms of OSA? If so based on what criteria? Do they refer to mild OSA without symptoms

	or any severity without symptoms? I know MOSAIC trial included minimally symptomatic OSA regardless of severity of OSA. It should be noted that respiratory polygraphy (vs. PSG) was used. Also ODI was used. ODI usually has good correlation with AHI but this certainly is not same as AHI and stratifying severity based on ODI is not a standard method. Was there AHI measures at all? Page 7, randomization section, it says 1:1 ratio incorporated minimization for OSA severity as assessed by ODI. Minimization? Not sure what this means in relation to randomization? On page 8, it denotes that the same investigator measured ECG indices. Was it manually using software caliper program? There can be quite interobsever variability. This is a major limitation. It's not clear how TpTe is measured. From which leads? Mean? Or max or min? In addition in measuring TpTe/QT ratio, what was used? QT max or QT min or QT average? Or certain lead? In data analysis section, 1st paragraph, Pmean, QT mean, QTc mean etc are mentioned but not clear how they were derived. Average of 12 lead measurements? PR is more commonly used term than PQ interval. On page 10 Results> Trial profile and Patient Characteristics section, "there was no evidence of any significant changes in treatment effects of CPAP on ODI…..". I think it should be significant difference rather than changes? Figure 1. Study flow shows that only 60 were excluded not meeting inclusion criteria. Does this mean only minority of the patients were symptomatic Results / Baseline analysis shows that there was no correlation between ODI and ECG markers at baseline. If this is the case, wouldn't it be unreasonable to expect change in ECG markers with CPAP therapy, which lessens severity of OSA? Discussion 1st paragraph, this should not be claimed as a RCT. It should be claimed as a substudy of RCT. It misleads readers as if this was what the original RCT was intended to study. Does Ref 9 include moderate to severe OSA with symptoms only? Again we should not forget that moderate to severe OSA is not equal to symptomatic OSA. In fact majority of the patients who are moderate to severe OSA do not have symptoms. Discussion/ "The prevalence of AF among patients with OSA is reported to be as high as 32%[17] to 56%[18]". This is not true or may be typo by authors. Perhaps wanted to say prevalence of OSA among patients with AF is reported…. "The 95% confidence interval for the treatment effect of CPAP on P-wave dispersion exclude a reduction greater than 3.4ms. Therefore based on our results, there seems to be no need for CPAP treatment in minimally symptomatic OSA patients from a cardiac electrophysiologist's view". This needs better explanation in terms of clinical significance in P wave dispersion reduction magnitude. Plus no EP physicians is going to determine treatment of OSA based simply on P wave index. "Thus CPAP appears to have no electrical and structural impact on the atria in minimally symptomatic OSA patients." – again minimally symptomatic OSA constitutes majority of people with OSA in community. I am not sure if we have solid evidence of opposite results in "highly symptomatic OSA patients" either. If so, please provide references that targeted this group only.

	Effect of CPAP on ECG risk markers for SCD/ 1st sentence, there is a typo “therefrom”? Authors in referencing study 9 states that “this might be due to the fact that more severe OSA patients were included”. Where is the evidence that more severe OSA patients would have higher baseline QTc and TpTec intervals? Please provide references for this.

REVIEWER	Waqas Qureshi Wake Forest University, Winston Salem, NC
REVIEW RETURNED	28-Nov-2015

GENERAL COMMENTS	Schlatzer et al reported ancillary findings of MOSAIC (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular) trial that randomized 303 minimally symptomatic OSA patients to receive either CPAP or standard care for six months. They observed that CPAP had no effect on ECG markers of atrial fibrillation or sudden cardiac death in 250 participants that had ECG data available. While it is commendable to perform such a study, there are a few comments that might add to your potential publication as follows: Major comments: I do not see medication related data. Please provide the medications that the patients were on. Were they on antiarrhythmics? Beta blocker? Etc. I see 45% were on antihypertensives in standard group. The number of hours for CPAP use is 2.7 hours which is quite short. Can you explain why is it so short? How many of the participants in the CPAP group did not use CPAP at all? Please mention if these outcomes were included in the design of study or this is a post hoc analysis. Did you also look at P axis? If possible, please add p axis analysis as well. Please see Rangel at al. Am J Cardiol. 2015 Oct 17 Was the study powered to detect the differences? Please write the sample size justification and please provide the power to detect these differences. Minor Comments: ABSTRACT: There are not much results discussed in the results section of the abstract. You can mention prevalence of some markers. Introduction: No need to discuss about LQTS as this is not a study pertaining to them. Results: The trial talks about minimal symptomatic sleep apnea patients however their symptoms are not presented. Only ODI is presented. Please provide more characteristics of the patients in regards to their symptoms and sleep study values. Apart from ODI, please provide apnea – hypopnea index, sleep quality data, if available. I see that there are afib patients in the cohort. Were these paroxysmal afib patients? If not, please mention. Discussion: Please cite Qureshi et al meta analysis of afib …. Am J Cardiol. 2015 Dec 1;116(11):1767-73. and explain more about the rationale of this trial in the discussion. Why was it important? Please explain if only 1 ECG was performed. The trial could have been strengthened by having holter to detect arrhythmia however this is not really related to the question asked in the study. Is there any data that you can discuss regarding the sensitivity and specificity of these measures for AF and SCD that you chose?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Statement 1 of reviewer #1:
Positive study may have made a case but it's hard to interpret negative results as in this study. I don't think we have good evidence of any relationship between OSA (presence or absence) or severity (regardless of symptomatology) and daytime awake 10 sec 12 lead ECG to begin with. As illustrated in this study, there was no such relationship at baseline. Therefore it's very hard to make a case what the effect of CPAP would be and if so, what to really make out of.

Response 1 to reviewer #1:
We agree that given the mean baseline values were normal, it is less likely that we could have produced a significant improvement. However, even within the normal range one might have seen a shift to shorter values following CPAP. AHI and ODI are relatively crude indices of OSA severity and not necessarily the best measure of factors that might have increased the ECG derivatives we looked at. Thus failure to find correlations between the ECG derivatives and ODI would not necessarily have precluded an effect of CPAP.

Statement 2 of reviewer #1:
In the abstract, "Effective treatment of OSA with continuous positive airway pressure (CPAP) could prevent the development of AF and SCD."- This is an overstatement. May be acceptable to say AF recurrence but not AF development.

Response 2 to reviewer #1:
We agree with the reviewer and changed the statement accordingly in the Objective section of the abstract as well as in the Introduction section of the manuscript.

Statement 3 of reviewer #1:
Reference 3 and 4 did limit their studies to only symptomatic OSA. We know that majority of patients with OSA included in clinical studies are largely without excessive daytime sleepiness.
"While there is good evidence for this relationship in patients with moderate to severe OSA, no data from randomized controlled trials (RCT) on this association is available in patients with minimally symptomatic OSA." -
I am not sure if we have good evidence for the relationship particularly in moderate to severe OSA necessarily. In addition authors continue to use a term "minimally symptomatic OSA" in contrast to moderate to severe OSA. What is the definition of this? Those without excessive daytime sleepiness or daytime symptoms of OSA as they stated? What is daytime symptoms of OSA? If so based on what criteria? Do they refer to mild OSA without symptoms or any severity without symptoms? I know MOSAIC trial included minimally symptomatic OSA regardless of severity of OSA.

Response 3 to reviewer #1:
We agree with the reviewer on the poor correlation between symptoms and severity of OSA. This may be due to inter-individual variation in the degree of brain arousal from apnoeas, the effect these arousals have on daytime function and an individual's lifestyle. The idea of the MOSAIC trial was to include OSA patients that had insufficient daytime symptoms (sleepiness, occupational problems due to disrupted sleep and/or sleepiness, road traffic accidents in the past due to daytime sleepiness, problems due to excessive snoring) associated with OSA to warrant CPAP therapy, regardless of OSA severity as assessed by ODI. There is little evidence on CPAP treatment effects on symptomatic benefit or a reduction in blood pressure or reduction of other cardiovascular risk factors and markers in this group of patients, as pointed out by The UK National Institute for Health and Clinical Excellence (NICE).
Our patients in the current study had a median ODI of 9.1 in the Standard care group and 9.9 in the CPAP group, as opposed by mean ODI values of 25.4 and 28.9 in the two groups in the trial by Rossi et al., with which results were compared. That is why we think a demarcation between the two studies is possible. It would be, however, not accurate to describe our patients as minimally symptomatic with mild-to-moderate OSA severity, as there were few patients with an ODI of 30 or greater.

Statement 4 of reviewer #1:
It should be noted that respiratory polygraphy (vs. PSG) was used

Response 4 to reviewer #1:
We mentioned this in the Methods section under subheading 'Sleep study' on page 6 of our manuscript.

Statement 5 of reviewer #1:
Also ODI was used. ODI usually has good correlation with AHI but this certainly is not same as AHI and stratifying severity based on ODI is not a standard method. Was there AHI measures at all?

Response 5 to reviewer #1:
We chose to use the ODI values that had been derived from an ambulatory pulse-oximetry recording that we used across all the centres, to ensure comparable assessments of OSA severity, as this will have increased the consistency across the three centres. AHI was not used to assess OSA severity in our trial.

Statement 6 of reviewer #1:
Page 7, randomization section, it says 1:1 ratio incorporated minimization for OSA severity as assessed by ODI. Minimization? Not sure what this means in relation to randomization?

Response 6 to reviewer #1:
Minimisation is a standard technique in RCTs to ensure that critical baseline characteristics are balanced between groups, and not importantly different by chance. A computer program slightly weights to which group to allocate a patient to ensure this.

Statement 7 (major limitation) of reviewer #1
On page 8, it denotes that the same investigator measured ECG indices. Was it manually using software caliper program? There can be quite interobsever variability. This is a major limitation.

Response 7 to reviewer #1:
Analysis of ECG intervals was done manually using software caliper program (DatInf Measure). http://datinf.eu/products/measure/index.shtml. We now highlight this in the Methods section under subheading Electrocardiography on page 8 of our manuscript.
Within the limitation section at the end of the discussion section on page 18 of our manuscript, we describe this limitation, which is usually associated with ECG measurements. However, as one investigator (CS) analysed all ECGs, inter-observer variability can be excluded. The outcome assessor was not aware of treatment allocation of individual patients, so intra-observer bias will not have affected the results of our study.

Statement 8 of reviewer #1:
It's not clear how TpTe is measured. From which leads? Mean? Or max or min? In addition in measuring TpTe/QT ratio, what was used? QT max or QT min or QT average? Or certain lead?
In data analysis section, 1st paragraph, Pmean, QT mean, QTc mean etc are mentioned but not clear how they were derived. Average of 12 lead measurements? PR is more commonly used term than PQ interval.

Response 8 to reviewer #1:
Please refer to the Methods section under subheading Electrocardiography on pages 7-8 of our manuscript. To maximize accuracy of ECG measures, all available consecutive heart cycles were used and in all 12 standard leads. For example; an individual TpTe interval was calculated as the mean value of all 12 leads, each consisting of the mean of all available heart cycles within one lead. Same for all other measures. For TpTe/QT ratio, mean TpTe was divided by mean QT (again derived

from all 12 leads). We now describe this clearer in the Methods section under subheading Electrocardiography on page 8 of our manuscript. Concerning PQ or PR intervals, we used the term PQ interval to describe atrioventricular conduction time, as is some leads and in some patients, Q waves are present.

Statement 9 of reviewer #1:
On page 10 Results> Trial profile and Patient Characteristics section, “there was no evidence of any significant changes in treatment effects of CPAP on ODI…..”. I think it should be significant difference rather than changes?

Response 9 to reviewer #1:
We thank the reviewer for pointing this error out to us. We have changed this accordingly as suggested by the reviewer in the Results section on page 10 of our manuscript.

Statement 10 of reviewer #1:
Figure 1. Study flow shows that only 60 were excluded not meeting inclusion criteria. Does this mean only minority of the patients were symptomatic.

Response 10 to reviewer #1:
We offered a detailed discussion between physician and patient about the evidence for possible benefits of CPAP versus the potentially lifelong nightly usage of a physical therapy. After discussion many patients preferred to start on CPAP therapy rather than taking part in a 6 month randomized trial, where Standard care was possible. So these patients are included under ‘Declined to participate (n=159)’.

Statement 11 of reviewer #1:
Results / Baseline analysis shows that there was no correlation between ODI and ECG markers at baseline. If this is the case, wouldn’t it be unreasonable to expect change in ECG markers with CPAP therapy, which lessens severity of OSA?

Response 11 to reviewer #1:
This is a good argument. However, whether or not CPAP would improve ECG risk markers for AF and SCD, was not previously investigated with randomized controlled data in this group of patients. This point is also discussed above, under statement 1.

Statement 12 of reviewer #1:
Discussion 1st paragraph, this should not be claimed as a RCT. It should be claimed as a substudy of RCT. It misleads readers as if this was what the original RCT was intended to study.

Response 12 to reviewer #1:
We now highlight this in the Discussion section on page 16 (lines 1 and 4) of our manuscript.

Statement 13 of reviewer #1:
Does Ref 9 include moderate to severe OSA with symptoms only? Again we should not forget that moderate to severe OSA is not equal to symptomatic OSA. In fact majority of the patients who are moderate to severe OSA do not have symptoms.

Response 13 to reviewer #1:
Ref 9 included moderate-to-severe OSA patients, if they were on CPAP for at least 12 month and if CPAP compliance was ≥ 4 h per night during the last 12 month (prior to taking part in the trial). This is in contrast to the patients of the current study, where CPAP compliance, despite taking part in a study, was much lower (median usage was 2.7 hours per night). Patients from Ref 9 would in all probability not be willing to wear their CPAP devices as regularly, if there were no OSA symptoms when CPAP was stopped.

Statement 14 of reviewer #1:
Discussion/
"The prevalence of AF among patients with OSA is reported to be as high as 32%[17] to 56%[18]". This is not true or may be typo by authors. Perhaps wanted to say prevalence of OSA among patients with AF is reported…

Response 14 to reviewer #1:
We would like to thank the reviewer for pointing this out to us. In fact, this was a typo and we now changed this accordingly in the Discussion section on page 16 of our manuscript.

Statement 15 of reviewer #1:
"The 95% confidence interval for the treatment effect of CPAP on P-wave dispersion exclude a reduction greater than 3.4ms. Therefore based on our results, there seems to be no need for CPAP treatment in minimally symptomatic OSA patients from a cardiac electrophysiologist's view". This needs better explanation in terms of clinical significance in P wave dispersion reduction magnitude. Plus no EP physicians is going to determine treatment of OSA based simply on P wave index.

Response 15 to reviewer #1:
We have attenuated this argument and now write that: 'Therefore our results do not support CPAP treatment in minimally symptomatic OSA patients in terms of risk reduction for progression and/or recurrence of AF'.

Statement 16 of reviewer #1:
"Thus CPAP appears to have no electrical and structural impact on the atria in minimally symptomatic OSA patients." – again minimally symptomatic OSA constitutes majority of people with OSA in community. I am not sure if we have solid evidence of opposite results in "highly symptomatic OSA patients" either. If so, please provide references that targeted this group only.

Response 16 to reviewer #1:
One could compare our results with Bayir et al. Ann Noninvasive Electrocardiol 2014;19(3):226–233, and Müller et al. in press Heart,Lung and Circulation(2015), http://dx.doi.org/10.1016/j.hlc.2015.05.004. In these two studies, CPAP led to significant electrical and mechanical left atrial remodelling and both studies included patients with high AHI values (mean 48 / 42) and higher ESS values (10.2) when compared with our participants (8.4). While there is certainly not a very close linear relationship between AHI and ODI, one can see that those studies included more severe OSA patients when compared with our study. Moreover, we preferred to solely describe that CPAP appears to have no electrical and structural impact on the atria in minimally symptomatic OSA patients, rather than comparing this with other studies or populations.

Statement 17 of reviewer #1:
Effect of CPAP on ECG risk markers for SCD/ 1st sentence, there is a typo "therefrom"?

Response 17 to reviewer #1:
We substituted 'therefrom' with 'hence' for a better understanding.

Statement 18 of reviewer #1:
Authors in referencing study 9 states that "this might be due to the fact that more severe OSA patients were included". Where is the evidence that more severe OSA patients would have higher baseline QTc and TpTec intervals? Please provide references for this.

Response 18 to reviewer #1:
In the cited CPAP withdrawal trial by Rossi et al., the increase in the length of the QTc and TpTec intervals was positively correlated with the change in the severity of sleep disordered breathing (AHI) ($r=0.60$, 95% CI 0.36–.77, $P< 0.001$ for QTc and $r=0.45$, 95% CI 0.17–0.67, $P=0.003$ for TpTe). We

now highlight this in the Discussion section on page 18 of our manuscript.

Reviewer 2:

Statement 1 (major comment) of reviewer #2:
I do not see medication related data. Please provide the medications that the patients were on. Were they on antiarrhythmics? Beta blocker? Etc. I see 45% were on antihypertensives in standard group.

Response 1 to reviewer #2:
Medication related data (Antihypertensive medication, Cholesterol-lowering medication, Glucose-lowering medication and Diuretics) are shown in table 1. Unfortunately, there is no data available on the use of antiarrhythmics or a breakdown of antihypertensive medication to include beta-blockers.

Statement 2 (major comment) of reviewer #2:
The number of hours for CPAP use is 2.7 hours which is quite short. Can you explain why is it so short? How many of the participants in the CPAP group did not use CPAP at all?

Response 2 to reviewer #2:
Many thanks for mentioning this interesting aspect. We think that minimally symptomatic OSA patients often do not feel an obvious benefit from CPAP therapy, while discomfort using the device can be apparent. When compared with other trials, for example with the trial by Rossi et al., one can see a large difference in CPAP compliance (mean compliance in the latter trial was greater than 6 hours per night on average). We think that this gives a good impression on differences in daytime symptoms of OSA between the two trials, as patients with excessive daytime sleepiness will be likely to tolerate CPAP treatment better due to their sense of symptom improvement.
36 patients (28%) in the CPAP group did not use their CPAP device at all. We now added this valuable information in the Results section on page 10 of our manuscript.

Statement 3 (major comment) of reviewer #2:
Please mention if these outcomes were included in the design of study or this is a post hoc analysis.

Response 3 to reviewer #2:
We now state in the Limitations section on page 18 of our manuscript that: ‘This study has some limitations. First, the presented analysis was not the primary objective of the MOSAIC trial, thus our interpretations must be regarded as hypothesis generating rather than fully robust’.

Statement 4 (major comment) of reviewer #2:
Did you also look at P axis? If possible, please add p axis analysis as well. Please see Rangel at al. Am J Cardiol. 2015 Oct 17

Response 4 to reviewer #2:
We have now done an analysis of p axis. According to the paper from Rangel et al., as suggested, 92% of our patients had normal p axis at baseline and 92% had normal p axis at follow up. We do not think that a more detailed analysis will add important information.

Statement 5 (major comment) of reviewer #2:
Was the study powered to detect the differences? Please write the sample size justification and please provide the power to detect these differences.

Response 5 to reviewer #2:
As mentioned in the Limitations section on page 18, the presented analysis was not the primary objective of the MOSAIC trial, thus our interpretations must be regarded as hypothesis generating rather than fully robust. Thus no sample size calculation for endpoints in the current study is available.

Of course the 95% CIs actually replace power calculations, because they are based on the real data, rather than assumptions about the likely trial effect.

The sample size calculation from Craig et al. 2012 Thorax 2012;67:1090–1096 was thus based on the primary outcome measure and repeated here.
A sample size calculation to ensure we did not miss a difference of one point on the ESS scale with 90% power indicated 220 patients should be randomised; this was based on a similar but smaller study of relatively asymptomatic patients with OSA treated with CPAP (Lovett JK et al. 2003). However, it was not possible to calculate a sample size for the risk score because of the absence of any appropriate data. Therefore, because BP and cholesterol were judged to be the dominant components likely to change in the risk score, these were used. Data from our previous studies in more severe patients (Robinson GV et al. 2004, Lavie L et al. 2003) indicated that approximately 360 patients should be randomised to ensure that we did not miss a 3mmHg change in BP, or a 0.3mmol/l change in cholesterol, with 80% power. We assumed 10% of patients would fail to attend their six month visit and thus the trial was designed to recruit a total of 400 patients.

Statement 6 of reviewer #2:
ABSTRACT: There are not much results discussed in the results section of the abstract. You can mention prevalence of some markers.

Response 6 to reviewer #2:
We have now added mean (SD) baseline ECG intervals in the Results section of the abstract.

Statement 7 of reviewer #2:
Introduction: No need to discuss about LQTS as this is not a study pertaining to them.

Response 7 to reviewer #2:
We have removed the statement about LQTS.

Statement 8 of reviewer #2:
Results:
The trial talks about minimal symptomatic sleep apnea patients however their symptoms are not presented. Only ODI is presented. Please provide more characteristics of the patients in regards to their symptoms and sleep study values.
Apart from ODI, please provide apnea – hypopnea index, sleep quality data, if available.

Response 8 to reviewer #2:
We have now added baseline results of the OSLER-test (Oxford Sleep Resistance test; a test which evaluates the ability to stay awake for 40 min in a quiet, darkened room.) in table 1. We also added information on this test within the Methods section on page 7 of our manuscript. The MOSAIC trial did not contain an assessment of AHI or additional measures of OSA severity or symptoms, other than those reported by the patients.

Statement 9 of reviewer #2:
I see that there are afib patients in the cohort. Were these paroxysmal afib patients? If not, please mention.

Response 9 to reviewer #2:
Paroxysmal atrial fibrillation or other cardiovascular disease was not an exclusion criterion. However, all patients with episodes of PAF at ECG baseline assessment were excluded from further analyses. Please refer to figure 1 and to the Results section on page 10 of our manuscript for detailed information. On page 10, we now have added the information that cardiovascular disease was not an exclusion criterion.

Statement 10 of reviewer #2:
Discussion: Please cite Qureshi et al meta analysis of afib …. Am J Cardiol. 2015 Dec 1;116(11):1767-73. and explain more about the rationale of this trial in the discussion. Why was it important?

Response 10 to reviewer #2:
We now discuss the suggested meta-analysis in the Discussion section on page 16 of our manuscript.

Statement 11 of reviewer #2:
Please explain if only 1 ECG was performed. The trial could have been strengthened by having holter to detect arrhythmia however this is not really related to the question asked in the study.

Response 11 to reviewer #2:
We agree with the reviewer that Holter ECG recordings would have been beneficial for a more detailed analysis of arrhythmias; however, we feel that Standard 12 lead ECG recordings are sufficient for analysis of our endpoints of interest.

Statement 12 of reviewer #2:
Is there any data that you can discuss regarding the sensitivity and specificity of these measures for AF and SCD that you chose?

Response 12 to reviewer #2:
We have added information on the impact of some ECG measures on the development of AF and SCD in the Discussion section on pages 16 and 17 of our manuscript.

VERSION 2 – REVIEW

REVIEWER	Younghoon Kwon University of Virginia
REVIEW RETURNED	21-Dec-2015

GENERAL COMMENTS	I think the authors should clarify terminology better. Even though OSA severity may not be the point of this study, the paper uses a term "Minimally symptomatic OSA" and then contrasts this with "moderate to severe OSA". Actually included subjects seem to be generally mild OSA if we are to base this on ODI. Then average reader will bring up a question as to what about minimally symptomatic moderate or severe OSA? what about symptomatic mild OSA? what about symptomatic moderate to severe OSA? There are all sorts of categories that needs to be addressed. Please see the attached "reviewer's response"

REVIEWER	Waqas Qureshi Wake Forest University
REVIEW RETURNED	15-Dec-2015

GENERAL COMMENTS	Thank you for answering to all the comments. No more comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Statement 1 of reviewer #1:
I think the authors should clarify terminology better. Even though OSA severity may not be the point of this study, the paper uses a term "Minimally symptomatic OSA" and then contrasts this with "moderate to severe OSA". Actually included subjects seem to be generally mild OSA if we are to base this on ODI.
Then average reader will bring up a question as to what about minimally symptomatic moderate or severe OSA? what about symptomatic mild OSA? what about symptomatic moderate to severe OSA? There are all sorts of categories that needs to be addressed. Please see the attached "reviewer's response"

Response 1 to reviewer #1:
We have clarified the terminology and describe the populations in the relevant studies, with which our results are compared, as symptomatic where applicable, in contrast to 'minimally symptomatic' as in our study.
The mean ODI in our subset of patients was low (9.1 in the Standard care group and 9.9 in the CPAP group), hence most patients had mild OSA. There were, however, 26 patients with an ODI of 30 or greater, and this is why we still feel that we should not describe our subset of patients as only having mild OSA.

VERSION 3 - REVIEW

REVIEWER	Younghoon Kwon University of Virginia
REVIEW RETURNED	24-Jan-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Waqas Qureshi Wake Forest university
REVIEW RETURNED	13-Jan-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.