BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019933
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2017
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Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE

Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE)– rationale and design: a prospective observational study using chest and thumb- ECG.

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ABSTRACT

Introduction: Atrial fibrillation (AF) causes ischemic stroke and based on risk factor evaluation warrants anticoagulation therapy. In stroke survivors, AF is typically detected with short-term ECG monitoring in the stroke unit. Prolonged continuous ECG monitoring is impractical and requires substantial resourceswhile insertable cardiac monitors are invasive and costly. Chest and thumb-ECG could provide an alternative for AF detection post-stroke.

The primary objective of our study is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG monitoring in patients with cryptogenic stroke. Secondary objectives are to assesses health-related quality of life (HRQoL) using SF-36 and the feasibility of the Coala Heart Monitor™ in patients with stroke.

Methods: Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischemic stroke without documented AF before or during ECG evaluation in the stroke unit will be evaluated by the chest and thumb-ECG system Coala Heart Monitor.™ The monitoring system is connected to a smartphone application which allows for remote monitoring and prompt advice on clinical management. Over a period of 28 days, patients will be monitored twice daily and may activate the ECG recording at symptoms. Upon completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF post-stroke, but the feasibility of this system in patients who recently suffered from a stroke is unknown. In addition HRQoL using SF-36 in comparison to Swedish population norms will be assessed. The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire.

Ethics and dissemination: The study was approved by The Regional Ethical Committee in Uppsala (2017/321) and registered at Clinical Trial Registration NCT03301662.

Strengths and limitations of this study

- Chest and thumb-ECG evaluation applied after 24-hour ECG Holter at the stroke unit after confirmation of ischemic stroke.
- Usage of a smartphone application for storage of chest and thumb-ECG which may improve compliance and facilitate fast evaluation by the health-care provider in order to prescribe an anticoagualant when indicated.
- Prospective design including consecutive patients which eliminate both selection and tertiary center bias.
- Management of short (30 seconds) AF episodes, detected by non 12-lead ECG, lack evidence from randomized controlled trials with regard to benefit of anticoagulation.
- The small sample size (n=100) may imply type-II errors in subgroup analyses.

Keywords: atrial fibrillation, cryptogenic stroke, ECG screening, health-related quality of life, SF-36, stroke, thumb-ECG

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolization, but these devastating events can be prevented by anticoagulant theraphy.[1] A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred choice and effectively reduce the risk of stroke and mortality.[2] A meta-analysis of the pivotal NOAC trials showed a 19% reduction of stroke/systemic embolism and 10% lower mortality compared to warfarin.[2] If AF is not diagnosed, antiplatelet medication is current practice following a stroke.[3] According to the European Society of Cardiology (ESC), antiplatelet monotherapy should not be considered in the presence of AF, regardless of the stroke risk.[4-6] Stroke is a leading cause of disability and death and is the incidence is increasing due to ageing populations and the growing prevalence risk factors such as diabetes and hypertension.[7-9] At least 20-30% of patients with ischemic stroke have a documented episode of AF before, during, or after the event, but in a quarter of these patients, the stroke is cryptogenic, meaning that no etiologic factor can be determined.[10-12] However, the proportion of cryptogenic stroke from studies varies due to heterogeneity of cohorts and evaluation tools.

Possibilities for AF detection include monitoring in the hospital ward, repeated electrocardiograms (ECG), Holter monitoring, external event or loop recorders, and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yields an AF diagnosis in 8.9% at 6 months and 12.4% at 12 months, but this strategy has not been endorsed in current practice as it requires considerable resources and imply high costs.[6,13] Episodes of AF may be silent, that is not recognized or reported by the patient, but are nevertheless associated with the same risk of embolization.[14-16] In patients with either dual-chamber pacemakers or implantable defibrillators and with no documented history of AF, 10.1% had episodes

of high-rate atrial tachycardia and this was also associated with an increased risk of stroke.[17]

Sequential stratified ECG monitoring detected AF in 24% of stroke patients in one study.[10] The diagnostic yield was 11.5% in a pooled analysis, but this yield varies with such study factors as timing, length of registration, and the monitoring tool.[18] In unselected stroke patients, 24-hour monitoring found AF in only 2.4%.[19] This may vary substantially with the recording technique; in a recent study, AF (defined as ≥ 30 seconds in duration) was detected in 16.1% of patients monitored by an 30-day event-triggered recorder compared to 3.2% of patients monitored by 24-hour ECG.[20] A large multicenter study of stroke patients on Holter monitoring reported new diagnoses of AF in 2.6% of patients at 24 hours and 4.3% at 72 hours.[12] In another study, AF was detected in 8.3% of stroke patients monitored by continuous ECG for a median of 89 hours in the stroke unit; ECG monitoring was superior to 24-hour Holter monitoring in detecting AF.[21]

Thus, while ECG monitoring for an extended period is important for stroke survivors post-discharge Holter monitoring is impractical, ECG data storage is limited, and data interpretation requires considerable resources.Therefore, the thumb-ECG offers advantages in that it monitors conveniently (typically twice daily) and can be activated to capture symptomatic episodes. For example, AF was detected in 11.4% of post-stroke patients monitored by thumb-ECG over 21 days versus 2.8% in those continuously monitored for 48 hours.[22]

The thumb-ECG monitor system Zenicor™ (Zenicor Medical Systems AB, Stockholm, Sweden) has been shown to diagnose previously unknown AF in 3.0% of the general population in Sweden aged 75 years.[23] The Zenicor™ system has been developed

and intregrated into the chest and thumb-ECG Coala Heart Monitor™ (Coala Life AB, Stockholm, Sweden). The monitoring system utilizes a smartphone application which allows for remote monitoring by a clinician. This system may help to evaluate the presence of AF post-stroke. However, feasibility of this system in patients who recently suffered a stroke has not been studied. In addition health-related quality of life (HRQoL) using SF-36 in comparison to Swedish population norms will be assessed.[24,25] The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire (see Supplement).

OBJECTIVES

The primary objective is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG in cryptogenic stroke patients.

The secondary objectives are to assesses HRQoL using SF-36 and the feasibility of the Coala Heart Monitor™ in patients with stroke.

METHODS

Setting and selection

Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified from daily checks of the medical records in the stroke unit. The recruitment is planned to start in October 2017.

Inclusion and exclusion

Patients, aged ≥18 years, with a validated diagnosis of ischemic cryptogenic stroke are eligible for the study. For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for

anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor, pregnancy, permanent indication for anticoagulation (including low-molecular weight heparin) due to atrial arrhythmia, mechanical heart valve, deep veinthrombosis, or pulmonary embolism. Patients with a life expectancy ≤6 months (e.g. severe heart failure New York Heart Association [NYHA] functional class IV or malignancy) are likewise excluded.

Variables

Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds. Patients characteristics are age, sex, date of current ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet theraphy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral vascular disease, aortic plaque, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from carotid-Doppler, computerized tomography, echocardiography, ortransesophageal echocardiography, as well as coagulation laboratory examination.

Outcome measurements

Outcome measurements are arrhythmias recorded by chest and thumb-ECG obtained during scheduled twice-daily recordings or by patient-activated recordings.

Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia, ventricular tachycardia, premature ventricular complex, or supraventricular ventricular complex. The date and time of each episode will be recorded.

Research questions and endpoints

The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.

Secondary endpoints

a) The prevalence of previously known atrial arrhythmia before cryptogenic stroke and the number of these patients who had anticoagulant therapy.

b) Compliance with chest and thumb-ECG at week four (number of recorded scheduled ECG tracings).

c) Patient-reported experience with chest and thumb-ECG measured at week six (questionnaire as Supplement).

d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb-ECG.

e) Cumulative incidence of stroke (and all-cause mortality) after three years in patients with AF versus without AF.

Chest and thumb-ECG

Patients will be asked to use the chest and thumb-ECG monitor device twice daily, once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00 p.m.

If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g. sudden onset of tiredness, presyncope, syncope) they are asked to record the episode with the smartphone application. Each patient is monitored for four consecutive weeks, after which the device is returned by mail to the investigators.

Power analysis

A power analysis[26] 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. There is likely to be drop-out of patients who are unable or unwilling to meet the monitoring requirements; thus, an estimated 120 patients should be included in order to have 100 patients complete the chest and thumb-ECG evaluation.

Statistics

Descriptive data will be reported as frequencies, percentages, means, and percentiles. Continuous variables are summarized as means, standard deviations, and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for categorical variables. Kaplan-Meier estimates are used to describe time to event analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical significance is defined as a two-sided *p*-value of <0.05. The data will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for analyses.

Ethics and dissemination

The Regional Ethical Committee in Uppsala approved the study the 20th of September 2017 (protocol number 2017/321). The study protocol, including variables and prespecfied research questions, were registered at Clinical Trial Registration NCT03301662 and approved 3rd of October 2017. The documentaton of research data and management of the study follow the Guideline for Good Clinical Practice.[27] Each patient is informed about the study by a physician and nurse and included after written consent. After the study is completed, the database will be closed and followed by statistical analyses, interpretation of results, and dissemination to scientific journals.

DISCUSSION

Since anticoagulation therapy has been proven effective in preventing ischemic stroke in patients with AF, reliable AF detection following cryptogenic stroke is crucial.[6] Hence, prolonged ECG monitoring is reasonable, especially in patients at high risk of embolization. Ischemic stroke risk stratification and the decision to prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of stroke counts for two points, which suffices as a rationale for anticoagulation.[6] The vast majority of stroke patients typically have multiple risk factors, and stroke risk increases with more risk factors.[28] ESC guidelines already allow for prolonged monitoring of these patients: “In stroke patients, additional ECG monitoring by long-term noninvasive or implanted loop recorders should be considered to document silent atrial fibrillation” (Class IIa recommendation, level of evidence B).[6] However, since the CRYSTAL-AF trial[13], current practice in Sweden remains unchanged with invasive monitoring rarely used for AF detection in stroke patients and still not endorsed by national authorities.[33] The noninvasive thumb-ECG has been advocated in that it provides an alternative and advantageous cost-benefit profile in mass screening.[30] Stroke patients have a higher risk for recurrent stroke and higher incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater benefit in this population.This has yet to be analyzed, and it is our hope that our study will advance the knowledge of thumb-ECG in this population particularly with regard to healthcare economics.

The use of the thumb-ECG has been studied in a Swedish setting for stroke patients, but the study was retrospective, with data gathered at different times after the stroke, and the monitoring method was selected based on the physician’s preference, which implies bias.Our prospective study includes consecutive stroke patients without referral center bias.[31] This will provide a basis to estimate AF incidence over an

extended period of 28 days. Continuous Holter monitoring may be associated with poor compliance, technical difficulties,and time-consuming analyses of extensive amounts of data bu healthcare providers.[31,32] The newly developed Coala Heart Monitor™ with the proven detection algorithms from Zenicor™ using a smartphone application seem to be a promising alternative, but feasibility remains to be studied. Therefore we added a questionnaire to address feasibility issues.

Although a thumb-ECG may provide an attractive method of noninvasive AF detection, there remain some controversies with regard to short-term anticoagulation for AF. The potential benefits of anticoagulation therapy for short-term AF would be challenging to study because it would require long-term follow-up, demands a large sample size, and raises ethical concerns about withholding anticoagulation from a stroke survivor. This proposed prospective observational trial of consecutive stroke patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and analyze the clinical feasability of the Coala Heart Monitor.™

Acknowledgements

The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed the manuscript for American English. Ulf Tossman and Philip Siberg from Coala Life for support regarding the Coala Life Monitor.™

Author contributions

PM: idea, design, project management, and writing of the manuscript. HK: critical revision GM: idea, design, project management, critical revision.

Funding

Region Gävleborg funded this research project and Coala Life provided free product Coala Heart Monitor™ during the study period.

Competing interests

The authors received free product from Coala Life.

Ethics approval

The study was approved by the Regional Ethical committee in Uppsala (Dnr 2017/321).

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BMJ Open

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Journal:	*BMJ Open*
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Article Type:	Protocol
Date Submitted by the Author:	28-Nov-2017
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Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified from daily checks of the medical records in the stroke unit. The recruitment is planned to start in October 2017.

Inclusion and exclusion

Patients, aged ≥18 years, with a validated diagnosis of ischemic cryptogenic stroke are eligible for the study. 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] For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor, pregnancy, permanent indication for anticoagulation (including low-molecular weight heparin) due to atrial arrhythmia, mechanical heart valve, deep veinthrombosis, or pulmonary embolism. Patients with a life expectancy ≤6 months (e.g. severe heart failure New York Heart Association [NYHA] functional class IV or malignancy) are likewise excluded.

Variables

Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds. Patients characteristics are age, sex, date of current ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet therapy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral vascular disease, aortic plaque, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from carotid-Doppler, computerized tomography, echocardiography, or transesophageal echocardiography, as well as coagulation laboratory examination.

Outcome measurements

Outcome measurements are arrhythmias recorded by chest and thumb-ECG obtained during scheduled twice-daily recordings or by patient-activated recordings.

Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia, ventricular tachycardia, premature ventricular complex, or supraventricular ventricular complex. The date and time of each episode will be recorded.

Research questions and endpoints

The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.

Secondary endpoints

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

b) Compliance with chest and thumb-ECG at week four (number of recorded scheduled ECG tracings).

c) Patient-reported experience with chest and thumb-ECG measured at week six (questionnaire as Supplement).

d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb-ECG.

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.

Chest and thumb-ECG

Patients will be asked to use the chest and thumb-ECG monitor device twice daily, once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00 p.m.

If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g. sudden onset of tiredness, presyncope, syncope) they are asked to record the episode with the smartphone application. Each patient is monitored for four consecutive weeks, after which the device is returned by mail to the investigators.

Each recording is stored in a web-based application that is accessible to 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.

Power analysis

A power analysis[28] 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. There is likely to be drop-out of patients who are unable or unwilling to meet the monitoring requirements; thus, an estimated 120 patients should be included in order to have 100 patients complete the chest and thumb-ECG evaluation.

Statistics

Descriptive data will be reported as frequencies, percentages, means, and percentiles. Continuous variables are summarized as means, standard deviations, and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for categorical variables. Kaplan-Meier estimates are used to describe time to event analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical significance is defined as a two-sided *p*-value of <0.05. The data will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for analyses.

Ethics and dissemination

The Regional Ethical Committee in Uppsala approved the study the 20th of September 2017 (protocol number 2017/321). The study protocol, including variables and prespecified research questions, were registered at Clinical Trial Registration NCT03301662 and approved 3rd of October 2017. The documentaton of research data and management of the study follow the Guideline for Good Clinical Practice.[29] Each patient is informed about the study by a physician and nurse and included after written consent. After the study is completed, the database will be closed and followed by statistical analyses, interpretation of results, and dissemination to scientific journals.

DISCUSSION

Since anticoagulation therapy has been proven effective in preventing ischemic stroke in patients with AF, reliable AF detection following cryptogenic stroke is crucial.[6] Hence, prolonged ECG monitoring is reasonable, especially in patients at high risk of embolization. Ischemic stroke risk stratification and the decision to prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of stroke counts for two points, which suffices as a rationale for anticoagulation.[6] The vast majority of stroke patients typically have multiple risk factors, and stroke risk increases with more risk factors.[30] ESC guidelines already allow for prolonged monitoring of these patients: “In stroke patients, additional ECG monitoring by long-term noninvasive or implanted loop recorders should be considered to document silent atrial fibrillation” (Class IIa recommendation, level of evidence B).[6] However, since the CRYSTAL-AF trial[13], current practice in Sweden remains unchanged with invasive monitoring rarely used for AF detection in stroke patients and still not endorsed by national authorities.[31] The noninvasive thumb-ECG has been advocated in that it provides an alternative and advantageous cost-benefit profile in mass

screening.[32] Stroke patients have a higher risk for recurrent stroke and higher incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater benefit in this population.This has yet to be analyzed, and it is our hope that our study will advance the knowledge of thumb-ECG in this population particularly with regard to healthcare economics.

The use of the thumb-ECG has been studied in a Swedish setting for stroke patients, but the study was retrospective, with data gathered at different times after the stroke, and the monitoring method was selected based on the physician's preference, which implies bias. Our prospective study includes consecutive stroke patients without referral center bias.[33] This will provide a basis to estimate AF incidence over an extended period of 28 days. Continuous Holter monitoring may be associated with poor compliance, technical difficulties,and time-consuming analyses of extensive amounts of data by healthcare providers.[33,34] The newly developed Coala Heart Monitor™ with the proven detection algorithms from Zenicor™ using a smartphone application seem to be a promising alternative, but feasibility remains to be studied. Therefore we added a questionnaire to address feasibility issues.

Although a thumb-ECG may provide an attractive method of noninvasive AF detection, there remain some controversies with regard to anticoagulation for short-term AF. The potential benefits of anticoagulation therapy for short-term AF would be challenging to study because it would require long-term follow-up, demands a large sample size, and raises ethical concerns about withholding anticoagulation from a stroke survivor. This proposed prospective observational trial of consecutive stroke patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and analyze the clinical feasability of the Coala Heart Monitor.™

Acknowledgements

The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed the manuscript for American English. Ulf Tossman, David Fällman, and Philip Siberg from Coala Life for support regarding the Coala Life Monitor.™

Author contributions

PM: idea, design, project management, and writing of the manuscript. HK: critical revision GM: idea, design, project management, critical revision.

Funding

Region Gävleborg funded this research project and Coala Life provided free product Coala Heart Monitor™ during the study period.

Competing interests

The authors received free product from Coala Life.

Ethics approval

The study was approved by the Regional Ethical committee in Uppsala (Dnr 2017/321).

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Region Gävleborg

TEASE-study, questionnaire

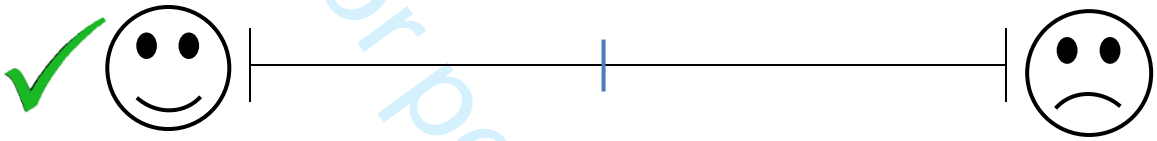
Code ☐☐☐

Name: _____

Personal ID:_____ - _____

Please describe your experience of using the chest- and thumb ECG. Follow the example below to make a clear vertical line.

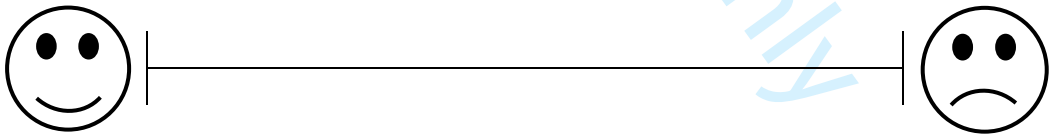
Exemple: **Correct**



Exemple: **Incorrect**

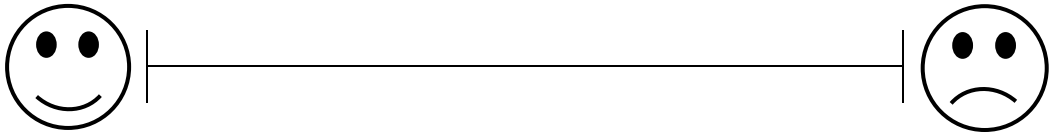
Frågor:

1. In summary, what do you think about the usage of the chest- and thumb ECG?



Very dissatisfied Very unsatisfied

2. How was the technical feasibility of the chest- and thumb ECG?

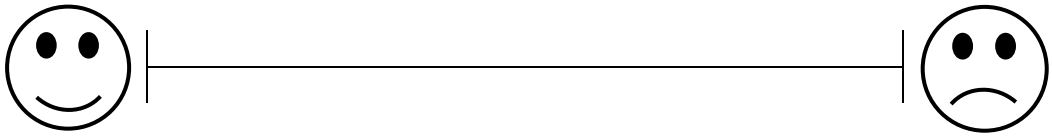


Very easy Very difficult

Region Gävleborg

TEASE-study, questionnaire

3. Did you remember to use the chest- and thumb ECG as scheduled?

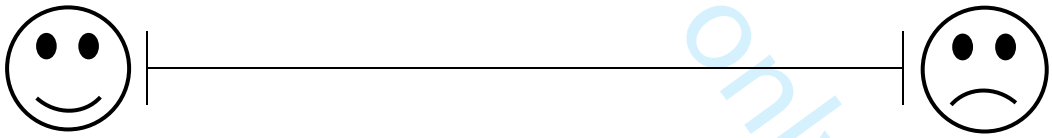


Always Never

4. How was it physically to apply the chest- and thumb ECG?

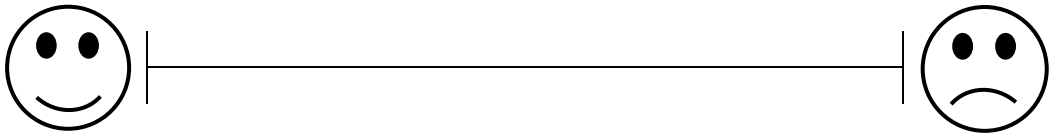
Very easy Very difficult

5. Did the ECG monitoring affect your feeling of security?



Much more secure Much less secure

6. Did you need help from others to perform the ECG-monitoring?

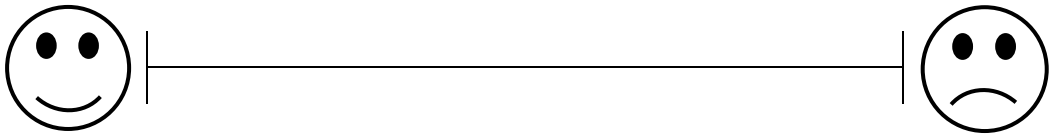


Always needed help Never needed help

Region Gävleborg

TEASE-study, questionnaire

7. Would you recommend other stroke patients to use the chest- and thumb ECG monitoring?



Strongly Not at all

Would you like to add any comment about using the chest- and thumb ECG? Please use the box below.

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TEASE-study, questionnaire

What symptoms remain after your stroke? Please underline the alternative that describes this best.

Speech ability impairment:	Severe	Moderate	Mildly	No
Impairment of ability to understand:	Severe	Moderate	Mild	No
Arm weakness:	Severe	Moderate	Mild	No
Leg weakness:	Severe	Moderate	Mild	No
Decreased sensibility:	Severe	Moderate	Mild	No
Memory deficit:	Severe	Moderate	Mild	No
Tiredness:	Severe	Moderate	Mild	No

Do you want add any further information, please use the box below.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
page 1, line 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
page 3, line 1 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
N/A	2b	All items from the World Health Organization Trial Registration Data Set
page 3, line 1 Protocol version	3	Date and version identifier
page 13, line 7 Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities page 1, line 10	5a	Names, affiliations, and roles of protocol contributors
page 1, line 10 page 13, lines 8	5b	Name and contact information for the trial sponsor
page 10, line 1	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
page 10, line 1	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
page 9, line 1 Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
N/A	6b	Explanation for choice of comparators
page 7, line 10 Objectives	7	Specific objectives or hypotheses
page 1, line 1 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
NA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
page 10, line 1	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
NA		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
page 10, line 21 page 11, lines	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
page 10, line 15	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
page 10 line 15		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
page 10, line 5	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

NA		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
NA	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
NA	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
page 11 line 2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
NA	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
page 11 line 7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
page 11, line 5	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
page 13, line 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
page 10, line 11	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
NA	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
page 11, line 7	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
NA		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019933.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Dec-2017
Complete List of Authors:	Magnusson, Peter; Karolinska Institutet, Cardiology Research Unit, Department of Medicine; Uppsala University, 2. Centre for Research and Development, Uppsala University/Region Gävleborg Koyi, Hirsh; Uppsala University, Centre for Research and Development, Uppsala University/Region Gävleborg Mattsson, Gustav; Uppsala University, Centre for Research and Development, Uppsala University/Region Gävleborg
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE

A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.

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ABSTRACT

Introduction: Atrial fibrillation (AF) causes ischemic stroke and based on risk factor evaluation warrants anticoagulation therapy. In stroke survivors, AF is typically detected with short-term ECG monitoring in the stroke unit. Prolonged continuous ECG monitoring requires substantial resources while insertable cardiac monitors are invasive and costly. Chest and thumb-ECG could provide an alternative for AF detection post-stroke.

The primary objective of our study is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG monitoring in cryptogenic stroke. Secondary objectives are to assesses health-related quality of life (HRQoL) using SF-36 and the feasibility of the Coala Heart Monitor™ in stroke patients.

Methods: Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischemic stroke without documented AF before or during ECG evaluation in the stroke unit will be evaluated by the chest and thumb-ECG system Coala Heart Monitor.™ The monitoring system is connected to a smartphone application which allows for remote monitoring and prompt advice on clinical management. Over a period of 28 days, patients will be monitored twice daily and may activate the ECG recording at symptoms. Upon completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF post-stroke, but the feasibility of this system in patients who recently suffered from a stroke is unknown. In addition HRQoL using SF-36 in comparison to Swedish population norms will be assessed. The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire.

Ethics and dissemination: The study was approved by The Regional Ethical Committee in Uppsala (2017/321) and registered at Clinical Trial Registration NCT03301662.The database will be closed after the last follow-up, followed by statistical analyses, interpretation of results, and dissemination to a scientific journal.

Strengths and limitations of this study

- Chest and thumb-ECG evaluation applied after 24-hour ECG Holter at the stroke unit after confirmation of ischemic stroke.
- Usage of a smartphone application for storage of chest and thumb-ECG which may improve compliance and facilitate fast evaluation by the health-care provider in order to prescribe an anticoagualant when indicated.
- Prospective design including consecutive patients which eliminate both selection and tertiary center bias.
- Management of short (30 seconds) AF episodes, detected by non 12-lead ECG, lack evidence from randomized controlled trials with regard to benefit of anticoagulation.
- The small sample size (n=100) may imply type-II errors in subgroup analyses.

Keywords: atrial fibrillation, cryptogenic stroke, ECG screening, health-related quality of life, SF-36, stroke, thumb-ECG

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolization, but these devastating events can be prevented by anticoagulant therapy.[1] A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred choice and effectively reduce the risk of stroke and mortality.[2] A meta-analysis of the pivotal NOAC trials showed a 19% reduction of stroke/systemic embolism and 10% lower mortality compared to warfarin.[2] If AF is not diagnosed, antiplatelet medication is current practice following a stroke.[3] According to the European Society of Cardiology (ESC), antiplatelet monotherapy should not be considered in the presence of AF, regardless of the stroke risk.[4-6] Stroke is a leading cause of disability and death and is the incidence is increasing due to ageing populations and the growing prevalence risk factors such as diabetes and hypertension.[7-9] At least 20-30% of patients with ischemic stroke have a documented episode of AF before, during, or after the event, but in a quarter of these patients, the stroke is cryptogenic, meaning that no etiologic factor can be determined.[10-12] However, the proportion of cryptogenic stroke from studies varies due to heterogeneity of cohorts and evaluation tools.

Possibilities for AF detection include monitoring in the hospital ward, repeated electrocardiograms (ECG), Holter monitoring, external event or loop recorders, and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yields an AF diagnosis in 8.9% at 6 months and 12.4% at 12 months, but this strategy has not been endorsed in current practice as it requires considerable resources and imply high costs, even though cost-effectiveness has been suggested.[6,13,14] Episodes of AF may be silent, thus not recognized or reported by the patient, but are nevertheless associated with the same risk of embolization.[15-17] In patients with either dual-chamber pacemakers or implantable defibrillators and with

no documented history of AF, 10.1% had episodes of high-rate atrial tachycardia and this was also associated with an increased risk of stroke.[18]

Sequential stratified ECG monitoring detected AF in 24% of stroke patients in one study.[10] The diagnostic yield was 11.5% in a pooled analysis, but this yield varies with such study factors as timing, length of registration, and the monitoring tool.[19] In unselected stroke patients, 24-hour monitoring found AF in only 2.4%.[20] This may vary substantially with the recording technique; in a recent study, AF (defined as ≥ 30 seconds in duration) was detected in 16.1% of patients monitored by an 30-day event-triggered recorder compared to 3.2% of patients monitored by 24-hour ECG.[21] A large multicenter study of stroke patients on Holter monitoring reported new diagnoses of AF in 2.6% of patients at 24 hours and 4.3% at 72 hours.[12] In another study, AF was detected in 8.3% of stroke patients monitored by continuous ECG for a median of 89 hours in the stroke unit; ECG monitoring was superior to 24-hour Holter monitoring in detecting AF.[22]

Thus, while ECG monitoring for an extended period is important for stroke survivors post-discharge Holter monitoring is impractical, ECG data storage is limited, and data interpretation requires considerable resources.Therefore, the thumb-ECG offers advantages in that it monitors conveniently (typically twice daily) and can be activated to capture symptomatic episodes. For example, AF was detected in 11.4% of post-stroke patients monitored by thumb-ECG over 21 days versus 2.8% in those continuously monitored for 48 hours.[23]

The thumb-ECG monitor system Zenicor™ (Zenicor Medical Systems AB, Stockholm, Sweden) has been shown to diagnose previously unknown AF in 3.0% of the general population in Sweden aged 75 years.[24] The Zenicor™ system has been developed

and intregrated into the chest and thumb-ECG Coala Heart Monitor™ (Coala Life AB, Stockholm, Sweden). The monitoring system utilizes a smartphone application which allows for remote monitoring by a clinician. This system may help to evaluate the presence of AF post-stroke. However, feasibility of this system in patients who recently suffered a stroke has not been studied. In addition health-related quality of life (HRQoL) using SF-36 in comparison to Swedish population norms will be assessed.[25,26] The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire (see Supplement).

OBJECTIVES

The primary objective is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG in cryptogenic stroke patients.

The secondary objectives are to assesses HRQoL using SF-36 and the feasibility of the Coala Heart Monitor™ in patients with stroke. 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.

METHODS

Setting and selection

Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified from daily checks of the medical records in the stroke unit. The recruitment is planned to start in October 2017.

Inclusion and exclusion

Patients, aged ≥18 years, with a validated diagnosis of ischemic cryptogenic stroke are eligible for the study. 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] For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor, pregnancy, permanent indication for anticoagulation (including low-molecular weight heparin) due to atrial arrhythmia, mechanical heart valve, deep veinthrombosis, or pulmonary embolism. Patients with a life expectancy ≤6 months (e.g. severe heart failure New York Heart Association [NYHA] functional class IV or malignancy) are likewise excluded.

Variables

Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds. Patients characteristics are age, sex, date of current ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet therapy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral vascular disease, aortic plaque, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from carotid-Doppler, computerized tomography, echocardiography, or transesophageal echocardiography, as well as coagulation laboratory examination.

Outcome measurements

Outcome measurements are arrhythmias recorded by chest and thumb-ECG obtained during scheduled twice-daily recordings or by patient-activated recordings.

Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia, ventricular tachycardia, premature ventricular complex, or supraventricular ventricular complex. The date and time of each episode will be recorded.

Research questions and endpoints

The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.

Secondary endpoints

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

b) Compliance with chest and thumb-ECG at week four (number of recorded scheduled ECG tracings).

c) Patient-reported experience with chest and thumb-ECG measured at week six (questionnaire as Supplement).

d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb-ECG.

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.

Chest and thumb-ECG

Patients will be asked to use the chest and thumb-ECG monitor device twice daily, once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00

p.m. 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.

If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g. sudden onset of tiredness, presyncope, syncope) they are asked to record the episode with the smartphone application. Each patient is monitored for four consecutive weeks, after which the device is returned by mail to the investigators.

Each recording is stored in a web-based application that is accessible to 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.

Power analysis

A power analysis[28] 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. There is likely to be drop-out of patients who are unable or unwilling to meet the monitoring requirements; thus, an estimated 120 patients should be included in order to have 100 patients complete the chest and thumb-ECG evaluation.

Statistics

Descriptive data will be reported as frequencies, percentages, means, and percentiles. Continuous variables are summarized as means, standard deviations, and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for

categorical variables. Kaplan-Meier estimates are used to describe time to event analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical significance is defined as a two-sided *p*-value of <0.05. The data will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for analyses.

Ethics and dissemination

The Regional Ethical Committee in Uppsala approved the study the 20th of September 2017 (protocol number 2017/321). The study protocol, including variables and prespecified research questions, were registered at Clinical Trial Registration NCT03301662 and approved 3rd of October 2017. The documentaton of research data and management of the study follow the Guideline for Good Clinical Practice.[29] Each patient is informed about the study by a physician and nurse and included after written consent. After the study is completed, the database will be closed and followed by statistical analyses, interpretation of results, and dissemination to scientific journals.

DISCUSSION

Since anticoagulation therapy has been proven effective in preventing ischemic stroke in patients with AF, reliable AF detection following cryptogenic stroke is crucial.[6] Hence, prolonged ECG monitoring is reasonable, especially in patients at high risk of embolization. Ischemic stroke risk stratification and the decision to prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of stroke counts for two points, which suffices as a rationale for anticoagulation.[6] The vast majority of stroke patients typically have multiple risk factors, and stroke risk increases with more risk factors.[30] ESC guidelines already allow for prolonged

monitoring of these patients: “In stroke patients, additional ECG monitoring by long-term noninvasive or implanted loop recorders should be considered to document silent atrial fibrillation” (Class IIa recommendation, level of evidence B).[6] However, since the CRYSTAL-AF trial[13], current practice in Sweden remains unchanged with invasive monitoring rarely used for AF detection in stroke patients and still not endorsed by national authorities.[31] The noninvasive thumb-ECG has been advocated in that it provides an alternative and advantageous cost-benefit profile in mass screening.[32] Stroke patients have a higher risk for recurrent stroke and higher incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater benefit in this population.This has yet to be analyzed, and it is our hope that our study will advance the knowledge of thumb-ECG in this population particularly with regard to healthcare economics.

The use of the thumb-ECG has been studied in a Swedish setting for stroke patients, but the study was retrospective, with data gathered at different times after the stroke, and the monitoring method was selected based on the physician’s preference, which implies bias. Our prospective study includes consecutive stroke patients without referral center bias.[33] This will provide a basis to estimate AF incidence over an extended period of 28 days. Continuous Holter monitoring may be associated with poor compliance, technical difficulties,and time-consuming analyses of extensive amounts of data by healthcare providers.[33,34] The newly developed Coala Heart Monitor™ with the proven detection algorithms from Zenicor™ using a smartphone application seem to be a promising alternative, but feasibility remains to be studied. Therefore we added a questionnaire to address feasibility issues.

Although a thumb-ECG may provide an attractive method of noninvasive AF detection, there remain some controversies with regard to anticoagulation for short-

term AF. The potential benefits of anticoagulation therapy for short-term AF would be challenging to study because it would require long-term follow-up, demands a large sample size, and raises ethical concerns about withholding anticoagulation from a stroke survivor. This proposed prospective observational trial of consecutive stroke patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and analyze the clinical feasability of the Coala Heart Monitor.™

Acknowledgements

The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed the manuscript for American English. Ulf Tossman, David Fällman, and Philip Siberg from Coala Life for support regarding the Coala Life Monitor.™

Author contributions

PM: idea, design, project management, and writing of the manuscript. HK: critical revision GM: idea, design, project management, critical revision.

Funding

Region Gävleborg funded this research project and Coala Life provided free product Coala Heart Monitor™ during the study period.

Competing interests

The authors received free product from Coala Life.

Ethics approval

The study was approved by the Regional Ethical committee in Uppsala (Dnr 2017/321).

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Region Gävleborg

TEASE-study, questionnaire

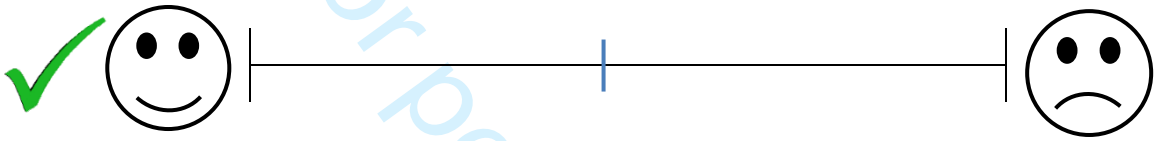
Code ☐☐☐

Name: _____

Personal ID:_____ - _____

Please describe your experience of using the chest- and thumb ECG. Follow the example below to make a clear vertical line.

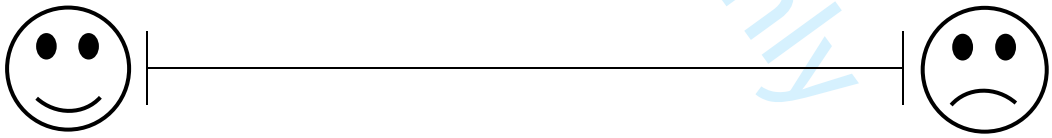
Exemple: **Correct**



Exemple: **Incorrect**

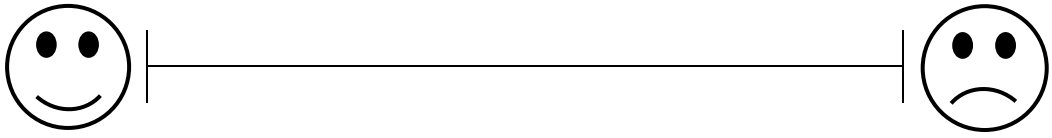
Frågor:

1. In summary, what do you think about the usage of the chest- and thumb ECG?



Very dissatisfied Very unsatisfied

2. How was the technical feasibility of the chest- and thumb ECG?

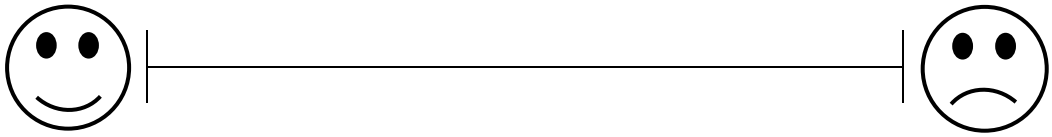


Very easy Very difficult

Region Gävleborg

TEASE-study, questionnaire

3. Did you remember to use the chest- and thumb ECG as scheduled?

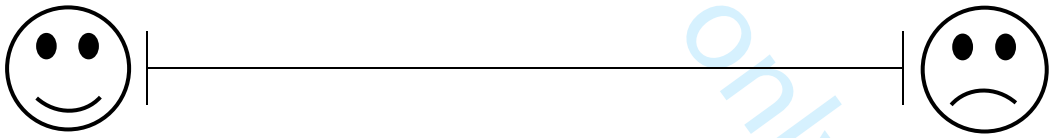


Always Never

4. How was it physically to apply the chest- and thumb ECG?

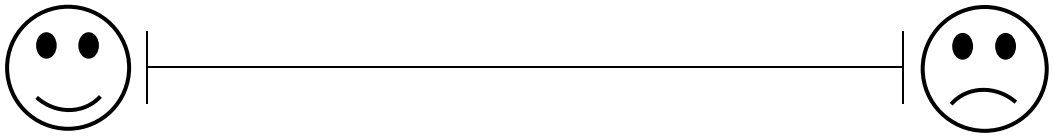
Very easy Very difficult

5. Did the ECG monitoring affect your feeling of security?



Much more secure Much less secure

6. Did you need help from others to perform the ECG-monitoring?

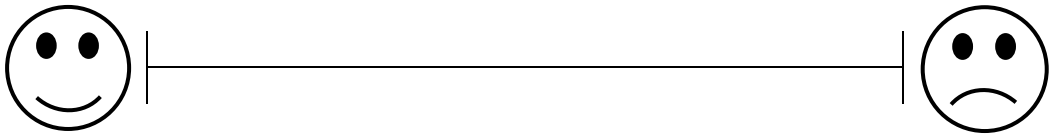


Always needed help Never needed help

Region Gävleborg

TEASE-study, questionnaire

7. Would you recommend other stroke patients to use the chest- and thumb ECG monitoring?



Strongly Not at all

Would you like to add any comment about using the chest- and thumb ECG? Please use the box below.

Region Gävleborg

TEASE-study, questionnaire

What symptoms remain after your stroke? Please underline the alternative that describes this best.

Speech ability impairment:	Severe	Moderate	Mildly	No
Impairment of ability to understand:	Severe	Moderate	Mild	No
Arm weakness:	Severe	Moderate	Mild	No
Leg weakness:	Severe	Moderate	Mild	No
Decreased sensibility:	Severe	Moderate	Mild	No
Memory deficit:	Severe	Moderate	Mild	No
Tiredness:	Severe	Moderate	Mild	No

Do you want add any further information, please use the box below.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
page 1, line 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
page 3, line 1 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
N/A	2b	All items from the World Health Organization Trial Registration Data Set
page 3, line 1 Protocol version	3	Date and version identifier
page 13, line 7 Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities page 1, line 10	5a	Names, affiliations, and roles of protocol contributors
page 1, line 10 page 13, lines 8	5b	Name and contact information for the trial sponsor
page 10, line 1	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
page 10, line 1	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
page 9, line 1 Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
N/A	6b	Explanation for choice of comparators
page 7, line 10 Objectives	7	Specific objectives or hypotheses
page 1, line 1 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
NA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
page 10, line 1	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
NA		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
page 10, line 21 page 11, lines	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
page 10, line 15	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
page 10 line 15		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
page 10, line 5	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

NA		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
NA	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
NA	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
page 11 line 2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
NA	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
page 11 line 7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
page 11, line 5	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
page 13, line 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
page 10, line 11	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
NA	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
page 11, line 7	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
NA		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.