

BMJ Open A protocol for a prospective observational study using chest and thumb ECG: transient ECG assessment in stroke evaluation (TEASE) in Sweden

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ABSTRACT

Introduction Atrial fibrillation (AF) causes ischaemic 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 poststroke. 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 assess health-related quality of life (HRQoL) using short-form health survey (SF-36) and the feasibility of the Coala Heart Monitor in patients who had a stroke.

Methods Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischaemic 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 two times a day and may activate the ECG recording at symptoms. On completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF poststroke, 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). The database will be closed after the last follow-up, followed by statistical analyses, interpretation of results and dissemination to a scientific journal.

Trial registration number NCT03301662; Pre-results.

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolisation, but these devastating events can be prevented by anticoagulant therapy.¹ A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred

Strengths and limitations of this study

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

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 with 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 the incidence is increasing due to ageing populations and the growing prevalence of risk factors such as diabetes and hypertension.^{7–9} At least 20%–30% of patients with ischaemic 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 aetiological 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 on the hospital ward, repeated ECG, Holter monitoring, external event or loop recorders and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yield 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 recognised or reported by the patient, but are nevertheless associated with the same risk of embolisation.^{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 patients who had a stroke 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 s in duration) was detected in 16.1% of patients monitored by a 30 day event-triggered recorder compared with 3.2% of patients monitored by 24-hour ECG.²¹ A large multicentre study of patients who had a stroke 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 patients who had a stroke 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 postdischarge, 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 two times a day) 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 integrated into the chest and thumb ECG Coala Heart Monitor (Coala Life AB, Stockholm, Sweden). The monitoring system uses a smartphone application which allows for remote monitoring by a clinician. This system may help to evaluate the presence of AF poststroke. However, the feasibility of this system in patients who recently suffered a stroke has not been studied. In addition, health-related quality of life (HRQoL) using short-form health survey (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 online supplementary file 1).

OBJECTIVES

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

The secondary objectives are to assess HRQoL using SF-36 and the feasibility of the Coala Heart Monitor in patients who had a stroke. In addition, patients who had a stroke, not eligible for the chest and thumb ECG monitoring, will be analysed with regard to prevalence of previous atrial arrhythmia (including whether they were anticoagulated), cumulative incidence of stroke after 3 years and all-cause mortality after 3 years in patients with AF versus no AF.

METHODS

Setting and selection

Patients with a clinically confirmed diagnosis of ischaemic 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 ischaemic cryptogenic stroke are eligible for the study. Cryptogenic stroke is defined as cerebral ischaemia of unknown aetiology, that is, not attributable to a source of cardiac embolism, large artery atherosclerosis or small artery disease despite a standard vascular, cardiac and serological 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 vein thrombosis or pulmonary embolism. Patients with a life expectancy ≤ 6 months (eg, severe heart failure New York Heart Association 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 s. Patients characteristics are age, sex, date of current ischaemic 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, 12-lead ECG, and when applicable imaging

from carotid-Doppler, CT, echocardiography, or transoesophageal echocardiography, as well as coagulation laboratory examination.

Outcome measurements

Outcome measurements are arrhythmias recorded by chest and thumb ECG obtained during scheduled two times a day 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

- Prevalence of previously known atrial arrhythmia before the inclusion in the study and the number of these patients who had anticoagulant therapy.
- Compliance with chest and thumb ECG at week 4 (number of recorded scheduled ECG tracings).
- Patient-reported experience with chest and thumb ECG measured at week 6 (questionnaire as online supplementary file 1).
- HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb ECG.
- Cumulative incidence of stroke after 3 years in patients with AF versus without AF.
- All-cause mortality after 3 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 two times a day, once between 06:00 and 10:00 hours and again between 18:00 and 22:00 hours. 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 (eg, 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/healthcare 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 analysis²⁸ based on previous research findings and estimation of outcome to 2.4%, 95% CI, width of CI 5%, SD 12% results in a sample size of 89. There is likely to be dropout 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 summarised as means, SDs and percentiles, and t-tests for group comparisons, while χ^2 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) and imported into SPSS V.22 (IBM) for analyses.

Ethics and dissemination

The study protocol, including variables and prespecified research questions, were registered at Clinical Trial Registration NCT03301662 and approved on 3 October 2017. The documentation 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 ischaemic 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 embolisation. Ischaemic 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 patients who had a stroke 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 Cryptogenic Stroke and Underlying AF trial,¹³ current practice in Sweden remains unchanged with invasive monitoring rarely used for AF detection in patients who had a stroke and still not endorsed by national authorities.³¹ The non-invasive thumb ECG has been advocated in that it provides an alternative and advantageous cost-benefit profile in

mass screening.³² Patients who had a stroke have a higher risk for recurrent stroke and higher incidences of AF, so non-invasive thumb ECG monitoring may be of even greater benefit in this population. This has yet to be analysed, 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 patients who had a stroke, 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 centre 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 seems 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 non-invasive 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 analyse the clinical feasibility of the Coala Heart Monitor.

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Competing interests The authors received free product from Coala Life.

Patient consent Not required.

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

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