PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.
AUTHORS	Magnusson, Peter; Koyi, Hirsh; Mattsson, Gustav

VERSION 1 – REVIEW

REVIEWER	Ryo Itabashi Kohnan Hospital, Japan
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	The author described the rationale and design of a study using chest and thumb-EEG to detect newly diagnosed AF in patients with cryptogenic stroke. The manuscript is well written and structed. I have a comment about the content of their manuscripts. The criteria for diagnosis of cryptogenic stroke should be described in the manuscript.

REVIEWER	Paulus Kirchhof University of Birmingham, UK
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	Dr Magnussen and colleagues describe a small prospective, single-arm study of a thumb ECG in survivors of a cryptogenic stroke. They plan to evaluate the new device in 100 survivors of such an event recruited in the Gavleborg region in Sweden. The new ECG system will not be compared to another method of ECG screening, and there is no control group planned. The topic in question, detection of silent, often paroxysmal AF, is of clinical relevance as detection of AF is – based on current knowledge – a clear reason to provide long-term oral anticoagulation in stroke survivors. It is unclear why the present study is limited to patients with a cryptogenic stroke, whereas published efforts to detect silent AF have been able to identify silent AF in unselected stroke survivors. The study has weaknesses as a technical validation study as there is no comparator method. The lack of a control group undergoing "usual care" is a weakness with a view to changing diagnostic patterns in clinical practice. The manuscript is well-written, and the rationale for detecting silent AF is explained eloquently. It remains much less clear how this small study will add to the existing knowledge on the effectiveness of ECG screening in stroke survivors.

REVIEWER	Amit Kishore University of Manchester Salford Royal NHS Foundation Trust Greater Manchester UK
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	This is an interesting study on non-invasive monitoring for cryptogenic strokes My comments are as follows Line 7- 'theraphy, should read 'therapy' Line 14-16- needs editing for grammar Line 17-20- Needs rephrasing- Perhaps something like 'antiplatelet monotherapy therapy should not be considered for secondary prevention for AF, regardless of stroke risk.' Authors need to carefully look at wording- usage of American spellings are sometimes mixed with British spellings. Line 45-55- The authors emphasise that it is expensive to use loop recorders but there are studies that have said that loop recorders are cost effective in stroke patients (Diamantopoulos et al 2016). Can the authors reflect on this a bit more in their study protocol? Can the authors clarify the definition of cryptogenic stroke to be used in the study? Can the authors clarify how the recordings are downloaded and analysed and by whom? This is important as anticoagulation is normally commenced at/by 2 weeks (or earlier in some minor strokes) and time from index event to anticoagulation needs to be recorded. Can the authors clarify if the use of 24h monitoring the standard of care after stroke in the unit where the research is to be undertaken? How soon after the initial monitoring is the Coala Heart monitor to be used? What do the researchers plan to do with the outcome of the study, if positive?

REVIEWER	Sanna T Catholic University of the Sacred Heart, Rome, Italy
REVIEW RETURNED	21-Nov-2017

GENERAL COMMENTS	The present study is designed to assess the incidence of atrial fibrillation in patients with cryptogenic stroke by using an intermittent monitoring strategy of 28-days duration. The SPIRIT 2013 Statement provides recommendations for a set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol and I advise the authors to follow the Spirit Checklist to revise their manuscript (http://www.spirit-statement.org/spirit-statement/) . The secondary endpoint (a) "The prevalence of previously known atrial arrhythmia before cryptogenic stroke and the number of these

	patients who had anticoagulant therapy" should be stated more clearly. The secondary end-points (e) "Cumulative incidence of stroke (and all-cause mortality) after three years in patients with AF versus without AF" is confusing: why "all-cause mortality" is in parentheses ? The secondary endpoints (c) (d) and (e) are intended to report their respective outcomes at 6 weeks, 12 months and three years. So, what is the time window of the study ? Will the study results be reported after three years? The power analysis "A power analysis based on previous research findings and estimation of outcome to 2.4%, 95% confidence interval, width of confidence interval 5, standard deviation 12 results in a sample size of 89" should be rephrased more clearly and units should be used. The study definition of "cryptogenic stroke" should be clearly stated

VERSION 1 – AUTHOR RESPONSE

EDITOR
Please revise your title so that it includes your study setting. This is the preferred format for the journal. We also suggest replacing 'rationale and design' with 'protocol' (=> "..a protocol for a prospective observational study using chest and thumb- ECG..")

Authors: Dear Editor. Thanks for your valuable input and selection of reviewers who provided suggestions for improvement of the manuscript.
We revised the title:
A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.
Page 1, line 1-3.

EDITOR
Please add a brief description of your dissemination plans to the abstract >> ethics and dissemination section.

Authors: Ok.
"Ethics and dissemination" in the Abstract.
"The database will be closed after the last follow-up, followed by statistical analyses, interpretation of results, and dissemination to a scientific journal."
Page 3, line 3-4.

EDITOR: Please thoroughly check the manuscript for typographical/ grammatical errors.

Authors: Agree. We corrected the spelling of "therapy"
Page 5, line 2 and page 8, line 14.

EDITOR: Whilst the SPIRIT checklist is designed for RCTs, we recommend completing/ including the SPIRIT checklist as per reviewer 4's suggestion. Alternatively you could complete the relevant items from the STROBE checklist. Please remember to include the relevant page number(s) from the manuscript next to each reporting item or state 'n/a' next to items that are not applicable to your study.

Author: Ok. We have uploaded this checklist (in the left margin is the referral to where in the manuscript the information appear.

REVIEWER 1: Ryo Itabashi
The author described the rationale and design of a study using chest and thumb-EEG to detect newly diagnosed AF in patients with cryptogenic stroke. The manuscript is well written and structured. I have a comment about the content of their manuscripts. The criteria for diagnosis of cryptogenic stroke should be described in the manuscript.

Author: Thanks for your review and your overall positive comment.
Agree. We added:
"Cryptogenic stroke is defined as cerebral ischemia of unknown etiology i.e. not attributable to a source of cardiac embolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation.27"
Page 7, line 22-23, Page 8, line 1-2.
Reference added:
27. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Stroke. 1993;24:35-41.

REVIEWER 2: Paulus Kirchhof
Dr Magnusson and colleagues describe a small prospective, single-arm study of a thumb ECG in survivors of a cryptogenic stroke. They plan to evaluate the new device in 100 survivors of such an event recruited in the Gävleborg region in Sweden. The new ECG system will not be compared to another method of ECG screening, and there is no control group planned.

Author: Thanks for your review and valuable comments.

REVIEWER 2: The topic in question, detection of silent, often paroxysmal AF, is of clinical relevance as detection of AF is – based on current knowledge – a clear reason to provide long-term oral anticoagulation in stroke survivors. It is unclear why the present study is limited to patients with a cryptogenic stroke, whereas published efforts to detect silent AF have been able to identify silent AF in unselected stroke survivors.

Author: We use a wide definition of cryptogenic stroke and have decided to study these patients as findings would be easier to generalize. To include patients with a clear attributable cause of stroke we think would make interpretation more difficult.

REVIEWER 2: The study has weaknesses as a technical validation study as there is no comparator method. The lack of a control group undergoing "usual care" is a weakness with a view to changing diagnostic patterns in clinical practice.

Author: This is a prospective observational study on incidence of arrhythmias. Thus the main purpose is not to compare with another method but "usual care". As no further ECG evaluation is done in these patients, the monitor may add benefit in diagnosing AF, which is the reason to not have a control group.

REVIEWER 2: The manuscript is well-written, and the rationale for detecting silent AF is explained eloquently. It remains much less clear how this small study will add to the existing knowledge on the effectiveness of ECG screening in stroke survivors.

Author: We are pleased to hear this positive impression.
This is the first prospective study using the Coala Heart MonitorTM in stroke patients. We have planned to recruit 100 patients which we believe will be enough in order to address the research questions based on current estimation of diagnostic yield.

An even larger study would make more subgroup analyses possible and are welcomed. Future initiatives on study other cohorts in different settings would be valuable.

REVIEWER 3: Amit Kishore
Line 7- 'theraphy, should read 'therapy'
Line 14-16- needs editing for grammar
Line 17-20- Needs rephrasing- Perhaps something like 'antiplatelet monotherapy therapy should not be considered for secondary prevention for AF, regardless of stroke risk.'
Authors need to carefully look at wording- usage of American spellings is sometimes mixed with British spellings.

Author: Agree. We corrected the spelling of "therapy"
Page 5, line 2 and page 8, line 14.

The suggestion 'antiplatelet monotherapy therapy should not be considered for secondary prevention for AF, regardless of stroke risk.' has been considered. However, it is not "secondary prevention for AF" but prevention of stroke.

As stated in the Acknowledgement section we consulted an experienced language editor: The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed the manuscript for American English. Based on your comment we reviewed the manuscript again for consistent use of American English.

REVIEWER 3: Line 45-55- The authors emphasize that it is expensive to use loop recorders but there are studies that have said that loop recorders are cost effective in stroke patients (Diamantopoulos et al 2016). Can the authors reflect on this a bit more in their study protocol?

Author:
We claim that loop recorders imply high costs but your remark that loop recorders may in fact be cost-effective is worth mentioning. Therefore we added
"…even though cost-effectiveness has been suggested suggested.6,13,14"
Page 5, line 22-23.
We added the reference below. Thanks for your suggestion.

14. Diamantopoulos A, Sawyer LM, Lip GY, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. Int J Stroke. 2016;11:302-12.

REVIEWER 3: Can the authors clarify the definition of cryptogenic stroke to be used in the study?

Author: Agree. We added:
"Cryptogenic stroke is defined as cerebral ischemia of unknown etiology i.e. not attributable to a source of cardiac embolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation.27"
Page 7, line 22-23, Page 8, line 1-2.
Reference added:
27. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Stroke. 1993;24:35-41.

REVIEWER 3: Can the authors clarify how the recordings are downloaded and analysed and by whom? This is important as anticoagulation is normally commenced at/by 2 weeks (or earlier in some minor strokes) and time from index event to anticoagulation needs to be recorded.

Author: We added “Each recording is stored in a web-based application that is accessible for the investigators. The investigators daily check all recordings. In the case of an AF-episode, we contact the patient (or relative/health care provider) as soon as possible, typically the same day. The reason for this is that they require anticoagulation and they typically need prompt protection (time is recorded). In the case of an AF-episode, two investigators, of whom one is an experienced cardiologist within the field of arrhythmia, interpret the recording.”
Page 10, line 1-7.

REVIEWER 3: What do the researchers plan to do with the outcome of the study, if positive?

Author: Patients with a positive finding i.e. detection of AF will be offered NOAC if no contraindication is present.
When the study is finished and results published we will continue to disseminate at lectures etc.

REVIEWER 4: Sanna T
The present study is designed to assess the incidence of atrial fibrillation in patients with cryptogenic stroke by using an intermittent monitoring strategy of 28-days duration.
The SPIRIT 2013 Statement provides recommendations for a set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol and I advise the authors to follow the Spirit Checklist to revise their manuscript (http://www.spirit-statement.org/spirit-statement/).

Author: Ok. We have uploaded this checklist (in the left margin is the referral to where in the manuscript the information appear.

REVIEWER 4: The secondary endpoint (a) “The prevalence of previously known atrial arrhythmia before cryptogenic stroke and the number of these patients who had anticoagulant therapy” should be stated more clearly.
The secondary end-points (e) “Cumulative incidence of stroke (and all-cause mortality) after three years in patients with AF versus without AF” is confusing: why “all-cause mortality” is in parentheses ?
The secondary endpoints (c) (d) and (e) are intended to report their respective outcomes at 6 weeks, 12 months and three years. So, what is the time window of the study? Will the study results be reported after three years?

Author: Thanks for pointing this out. We have clarified.

a) Prevalence of previously known atrial arrhythmia before the inclusion in the study and the number of these patients who had anticoagulant therapy.

We divided e) into e) and f) for clarity.

e) Cumulative incidence of stroke after three years in patients with AF versus without AF.

f) All-cause mortality after three years in patients with AF versus no AF.

Yes, the endpoints c) d) and e) requires 3 years follow-up to be completed.

The primary end-point will be reported as soon as the database is complete in this regard (i.e. before three years).
Ok. We added units for the power calculation.

A power analysis based on previous research findings and estimation of outcome to 2.4%, 95% confidence interval, width of confidence interval 5%, standard deviation 12% results in a sample size of 89.

The power analysis “A power analysis based on previous research findings and estimation of outcome to 2.4%, 95% confidence interval, width of confidence interval 5, standard deviation 12 results in a sample size of 89” should be rephrased more clearly and units should be used.

REVIEWER 4:The study definition of “cryptogenic stroke” should be clearly stated.

Author: Agree. We added:

“Cryptogenic stroke is defined as cerebral ischemia of unknown etiology i.e. not attributable to a source of cardiac embolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation.27”
Page 7, line 22-23, Page 8, line 1-2.
Reference added:
27. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Stroke. 1993;24:35-41.

VERSION 2 – REVIEW

REVIEWER	Paulus Kirchhof University of Birmingham, UK
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	I have no further comments.

REVIEWER	Amit Kishore Salford Royal NHS foundation Trust, University of Manchester, UK
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	Thank you for revising the manuscript. Abstract: The sentence beginning- "Prolonged continuous ECG monitoring is impractical " is inaccurate as most recent guidelines suggest prolonged continuous ECG monitoring and is probably the most practical way of non-invasive cardiac monitoring after stroke. Line 19 in the abstract, regarding primary objective- 'Frequency' of AF detection rather than 'incidence' of AF detection is a better reflection Manuscript: Line number 20-26- Needs semantic/grammar correction. The authors have still not clarified the 'index event ' i.e. stroke to 'Intervention' period- how soon after stroke is the Coala monitor to be applied or the upper limit of time period after stroke(for example within 2 weeks, 60 days, 90 days etc.)

	Can the authors clarify if it will be feasible for a basic health economic analysis to be provided, and if not , perhaps suggest that in the conclusion?

REVIEWER	Sanna T Catholic University of the Sacred Heart, Rome, Italy
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	I appreciate the revisions made by the authors. However, it is still unclear to me how to reconcile the following statements : (pg.8 Lines 5-7 referring to exclusion criteria) For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for anticoagulation. (pg. 9 line 11 referring to secondary end-points of the study) Prevalence of previously known atrial arrhythmia before the inclusion in the study and the number of these patients who had anticoagulant therapy. I would appreciate a comment of the authors explaining in more detail the mentioned secondary end-point of the study. Did you mean “anticoagulation as a result of AF detection with the investigational monitoring tool” and “anticoagulation as a result of AF detection with the investigational monitoring tool in patients with pre-enrollment evidence of atrial arrhythmia other than AF or A flutter?”. If so, the current statement should be rephrased as suggested. If not, please explain the secondary endpoint in a different way.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3:
1. Abstract: The sentence beginning- "Prolonged continuous ECG monitoring is impractical " is inaccurate as most recent guidelines suggest prolonged continuous ECG monitoring and is probably the most practical way of non-invasive cardiac monitoring after stroke. Line 19 in the abstract, regarding primary objective- 'Frequency' of AF detection rather than 'incidence' of AF detection is a better reflection

Authors: Ok. We removed the wording “is impractical and”

Page 2, line 5.

The word “incidence” used in epidemiology is correct, not frequency.

2. Line number 20-26- Needs semantic/grammar correction.

Author: Ok. We replaced “that is” with “thus”.

Page 5, line 23.

3. The authors have still not clarified the 'index event ' i.e. stroke to 'Intervention' period- how soon after stroke is the Coala monitor to be applied or the upper limit of time period after stroke (for example within 2 weeks, 60 days, 90 days etc.)

Author:Ok. It may take a few days to confirm the diagnosis of stroke and complete standard evaluation. We added:

The monitoring will start within a few days when the diagnosis of stroke has been confirmed and standard evaluation is complete, typically 1-5 days.

Page 10, line 1-2.

4. Can the authors clarify if it will be feasible for a basic health economic analysis to be provided, and if not, perhaps suggest that in the conclusion?

Author: It is possible that a health economy analysis will be feasible but it has not been planned in the current protocol. If it is to be performed, it has to be done as post-hoc analysis.

Reviewer 4.

5. (pg.8 Lines 5-7 referring to exclusion criteria) For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for anticoagulation.
(pg. 9 line 11 referring to secondary end-points of the study) Prevalence of previously known atrial arrhythmia before the inclusion in the study and the number of these patients who had anticoagulant therapy.
I would appreciate a comment of the authors explaining in more detail the mentioned secondary end-point of the study. Did you mean “anticoagulation as a result of AF detection with the investigational monitoring tool” and “anticoagulation as a result of AF detection with the investigational monitoring tool in patients with pre-enrollment evidence of atrial arrhythmia other than AF or A flutter?.” If so, the current statement should be rephrased as suggested. If not, please explain the secondary endpoint in a different way.

Author: Thanks for your review.

We have clarified this by adding:

“In addition, stroke patients, not eligible for the chest and thumb-ECG monitoring, will be analyzed with regard to prevalence of previous atrial arrhythmia (including whether they were anticoagulated), cumulative incidence of stroke after three years, and all-cause mortality after three years in patients with AF versus no AF.”

Page 7, line 13-17.