Author's response to reviews

Title: Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias

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Author's response to reviews: see over
To:
Executive Editor
Timothy Shipley,

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 Themistoklis Maounis

Minor Revisions:
1) It should be stressed that the choice of recording method (intermittent recording vs 24-48h recording) is mainly based on the frequency of the episodes. When the episodes are Infrequent it is unlikely that the 24h recording will be of value. In the present study this most important information is found nowhere in the text. It is hidden in the table 1. I wonder about the high number of reported episodes (110 mean). In such a high frequency of episodes I would expect the sensitivity of the 24h recording to be much higher; grossly one out of three recordings should be associated with symptoms. Furthermore how were the patients able to recall accurately this high number of episodes. Did they report number of episodes as a continuous value or categorical (eg 1-5, 5-10,10-50, etc)? I would seriously question the accuracy of the response in the presence of such high number of episodes.

We agree. We also doubt the accuracy of the response. Presented data on the earlier amount and duration of palpitation episodes are moreover not fully reliable as they were only collected from about half of the study population. Furthermore these data show a very wide range. We chose therefore only to report median and IQR giving a slightly more accurate impression. No statistical difference comparing earlier amount and duration of palpitations was seen between the groups with AF/PSVT and without AF/PSVT.

We added two lines to table 1 showing that 40 patients reported symptoms during Holter ECG and 31 patients during intermittent ECG. So actually quite a lot of patients reported symptoms, but most of these registrations showed only SVES, VES or normal sinus rhythm and were not considered relevant arrhythmias.

2) The authors are careful to state that the patients with recorded Afib episodes are "potential" candidates for anticoagulation. Since all the data that we have concerning the value of anticoagulation are derived from studies with clinically documented AFib and not device detected Afib, it should be more clearly mentioned that potentially increased risk for embolic events doesn't automatically translate into proven value of anticoagulation in those patients.

We agree, at the end of discussion, in the limitations section (page 13, last paragraph) we mention that 'The AF definition used by the European Society of Cardiology in its Guidelines
Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF, is based on consensus and the clinical implication for risk of stroke is as yet not fully understood.

3) Another limitation of the study is the fact that the high compliance of the patients to obtain intermittent recordings included in this study conducted under a protocol and who were apparently closely followed, might not be reproduced in clinical practice.

We do agree that compliance was very good. In general our patients were not closely followed during these 28 days and recordings were only analysed afterwards. Another ongoing study in Sweden, (method published last year: Friberg L., Engdahl J., et al. (2013).”Populations screening of 75- and 76-year-old men and women for silent atrial fibrillation. (STROKESTOP)” Europace. 2013 Jan;15(1):135-40), including thousands of potential AF patients shows similar amount of registrations. In other settings this compliance might be less good though.

Reviewer 2 Nicole Lowres

MINOR ESSENTIAL REVISIONS

BACKGROUND:
1. A reference is needed to support the statement in the 1st sentence of the 2nd paragraph.

Patient-operated intermittent ECG recordings could potentially improve the diagnosis of transitory ECG changes in such patients and may give results comparable to standard external loop event recorders. [5, 6]

We don’t know about any study comparing a patient-operated intermittent (handheld) ECG device directly with 24 hour Holter in patients with palpitations and dizziness/presyncope. There are several studies comparing efficacy of 24- or 48-hour Holter with a patient-operated event recorder such as Kinlay et al., Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. Ann Intern Med. 1996 Jan 1;124(1 Pt 1):16-20 or Scalivini et al., Cardiac event recording yields more diagnoses than 24-hour Holter monitoring in patients with palpitations. J Telemed Telecare. 2005;11 Suppl 1:14-6.

References 5 and 6 at the end of the same 1st sentence of the second paragraph compare a handheld device with a standard event monitor and with a standard 12-lead ECG respectively. It is only our hypothesis that a patient-operated intermittent (handheld) ECG device could potentially improve the diagnosis of transitory ECG changes in patients with palpitations and dizziness/presyncope.

METHODS:
2. Intervention section: Who performed the 24-hour holter recordings and who gave out the handheld ECGs.

Both the 24 hour Holter and the handheld ECG devices were handed out at the Department of Clinical Physiology, Norrland University Hospital, Umeå. All included patients were referred to this department for 24-hour ECG (Methods, Design, study population and setting, 3rd
sentence). Holter ECG’s were analyzed by Rolf Hörnsten, intermittent ECG registrations were analyzed by Tijn Hendrikx.

3. The handheld device section: Last sentence: Who collected the data for the database.

The study nurses at the Department of Clinical Physiology, Norrland University Hospital, Umeå, mentioned under acknowledgments. These also handed out the Handheld devices and instructed patients on how to use them. Data were transmitted automatically from the device to a central database and analyzed afterwards.

RESULTS
Atrial fibrillation section
4. Did all 9 patients identified with AF have symptomatic registrations? You present the IQR of 2-9 in table 3, however this may mean that one patient did not have symptoms at all. For a sample of n=9 it may be better to present the entire range within the text.

Two AF patients out of nine were asymptomatic, one of them having asymptomatic AF in all 61 recordings. One AF patient had several symptomatic recordings but none of them related to actual AF. We have presented the entire range within the text.

5. Sentence 5: “These patients had four registrations (median) that showed AF, thus representing 6.6% of registrations.” I am not sure what this refers to, therefore I would suggest re-wording for improved clarity. Does it mean that 4/61 recordings were in AF? And if, from the previous sentence, 9/61 were symptomatic this suggests that 5/61 were symptomatic without any arrhythmia present.

One AF patient had 61 asymptomatic AF registrations. This patient was also detected with Holter, even there without reporting symptoms. (This persistent AF was not known at the time of inclusion in the study. The 12 lead ECG which was done before referring the patient for Holter ECG was showing sinus rhythm). As there were only nine AF patients this affects means, SD and ranges a lot. We therefore chose to use medians and IQR. When using medians we get 14.8% symptomatic registrations and 6.6% AF registrations which seems more representative than using all actual registrations and means giving 11.8% and 15.1%, underestimating symptoms and overestimating AF prevalence. We have added the mean, SD and range for total number of registrations, symptomatic registrations and registrations with AF to the text in the atrial fibrillation section.

Symptomatic registrations without AF: Median 6; Mean 5.44; SD ±4.47; Range 0-12
Symptomatic registrations with AF: Median 2; Mean 2; SD ±1.89; Range 0-5

6. I would suggest reporting the timepoint at which the 9th participant was detected with AF, therefore giving the reader the understanding of how long they would need to record for to pick up these additional cases. It is not clear on which day this occurred from Figure 3 as only the total for all three arrhythmias is presented in this graph (see additional comment on Figure 3) and the discussion section states that only two thirds of all arrhythmias were picked up by day 14.

We have added to the text in the atrial fibrillation section that the last AF patient was detected on day 26. There was only one patient detected on day 1. At the bottom of table 3 (time to detection) you can see that six out of nine AF patients were detected within 14 days.
Atrioventricular-block II section
7. There was one patient with AV-block II not picked up by the handheld device during the 24-hour holter period. This raises the question for me as to why it was not detected. Was it because the arrhythmia was intermittent and not present at the time of the handheld recording (comparing the time-stamps of the readings) or was it that the device was not sensitive enough to detect this?

Both patients with AV-block II detected by Holter and handheld ECG respectively had an intermittent AV-block II.

DISCUSSION
Relevance section
8. The last sentence: “However, the fact that all patients had a CHA2DS2-VASc score # 1” needs further clarification as table 3 states 19 of non AF participants had CHA2DS2-VASc score = 0.

I have added that all AF patients had a CHA2DS2-VASc score # 1.

Limitations section
9. Second sentence: I am not sure why this is a limitation of the screening. This is the first time that respiratory sinus bradycardia is discussed in the manuscript. Is it a limitation because it was detected on 24-hour holter monitoring and not on the handheld device? I would suggest that perhaps a sentence regarding “no detection of respiratory sinus bradycardia” should be added to the results section or better still only mentioned there unless the device was not sensitive enough to detect it.

We have removed this sentence as it doesn’t have anything to do with the sensitivity of the device.

10. There is no mention of the potential effect of the sample size or the generalizability (external validity) of the results in the limitations section as per the STROBE guidelines for reporting of observational studies.

We have added a short discussion on generalizability (internal and external validity) to the discussion.

FIGURE 3
11. This graph is confusing. I thought from the text that 2 patients were identified with AF in the first 24 hours however the graph writes n=1 in the first time-point of one day, which does not seem consistent.

Only one patient with AF was discovered during the first 24 hours. See even Discussion, atrial fibrillation section. Point 6.

DISCRETIONARY REVISIONS
1. METHODS:
Design, study population and setting section (lines 9-12). I would suggest using semicolons to improve the distinction of the exclusion criteria: “eg Exclusion criteria were: known arrhythmia, based on previous history or 12-lead ECG performed at the time of referral;
referral for syncope, defined as temporary loss of consciousness; or comorbidity with cognitive or other functional impairments impeding the use of the handheld device”

We have changed this according to your suggestion.

2. RESULTS:
Demographics section, paragraph three outlines the non-analysable registrations. Were the majority of the non-analysable registrations from the one participant or across a mix of participants? If mainly from one participant you may wish to expand on this.

These non-analysable registrations with handheld ECG were from across a mix of participants, most of them having only a few non-analysable registrations. Two patients (without arrhythmia detection) had more non-analysable registrations, respectively 22 (out of 56) and 39 (out of 62). With Holter all patients except one had more than 20 hours of analysable registration. This one patient only had 11 hours.

3. RESULTS: Atrial fibrillation section, sentence 2 and 3 (lines 1-3) are repeated from the previous section. I would suggest re-writing so not repetitive.

Rephrased according to your suggestion.

4. RESULTS: Atrial fibrillation section, sentence 4 (“Out of a total of 61 intermittent registrations (median) for AF patients only nine (median) were symptomatic (14.8%). (Table 3.) is difficult to understand, therefore I would suggest re-wording for improved clarity. I am not sure if I have understood this correctly, however I suggest something along the lines of: “The nine AF patients performed a median of 61 intermittent registrations of which only nine (median) were symptomatic (14.8%)”

We have rephrased this sentence for improved clarity.

5. RESULTS: Atrial fibrillation section. This paragraph does not state that the AF patients were referred for treatment (and neither does the AV-block section), however you state in the PSVT section that PSVT patients were referred for treatment. I would suggest being consistent with all three arrhythmias and stating what happened for each in the results section, or only stating it as he methodology in the methods section.

We have only left this statement in the methodology section after your suggestion.

6. FIGURE 2:
I would suggest separating the two figures so they are better distinguishable from each other and using subheadings to identify the diagnoses, as the computer generated diagnosis is quite small and hard to see amongst all the other information

We still think the image is quite clear and as the other two reviewers did not have a problem with it we decided not to change it into two figures. We think three images in total is enough for this publication.
7. ACKNOWLEDGEMENTS:
What role did these nurses assist with?

The study nurses at the Department of Clinical Physiology, Norrland University Hospital, Ume, mentioned under acknowledgments, handed out the Handheld devices, instructed patients on how to use them and collected data for the database.

Reviewer 3 Xenophon Costeas

No comments

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