Author’s response to reviews

Title: Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: A prospective cohort study

Authors:
Tove Fredriksson (tove.fredriksson@sll.se)
Katrin Kemp Gudmundsdottir (katrin.kemp-gudmundsdottir@sll.se)
Viveka Frykman (viveka.frykman-kull@sll.se)
Leif Friberg (leif@fribergresearch.com)
Faris Al-Khalili (faris-al-khalili@hlamottagningen.se)
Johan Engdahl (johan.engdahl@sll.se)
Emma Svennberg (emma.svennberg@sll.se)

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To the Editor-in-Chief Professor C.M. Fitzpatrick, Dr D. Solera and reviewers,

Thank you for your letter with reviewers’ comments and feedback on our manuscript entitled "Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: A prospective cohort study". Your kind comments were very helpful for revising and improving our paper. We have carefully considered each comment and when possible adjusted the paper accordingly. We have submitted all files with changes in two versions, one with changes marked in yellow and one final version. The response to reviewers’ comments are provided below.

On behalf of the authors, Sincerely yours,

Tove Fredriksson, M.D.
Karolinska-Institutet, Danderyds Hospital
Dept of Clinical Sciences
Stockholm, Sweden
Response to reviewers’ comments to author:

Sotirios Nedios (Reviewer 1):
This is a case-control study evaluating the association of micro-AF (sudden irregular bursts of ≥5 APCs with <30 sec. duration) with undiagnosed silent atrial fibrillation. Out of 3,763 participants of the STROKESTOP II trial in Sweden (75-76 years old, NT-proBNP ≥125 ng/L) with intermittent ECG screening (4x30 sec./d over two weeks) 221 had micro-AF, 196 were followed with continuous ECG monitoring and 26 were finally diagnosed with AF. The micro-AF patients were compared with a control group without micro-AF (n=250), were continuous monitoring detected 7 new AF cases. Thus the authors conclude that micro-AF is associated with higher AF risk (13% vs. 3%, p<0.001). Thus individuals with micro-AF may benefit from extended and early AF screening.

The authors are commended for their elaborate work and the data provided. The manuscript is well written. However, there are several issues that need to be addressed prior to considering publication in the BMC Journal for Cardiovascular Disorders.

Specific comments:
1. Methods/Results: The authors define "micro-AF" as sudden onset irregular bursts of ≥5 APCs with <30 sec. duration. Since most participants with micro-AF had an average of only 6 beats (IQR 5-8), this term should not be interpreted as reflecting a higher thromboembolic risk. The study reports a five-fold higher risk for AF related with "micro-AF", but it did not evaluate the increase in thromboembolic risk and the clinical implications for "micro-AF" warrant further studies. Please comment.

Thank you for this comment, which certainly describes a relevant clinical problem. An earlier register study of individuals with SVTs consisting of ≥ 20 SVEBs or ≥30 SVEBs/hour identified a stroke risk in this group comparable to the stroke risk in AF patients [1]. However, the risk of thromboembolism is beyond the scope of this particular study, which was powered for analysing if patients with micro-AF have an increased risk of AF. To evaluate the stroke risk a larger cohort would be needed. We have added this information to the limitations section. Certainly, this would be an interesting next step.

Page 12, paragraph 3: "Our study was not powered to detect associations between micro-AF and thromboembolic risk; further studies are needed to study the association.”

2. Methods/Results: Duration between two ECG screenings was zero for the control group. How (based on what criteria) were patients selected to undergo a continuous ECG monitoring?

Thanks for pointing this out. The selection process is now described in more detail in methods.

Page 6, paragraph 2: ”All participants with micro-AF and an unmatched control group free from AF were invited to undergo continuous ECG monitoring in parallel or within a short period of time after their intermittent ECG monitoring. Participants in the control group were recruited consecutively during the last months of the STROKESTOP II study.”

3. Methods/Results: Participants in the micro-AF group were taller, younger, had lower CHA2DS2-VASc scores and higher often diabetes mellitus than the control group. Additionally, individuals diagnosed with AF were taller compared to individuals free from AF and had longer duration of analyzed signal time during continuous event recording. The authors use logistic regression with 2 different multivariable models for the development of AF: one adjusting for height & analyzed
signal time and one for age, hypertension, heart failure & stroke. Why use two different models? What precluded the use of all variables in one model? Why was there no adjustment for CHADS-VASc score? Was micro-AF the only predictor or AF? Did any other predictors remain significant after adjustment in the model?

Thank you for highlighting this. We did two different multivariable models to control the robustness of micro-AF as a predictor for AF. According to your advice we now added a third multivariable model in Table 3, where all variables from model 1 and 2 are included. In the multivariable analysis we included age, hypertension, heart failure & stroke, all accounted for in CHADs-VASc score, if we would also add the score itself it would lead to double adjustments for the same variables. No variables except from micro-AF remained significant after multivariable adjustments.

4. Methods/Results: What is the predictive value of SVEBs when used as a continuous variable? What is the cut-off value that combines the best sensitivity and specificity? In other words, would changing the cut-off better predict AF (including control pts.)?

Due to co-variation with micro-AF we did not include SVEBs in our multivariable analysis for prediction of AF. SVEBs per 30 seconds ECG was not a linear variable and therefore we did not analyze the increase in risk per beat. When looking at the spread of SVEB burden we noticed that most participants had SVEB count ≤2 per 30 second ECG. We divided all participants into two groups, one with high SVEB count (≥2 per 30 second ECG) and one with low (≤2 per 30 second ECG). When excluding micro-AF from the multivariable analyses and instead including SVEBs, we got the result seen in supplemental figure a.

The association between high SVEB burden and AF did not remain significant in multivariable analysis. We decided to not include this figure in our manuscript as the study is not designed to evaluate the association between high burden of isolated SVEBs and AF, and we did not specifically include individuals high amount of SVEBs as intermittent ECG is not a standardized or validated method for estimation of SVEB burden.

We were also interested in analyzing the length of- and number of micro-AF episodes as a predictor for AF, but decided not to include those variables in the multivariate analysis due to interaction with “the presence of micro-AF variable”. When excluding presence of micro-AF from the multivariable analyses and instead including length of longest micro-AF episode and number of micro-AF episodes, we got the result seen in supplementary figure b.

We would probably have needed a larger cohort to detect any significant associations. We decided not to include this figure in the manuscript, as the aim of the study was to determine the association between presence of micro-AF during intermittent ECG and AF.

5. Methods/Results: What was the average duration of diagnosed AF?

Thank you for the question. The median AF burden reported by the software through out the two weeks screening period was 4 (0.7-15) hours. The average percent AF detected by the continuous event-recorder device is reported on page 8, paragraph 5: “For participants diagnosed with AF, the median AF burden reported by the software was 1% (0-4).”

We have not added more details regarding this into the paper as the exact AF burden is not known, due
to the fact that the continuous event-recorder does not store full disclosure ECGs of all episodes marked as AF.

How many patients were symptomatic?

This is a valid question. Only 15% (n=5/33) of the participants diagnosed with AF were symptomatic during their two-weeks registration, although none of them reported symptoms at the exact time of an AF event. We have added this information to the manuscript.

Page 6, paragraph 2: “All participants were asked to fill out a questionnaire with regards to AF-related symptoms during their two weeks ECG registration.”

Page 8, paragraph 5: “Of participants diagnosed with AF, 15% (n=5/33) reported typical AF symptoms during their two-weeks registration, although none of them reported symptoms at the exact time of the AF event.”

6. Figure 3: Report p values

Thank your for the suggestion, p values have been added as requested, see Figure 3.

7. Supplementary Table 1: Report per group

Arrhythmia findings in our participants are not reported in Supplementary Table 1. It contains information of our settings for the continuous event-recorder regarding storage of arrhythmia episodes. We have clarified this by changing the heading of Supplementary Table 1 to: “Settings for number of ECG findings stored by R-test 4”

Trygve Berge, M.D., Ph.D. (Reviewer 2): Thank you for the opportunity to read and review your manuscript, "Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: A prospective cohort study". The manuscript is well written, easy to read, and the language is generally good.

Thank you.

The Background section provides a precise and to-the-point introduction to the topic. The term "micro-AF" is easy to understand. However, it does not seem completely clear to the reader whether this term has been used previously, or whether the term is presented by the Authors now. Although it becomes reasonably clear later, in the Discussion section; "...our micro-AF definition" (page 10, line 48), you may consider pointing this out more clearly (but briefly) earlier in the manuscript.

Thank you for pointing this out, micro-AF is a new term and we have tried to make it clear earlier in the manuscript.

Page 4, paragraph 1: “The aim of our study is to determine if short episodes of AF-like activity, that we term micro-AF, are not only a risk factor for future AF, but are markers for already existing undetected AF.”

The Methods section is good and well written, and it is of great value that you have explained advantages and disadvantages of the R-test device.
Thank you.

The Results section is well written, with clearly presented results (including results tables). The only aspect of potential interest that I miss, is the prevalence of SVEBs and SVTs found on the R test readings. As currently presented, the R test is only used to identify "true" AF and AF burden (with the obvious limitations inherent in the R test). What about stored episodes of SVEBs and SVTs, which you according to Suppl Table 1 had preset the R test to store? Although many of these would have been missed, due to the limited 60-minute storage time, it could be of interest whether there was an observed difference in the prevalence of these findings between the micro-AF and control group.

As you point out the limited storage time precluded correct analysis of SVEB count and SVTs in our participants. Hence, we decided to not interpret SVEB count and SVTs seen during continuous event recordings. It is well known that most elderly individuals have some supraventricular activity during a two weeks period and the device does not store all or full disclosure ECG, making it difficult to compare the supraventricular burden between the participants. One study using 24-hour electrocardiographic monitoring has shown that 58% of participants ≥ 70 years had SVEBs and 40% had SVTs [2].

It may also be of some value to state whether any action was needed (or not) from other R test findings. E.g., did you identify any VT or pauses that prompted further investigations of the study participants?

This is an interesting question, thank you for bringing it up. We identified several other arrhythmias that prompted further investigation and have added this information to the manuscript.

Page 9, paragraph 1: “Continuous event recording also detected several other arrhythmias that prompted further investigation. Suspected ventricular tachycardia was detected in 6.7% (n=29/446), 2nd degree atrioventricular block type 2 was found in 2.5% (n=11/446) and 11.4% (n=51/446) of participants had other pauses lasting &gt;2 seconds daytime and &gt;3 seconds night time.”

The Discussion section is also well written, however the section describing the Swedish cohort (Johnson et al, ref 15), at page 10 (line 31-51), is a bit detailed and the point could have been presented a bit shorter.

Thank you for your advice, we have shortened the section accordingly.

Page 10, paragraph 3: “In a Swedish cohort study, individuals free from AF with a mean age of 64.5 years underwent 24-hour ECG monitoring and were followed prospectively for &gt;13 years. SVTs with different characteristics were compared and irregular SVTs without P waves showed the strongest association with clinical AF, with a cumulative incidence of 47.4% [3]. For irregular SVTs without P waves a similar classification as our micro-AF definition was used.”

Furthermore, the crucial point made on page 11 (line 10-17) could be elaborated a bit more, and I am not sure if I completely agree that these findings "indicate" that micro-AF is both a risk marker for AF and a sign for undetected AF? You may, at least, consider to tone down the statement by replacing "indicating" with "suggesting".

Thank you for your recommendation, we have now toned down the statement.

Page 11, paragraph 2: “This suggests that AF, SVTs and SVEBs could be signs of atrial
cardiomyopathy and might thereby be independently associated with an increase in stroke risk.”

Other minor/discretionary comments:
Page 5, line 24-34: You have written both "one-lead" and "1-lead" ECG, and may decide for one of these phrases (the same applies for the rest of the manuscript, where both terms are used).

Thank you for pointing this out. We have changed one-lead to 1-lead throughout the manuscript.

I assume the "baseline" 1-lead ECG performed on all participants was also made using the Zenicor device? This is not completely clear as the manuscript is written now.

Thank you for noticing this need for clarification. The baseline ECG was recorded using the Zenicor device, we have made this clear in the text now.

Page 5, paragraph 2: “All participants performed an index ECG using a one-lead ambulatory handheld Zenicor II device (Zenicor Medical Systems, Stockholm, Sweden). Those without a prior diagnosis of AF and NT-proBNP ≥125 ng/L were asked to perform intermittent ECG recordings 30 seconds four times daily for two weeks and to make extra recordings if palpitations occurred, using the same handheld Zenicor device. For intermittent recordings. The Zenicor device has been validated with 92% sensitivity and 96% specificity for AF detection compared to a 12-lead ECG [4].”

Page 6, line 39: "significant arrhythmias"; according to the R test settings presented in Suppl table 1, it may be more correct to write "significant ECG characteristics/findings"?

Thank you for the advice, we have made changes accordingly.

Page 6, paragraph 2: “The device was programmed to store not only AF suspicious activity, but also other significant ECG findings, Supplementary table 1.”

The heading of Supplementary Table 1 is changed to: “Settings for number of ECG findings stored by R-test 4”

Li-Wei Lo (Reviewer 3): In this manuscript, the author aimed to assess if the presence of very short-lasting episodes of AF-like activity (micro-AF) can be used as a marker of undiagnosed silent atrial fibrillation (AF). It was a sub-study of STROKESTOP II, which was a Swedish mass-screening prospective study for AF in 75- and 76-year-olds. In summary, the authors reported that the presence of very short-lasting episodes of AF-like activity (micro-AF) indicates an increased likelihood for undetected AF. Continuous screening, therefore, seems recommendable if a finding of AF would change clinical management. Frequent APC or short burst APCs had been described in association with future development of AF for more than 10 years ago. Therefore, the concept is not novel.

Thank you for your comments. We agree that there are earlier studies evaluating SVEBs and SVTs as predictors for future AF. However, prior studies are register studies with follow-up periods that commonly stretch over more than 10 years. Except from our earlier study discussed in the manuscript, this is to our knowledge the only study where extended AF screening is used in individuals with supraventricular activity. We believe this adds novel information in the practical management of patients with brief episodes of AF.

In addition, there are some limitations. First, the micro-AF group underwent continuous event
recording in median 3.3 months later than the control group, which might cause detection bias, and more AF cases might have been found in the control group using the same follow-up time.

This is an accurate observation. Unfortunately, this might have introduced detection bias. We have included this limitation in our limitation section accordingly.

Page 12, paragraph 4: “One limitation in our study is that the micro-AF group underwent continuous event recording in a median of 3.3 months later than the control group. It is possible that this introduced detection bias, and more AF cases might have been found in the control group using the same follow-up time. This could lead to overestimation of our findings.”

Furthermore, the study used both the Zenicor device and the Rtest4 device, both of which were 1-lead ECG devices. It sometimes made detection of atrial activity challenging. This could possibly lead to misdiagnosis and introduce a misclassification bias by underestimation of true cases.

Indeed, p-waves can be difficult to discern using 1-lead devices, which might lead to underestimating true cases of atrial fibrillation, or even more so with regards to atrial flutter. However, this potential misdiagnosis is likely to affect the micro-AF group more as the prevalence of atrial fibrillation is higher in this group, and would have the potential to reduce the significance of our findings. We have included some limitations with regards to the devices in our limitation section.

Page 13, paragraph 2: “Both the Zenicor device and the Rtest4 are 1-lead ECG devices which sometimes make detection of atrial activity challenging. This could possibly lead to misdiagnosis of both AF and atrial flutter and introduce a misclassification bias by underestimation of true cases. However, this potential misdiagnosis is likely to affect the micro-AF group more as the prevalence of atrial fibrillation is higher in this group, and would have the potential to reduce the significance of our findings.”

Detailed comments as below:

1. The fact that only 471 (13%) patients received intermittent recordings for micro-AF detection opens the possibility that outcomes might not be as significant as stated.

In total 446/3766 (12%) participants from STROKESTOP II participated in the extended AF screening using continuous ECG. We invited all participants with micro-AF in STROKESTOP II to participate, of whom 89% accepted. This sample size was deemed large enough in our power calculation.

2. In the methods, page 5, the definition of micro-AF should be stated more clearly. Can the authors mention in detailed about how to differentiate micro-AF from other SVT such as burst APCs or AT?

Thank you, we agree with this concern. Our definition of micro-AF differs from the common definition of AF in two aspects. First, the duration of AF is set to 30 seconds, for micro-AF it is ≥5 beats and less than 30 seconds. Second, the diagnostic criteria for AF do not include a tachycardia criterion, as we have for micro-AF (≥100 beats/min). We have clarified this in the introduction by introducing the term from the beginning:

Page 4, paragraph 1: “The aim of our study is to determine if short episodes of AF-like activity, that we term micro-AF, are not only a risk factor for future AF, but are markers for already existing undetected AF.”
Irregularity and P wave analysis in AF diagnostics are commonly performed by visual inspection of an episode, rather than specific measurements. We applied the same strategy in verification of micro-AF episode, but added the tachycardia criteria. We differentiated micro-AF from macro re-entry tachycardias with the irregularity criterion. Bursts of APC from different foci will look very similar to micro-AF unless there are clear P waves and might hence be classified as micro-AF. In the methods section we have clarified the micro-AF criteria:

Page 6, paragraph 1: “We defined micro-AF as an irregular tachycardia of sudden onset with episodes of ≥5 consecutive supraventricular beats without P waves lasting for less than 30 seconds, Figure 1. Tachycardia was defined as an average heart rate of ≥100 beats per minute during the episode. P wave analysis and irregularity was determined by visual inspection like commonly in AF diagnostics.”

3. Since participants in the micro-AF group were taller, and more frequently had diabetes mellitus compared to the control group. Higher body height has already been shown to be associated with higher incidence of AF development. Can the authors provide detailed information about patients' clinical outcomes? Did these two groups have significant differences in stroke events in addition to AF incidences?

Thank you for your suggestion. This is certainly a highly interesting endpoint; however, this study was only powered to compare differences in AF detection. There were no stroke events during the short follow-up period in-between use of the two screening methods in our study. We have added to our discussion a section about the future need for studies studying this association.

Page 12, paragraph 3: “Our study was not powered to detect associations between micro-AF and thromboembolic risk; further studies are needed to study the association.”

4. Participants in this study only received a single-lead device for AF detection. Did different types of rhythm devices show different results? Can the authors provide a detailed validation of AF diagnosed based on conventional Holter monitoring or 12-lead ECG?

The aim of the study was not to validate or compare the two screening devices regarding arrhythmia detection. The two devices were not used in parallel in all participants, making comparisons difficult. Both screening devices are already validated as mentioned in the manuscript. The intermittent ECG from Zenicor has been compared to 12-lead ECG and have a 92% sensitivity and a 96% specificity for AF detection [4] The continuous ECG, Rtest 4, has been validated compared to continuous ECG and have an automated algorithm with 92% sensitivity and a 87% specificity for AF detection [5].

5. There are some grammar mistakes throughout the whole manuscript. Please revise them accordingly.

Thank you for making us aware of this. According to your recommendation we have sent the manuscript for English language check. All language changes are seen as traceable changes in the document.
References


