Reviewer's report

Title: Detection of occult paroxysmal atrial fibrilation by implantable long-term electrocardiographic monitoring in cryptogenic stroke and transient ischemic attack population: a study protocol for prospective case-control study.

Version: 2
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Reviewer: Evan L Thacker

Reviewer's report:

This manuscript outlines the rationale and protocol for a 12-month prospective cohort study of 100 cryptogenic stroke or TIA patients and 30 age- and sex-matched controls, including measurement of PITX2 and ZFHX3 polymorphisms and continuous ECG monitoring for detecting occult paroxysmal AF.

Major Compulsory Revisions:

1. Although the manuscript is an important document for the investigators who wrote it, to guide the implementation of their study, the value of this manuscript for other researchers or clinicians is not clear. Could the authors clarify the purpose of publishing this manuscript? Why will it be useful to the field?

2. The authors review an extensive literature showing that long-term ECG monitoring is already known to be beneficial for detecting occult paroxysmal AF in cryptogenic stroke patients. Could the authors clarify what knowledge they hope to gain from performing their study, beyond what is already known?

3. Title: The authors refer to their study as a “prospective case-control study.” However, based on their description of the study, I would consider it a “prospective matched cohort study.” There is a cohort of cryptogenic stroke patients, followed over time; there is a matched cohort of healthy people, also followed over time.

4. Abstract: The authors state as a conclusion “The combination of high-resolution long-term ECG monitoring with genetic susceptibility to developing AF would be promising in identifying high risk TIA and ischemic stroke patients.” Is this actually a “conclusion,” or is it a “hypothesis?”

5. I found the Background section a bit hard to follow, maybe due to some organizational weaknesses in how the information was presented. The authors seem to be stringing together many bits of information without driving towards a point. I suggest breaking the Background section into multiple paragraphs, and concluding the Background section with a clear statement of the study’s purpose or objective. What are the hypotheses?

6. In the Background, and again in the Discussion and Conclusion sections, the
authors mention genetic testing for polymorphisms associated with AF. However, the genetic aspects of the study are not explained in the Methods, except to say that the polymorphisms will be measured. Could the authors explain more clearly how they intend to use the genetic information? What hypotheses do the authors have related to the genetic information? How will those hypotheses be tested?

7. Methods: How will the 30 healthy participants be identified? What is the definition of “healthy?”

8. Discussion and Conclusion: There are three sentences that express ideas that do not seem to be adequately fleshed out in the description of study methods: (1) (lines 169-170) “The use of a new algorithm for PAF detection in standard clinical practice should be of great interest.” (2) (line 172) “Genetic data may also provide additional information to characterize stroke subtypes.” (3) (lines 188-189) “Selected genes expression profile may have power in PAF candidates selection.” Do the authors intend to develop or implement a “new algorithm?” Do the authors intend to use genetic data to “characterize stroke subtypes?” Do the authors intend to carry out “genes expression profile” studies? If so, the methods for these efforts should be detailed in the Methods section.

9. The use of English in the manuscript could be improved by a native English speaking editor.

Minor Essential Revisions:

10. Methods: The following sentence (lines 138-140) makes it sound like the 12-month ECG monitoring for the 30 healthy participants is done only if the investigator chooses to do so. Is that correct or does the wording need to be changed? “Control group persons undergo assessment at scheduled and unscheduled visits with 12 months non-stop ACG monitoring performed at the discretion of the investigator.”

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.