Author's response to reviews

**Title:** Screening for atrial fibrillation with intermittent ECG recording in an out-of-hospital population

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**Author's response to reviews:** see over
To:
Executive editor
Christopher Foote

Thank you very much for giving the opportunity to address the reviewers’ comments in a revised manuscript. The following cover letter will give a point-to-point response to the concerns.

Reviewer 1

Major comments:

1) The major limitation I observed with this study is the very high incident rate of AF. The authors attempted to exclude patients with baseline AF, which I believe is critical for this type of study. However, 10 of the 37 patients were found to have AF on Day 1, which suggests that they would have been identified on baseline ECG screening, which was not done for this study. Although the authors acknowledge this in the discussion, they still included these patients in their total count. These subjects should have been excluded.

In this study we describe the detection rate of any previously unknown AF, both paroxysmal and persistent. We excluded patients with a previous history of AF but not baseline AF. This is the reason we describe both the patients discovered on day 1 and the patients discovered later on during the study. As the patients discovered on day 1 would also have been found with other methods such as 12-lead ECG or pulse check, these are discussed separately in the Discussion under limitations, first paragraph, page 11. A prevalence of about 1% on day 1 is confirmed in other studies using 12-lead ECG/pulse check. (Ref. 21, 22, 23).

2) Another major limitation is the lack of assessment of accuracy of this device. There is comment that the sensitivity and specificity of AF detection are 96% and 92% respectively, however, no direct reference is made (only a reference for technical description). The major concern is that accuracy of spot-checking will have a higher false-positive rate. Many patients have short (< 30 second) runs of atrial tachycardia which can easily be mislabeled as an episode of AF on this type of recording. The high rates of “new AF” makes me suspect some of these will indeed be false positives. Ideally, this study should have been performed along with a more continuous monitoring device to help assess the accuracy of the outcomes…however, given the study is complete and continuous recordings are not available, the authors should address further this major limitation in the discussion.

The reference for sensitivity and specificity is the same as for the technical description; Doliwa, 2009, (ref. 25): ‘Atrial fibrillation was diagnosed in 49 patients with short-term ECG which corresponded correctly to 47 diagnoses made with 12-lead ECG. The ability to correctly diagnose atrial fibrillation (sensitivity) was thus correct in 96%. Short-term ECG recordings showed sinus rhythm in 51 patients,
which correctly corresponded in 47 12-lead ECG registrations, hence showing a specificity of 92%. Of the 100 collected ECGs six were misdiagnosed. In four patients atrial flutter was misdiagnosed as sinus rhythm and in two instances sinus rhythm was misdiagnosed as atrial fibrillation.’ The direct reference has been added to the manuscript.

We do agree with Reviewer 1 that, ideally, this study should have been performed along with a more continuous monitoring device to help assess the accuracy of the outcomes. Unfortunately this was not done. Although there certainly is a risk of overestimating AF, we do not think there has been a large overestimation, as we have sincerely tried to exclude all uncertain cases. As mentioned in the text, 24 patients with short repetitive runs of irregular supraventricular extrasystoles performed an additional 24 hour Holter ECG, confirming AF in seven cases. Patients had AF on average in more than 30% of their registrations. Only two patients had a single registration with AF. Before providing lifelong anticoagulation to such patients their diagnosis should certainly be confirmed by further ECG registration. This concern is addressed in the Discussion under limitations, last paragraph, page 12.

Minor comments:

1) Were the patients who subsequently had their charts/ECGs reviewed and found to have had histories of AF prior to enrollment excluded? These patients should also be excluded.

   These patients were excluded. After your comment we made an additional check of all patients in whom AF was detected. All clinics in this study use electronic patient charts recording all previous contacts, diagnoses and ECG’s. We discovered that one more patient had an unreported AF episode before entering the study and additionally excluded him. Therefore only 928 patients completed their registration instead of 929. This is changed in the manuscript, tables and flowchart.

2) Since the focus is on the device itself, the authors should address the potential advantages/disadvantages and performance of this type of device compared to other existing technologies, such as patch-based continuous monitoring (Zio) etc.

   In this study we have focused on the method of a combination of regular and symptomatic recordings during a longer time period. Any other device using the same method would do. This study started in 2007, but the Zio patch was not available before 2009. The possibility of patch-based continuous monitoring is certainly a breakthrough which will result in better compliance and even higher detection rates of AF. An advantage of the device and method we used compared to the Zio patch is the possibility of monitoring more than 14 days. This has been added to Discussion, page 10, first paragraph with a new reference, (ref. 27).

3) The term “prevalence” is misused throughout the manuscript, including Table 1 and in the discussion. Prevalent AF is the frequency of AF in a cross-sectional sample. In this study, those with “prevalent” AF should have been excluded. The AF that was subsequently detected is “incident” AF.
Because of divided opinions on the subject we have decided to replace prevalence with detection rate in the whole manuscript.

4) It is not correct to “average” CHADS2 score and report and compare the means. CHADS2 is a categorical variable, not a continuous variable. The difference between CHADS2 of 2 vs 3 is not the same as 3 vs. 4. Therefore, CHADS2 should be split into categories and compared using chi sq. The top of table 1 appeared to do this correctly, but then mean CHADS2 were compared incorrectly at the bottom of table 1 and results reported in the text.

Mean CHADS2 has been removed, instead we use CHADS2 categories (using Chi sq for comparison) and for additional information median plus range. This is changed in the text and table 1.

5) May be helpful to also report CHADS-VASC scores if the data is available.

Unfortunately when we started with the first patients 2007 CHADS-VASC was not in regular use (at least in Sweden). We do not have complete CHADS-VASC scores for this study.

6) Table 2 reports “persisting” AF. This should be “persistent” AF and should be defined. I assume these are the patients that went into AF after enrollment and stayed in AF for > 7 days, but this should be clearly defined. If there are patients who were in AF at Day 1, and remained in AF throughout the study, these were likely permanent AF patients, and should have been excluded.

Persisting has been changed in persistent in the manuscript. A definition of paroxysmal and persistent AF is added to the manuscript in the Methods section under Outcome measures (page 5). We defined persistent AF as an AF episode that either lasts longer than 7 days (but less than a year) or requires termination by cardioversion, either with drugs or by direct current cardioversion according to European Guidelines, (ref. 9). These patients were not followed long enough to call them permanent. As mentioned under major comment 1, we did not want to exclude baseline patients. We excluded only previously known AF. All six persistent AF patients were found on day 1. Three paroxysmal AF patients were also found on day one. Follow-up of their charts and ECG’s showed they did not have persistent AF (yet).

7) Bottom of table 2 reports Mean, SD and Range, but SD and Range don’t make sense for the categorical values. Perhaps the authors meant to report standard errors of the mean? Or n(%).

The bottom of table two shows continuous values, such as percentage 0-100%, days and beats/second.

As the total number of registrations for each AF patient varied greatly, (most patients with AF on day 1 for example discontinued registration), we decided to show data on AF registration, AF time point (morning or evening) and AF symptom correlation as an average of each patient’s percentage (and not number) of such registrations. The average number of such registrations would not give a proper idea as patients with a lot of registrations would have a far larger impact than patients with few registrations.
Especially as there are only 28 patients with their AF diagnosed with the intermittent method only.

8) Picking up 5 patients with conduction system disease who subsequently needed PPM is quite significant and this information should be expanded. This seems like a very high rate for otherwise asymptomatic patients.

This is certainly a large number of patients with conduction system disease in need of a pacemaker. All five patients were symptomatic, though. This finding is expanded under Discussion as a separate entry Detection of patients with conduction system disease (page 11). Other ‘incidental findings’ of this study were two patients with gastrointestinal bleeding, having sinus tachycardia on each recorded ECG. This is not mentioned in the manuscript.

9) In the range for time to first AF in Table 2, there is a range of 1-38. The authors noted that the study was for 28 days. Were events after 28 days excluded? If not, authors should state this more clearly.

Some patients continued to make registrations at home after 28 days. One patient even continued for forty days and we saw AF on day 38. After your comment and discussion in our research group we decided not to count this as an AF patient discovered within the study framework. This, together with Minor comment 1 results in only 35 (3.8%) instead of 37 (4.0%) previously unknown AF patients found within 28 days. This is changed in the manuscript.

Quality of written English: The revised manuscript has been edited before resubmission.

Reviewer 2

1) You are to be commended on producing an important study on AF screening using an inexpensive technology. The manuscript is clear and well written with a good descriptive analysis of the device and patient population. I believe you have adequately surveyed the prior relevant literature and placed this screening device in its proper context.

No comments

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