SØRLANDET SYKEHUS

1 The South-Norway Atrial Fibrillation Screening Study

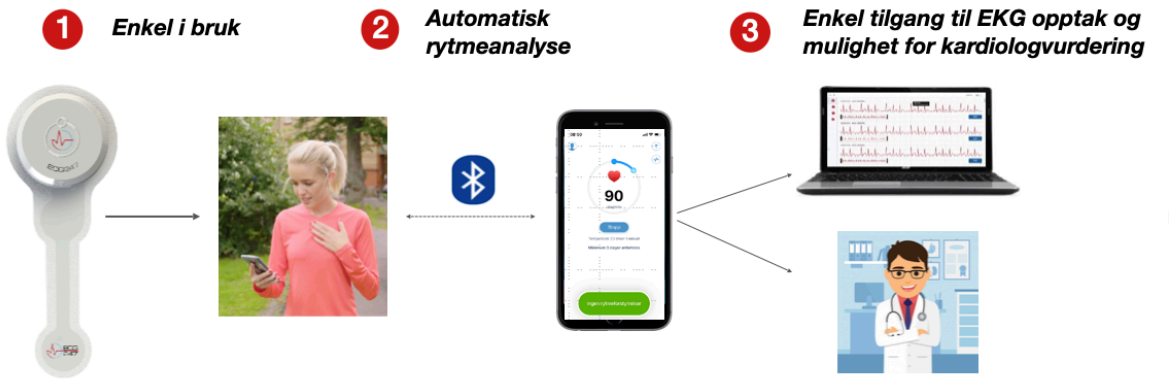
2 Introduction

Arrhythmia is a major health challenge worldwide. Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, affecting approximately 6 million people in Europe, and is an increasing global health care problem.[1-4] AF has been described as at epidemic proportion, with prevalence predicted to triple by 2050.[5] The most serious common complication of AF is arterial thromboembolism, with ischemic stroke as the most clinically evident thromboembolic event.[6-8] AF confers a 5-fold risk of stroke, and 20-30% of all strokes is attributed to this arrhythmia.[7] Anticoagulation therapy effectively reduces the risk of stroke in patients with AF.[9] However, up to one third of AF cases are undiagnosed due to the asymptomatic and intermittent nature of AF (silent AF).[7,10] Screening for silent AF is cost-effective in the population >65 years with an estimated number needed to screen of 70.[11] The European Society of Cardiology recommend opportunistic screening for AF in patients >65 years of age by an ECG rhythm strip.[12] Unfortunately, many patients have a paroxysmal AF not detectable by a single measurement, and pulse taking or a single ECG strip has low sensitivity for paroxysmal AF. Prolonged ECG monitoring enhances the detection of undiagnosed AF.

Ambulatory Holter monitors diagnosing cardiac rhythm disorders, have been a mainstay of clinical practice since the early 60´s.[13] A Holter monitor traditionally records every heartbeat for 24 hours but requires carrying a recording system that is usually worn on a belt or on a holster strap coupled to at least 3 cables attached to monitoring electrodes on the chest and abdomen. Such systems are bulky, difficult to conceal at work/public venues, are not waterproof, and are sensitive to other electric disturbances. The electrodes often disconnect during physical activity or sleep. Event monitors (e.g. Zenicor and Apple watch) as used in the Akershus Cardiac Examinations 1950 Study have limited heart rhythm monitoring time (30 sec).[14] A patch monitor with continuous ECG analysis, however, addresses most of the challenges at Holter systems and event recorders. The ECG247 Smart Heart Sensor is a new Norwegian digital clinical tool for out-of-hospital self-testing of silent atrial fibrillation detection. The innovation project has originated from the University of Agder and Sorlandet Hospital. The concept consists of a disposable one-time-use ECG electrode patch, a re-usable sensor, a medical grade smartphone app and a secure medical back-end cloud service with ECG analysis based on artificial intelligence (figure 1). The system is developed in close collaboration with international experts in cardiology and in wireless ECG technology. The system is ISO13485 and CE (2460) certified according to EU Medical Device Regulation (MEDDEV 2.7/1).

The COVID19 pandemic is realising more than ever the need for single-use self-testing out-of-hospital diagnostic tools. This study may therefore contribute to new innovative ways of conducting medical diagnostics.

Figure 1. The ECG247 atrial fibrillation screening system



2.1 Importance and innovation of the research project

Given that silent AF is common in adults, and AF is a frequent cause of morbidity and mortality, the project will be of importance for a wide range of people and for the community. In patients being diagnosed with AF, treatment with oral anticoagulation could be initiated, reducing the risk of stroke in these patients. By preventing stroke, major personal and socio-economic consequences can be avoided.

The Norwegian developed and produced patch ECG sensor is unique and there are no other medical devices with the same ability for quick, easy and cheap continuous AF screening. As far as we know, there has never been a large-scale AF study screening for AF with a continuous patch ECG recording system.

The study will evaluate a low-cost intervention with the potential to identify patients with silent AF at high risk of getting a stroke. The results will be of interest for a large group of people as well as for health care personnel and the authorities.

3 Hypotheses, aims and objectives

The general aim of this study is to investigate the yield of AF screening with a continuous ECG monitor and to estimate the prevalence of silent AF in a cohort of 65-year-old individuals with additional risk factors for stroke.

We will use our unique collaboration between cardiologists, engineers, general practitioners and user association to address following specific aims**:**

- Aim 1: To assess the quality of the ECG247 Heart Sensor recordings compared to a Holter monitor.
- Aim 2: To investigate the yield of screening for AF by systematic minimum three-day continuous ECG recording
- Aim 3: To determine the prevalence of unknown AF in a cohort of individuals >65 years old from the general population with at least one risk factor for stroke
- Aim 4: To establish predictors for silent AF.
- Aim 5: To investigate the ability and usability of out-of-hospital self-testing of silent atrial fibrillation

4 Project methodology

4.1 Project arrangement, method selection and analyses

4.1.1 Study design

An open non-randomized study

4.1.2 Study population

A total of 1500 people from the general population satisfying the inclusion criteria will be recruited after informed written consent for study participation.

4.1.2.1 Inclusion criteria:

- Men and women
- Age >65 years
- Diabetes, heart failure, hypertension, previous stroke/TIA or other cardiovascular disease (minimum 1 risk factor)
- Informed written consent for participation

4.1.2.2 Exclusion criteria:

- Chronic AF
- Lack of ability to cooperate

4.1.3 Study procedure

A total of 1500 participants meeting the inclusion criteria will be included after informed consent for participation. Recruitment will be done by advertising in newspapers and social medias, and by general practitioners (GP) and cardiologists. The AF screening device can be picked up from pick-up points (e.g. medical centres and outpatient clinics). User guide will be prepared and staff at the pick-up point can assist the test subjects if needed.

All ECG recording will be reviewed by independent and experienced cardiologists. For each investigation, the cardiologists will have to fill in a questionnaire defining the heart rhythm (sinus rhythm, atrial fibrillation, supraventricular tachycardias (SVT), ventricular arrhythmias, SA/AV-block and other arrhythmias). The patch monitor systems have incorporated

algorithms for arrhythmia detections, and after the participant's termination of the test-period, independent cardiologists will evaluate the actual arrhythmia episodes for correctness in the arrhythmia classifications.

A total of 150 study participants will be randomly selected for parallel studies with Holter monitor and ECG247 Smart Heart Sensor.

Participants with clinically significant findings at the ECGs will be offered follow-up according to clinical guidelines at local hospitals, out-of-hospital cardiologists or GP as appropriate.

The test-persons will have to fill in a questionnaire (using Services for sensitive data (TSD) at University of Oslo) after termination of test, focusing symptoms (e.g. palpitations, dyspnoea), lifestyle, (e.g. smoking, physical activity) usability, adverse events and device defencies.

4.1.4 Data handling and storage

Data will be stored de-identified in a secure electronic database (e-CRF) at Sørlandet Hospital, which is responsible for the data protection:

- Study number
- Gender
- Age
- History of heart failure, hypertension, diabetes, heart surgery and coronary heart disease
- History of arrhythmias
- Weight and height
- Smoking status
- Medication (cardiovascular drugs)
- ECG recordings
- Study questionnaire results

4.1.5 Statistical analyses

The size of the study population is a balance between time and financial opportunities, and a desire to identify a high number of individuals with unknown AF. For the estimation of AF prevalence, the Akershus Cardiac Examinations (ACE) 1950 Study was used. The total prevalence of ECG-validated AF after screening among 1742 65-years-olds with risk factors for stroke was 7.6% (95% CI 6.4-8.9).[14] The study used an event recorder and the number of patients with silent AF is expected to be higher with continuous monitoring. Estimated number of participants needed to find an equivalent number of patients with previously unrecognized AF is 1500 individuals.

For comparison with Holter a sample size of 150 is required when a non-inferiority limit of 5% in identification of the heart rhythm is accepted ("success" rate estimated to 98% in both methods, power >80% and significance level 5%).

Continuous and categorical data will be presented using descriptive statistics. Logistic and Poisson regression will be used for identification of risk factors for AF. Appropriate statistical software will be used for analysis.

4.2 Participants, organization and collaborations

The project group includes experts in clinical cardiology and technology with long relevant research experience. Importantly, the research group also includes members with expertise in general practice. A biostatistician will also support the project.

Research group

Name	Title	Institution	Study role and specialty
Jarle Jortveit	MD, PhD	Sørlandet Hospital, Arendal	Project leader and main supervisor. Cardiology
Sigrun Halvorsen	MD, PhD, Professor	Oslo University Hospital & University of Oslo	Co-supervisor. Cardiology
Dan Atar	MD, PhD, Professor	Oslo University Hospital & University of Oslo	Co-supervisor. Cardiology
Gabrielle Danielsen	MD	General practitioner (GP), Grimstad	Sub investigator. General practice
Bjørnar Grenne	MD, PhD	St Olav´s Hospital/NTNU, Trondheim	Sub investigator. Cardiology
Trygve Berge	MD, PhD	Vestre Viken Hospital, Bærum /Norwegian Atrial Fibrillation Research Network	Sub investigator. Cardiology
Jostein Grimsmo	MD, PhD	The National Association for Heart and Lung Disease	User association
Tom R Omdal	MD	Haukeland University Hospital, Bergen	Sub investigator. Cardiology
Rune Fensli	PhD, professor	University of Agder, Grimstad	Sub investigator. Technology

4.3 Budget

- Three years standard grant for a PhD student with ordinary additions for social expenses and project costs – approximately NOK 3 468 000,-
- Medical equipment (ECG recording device) for use in the study – approximately NOK 1 500 000,- . The equipment manufacturer has financial support from Forskningsmobilisering Agder for the study and guarantees the supply of sufficient number of devices.

The funders will have no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the scientific papers.

4.4 Plan for activities, visibility and dissemination

M1, Project approved (REC); M2, Preliminary analyses performed; M3, Last participant included; M4, Thesis and Dissertation (PhD Student).

	2020	2021		2022		2023	
		H1	H2	H1	H2	H1	H2
WP 1 Project Coordination							
T1.1 Project execution	M1						
T1.2 Financial and legal issues							
T1.2 Networking and proposals							
WP 2 Study Conduction							
T2.1 Inclusion of participants				M3			
T2.3 Data handling			M2				
WP 3 Analysis of study data							
T3.1 Finish the Statistical Analysis Plan							
T3.2 Perform analysis							
WP 4 Dissemination, communication and Exploitation							
T4.1 Dissemination of scientific work							
T4.2 Communication with users and patients							
T4.3 Exploitation and innovation action							
T4.4 Thesis and dissertation							M4

Planned publications:

The results of this project will be published in international peer-reviewed journals, with corresponding presentations at scientific meetings.

The following papers are planned:

- Long-term continuous patch ECG recording system compared to Holter monitor in detection of arrhythmias
- Screening for atrial fibrillation using a long-term continuous patch ECG recording system
- Prevalence of unrecognized atrial fibrillation in a population with risk factors for stroke
- Predictors of unrecognized AF in the general population
- Usability of a long-term continuous patch ECG recording system in detection of AF

4.5 Plan for implementation

The goal is to publish the study results within the three-year study period. If the study results indicate that easy-to-use continuous AF-screening-devices designed for self-testing can identify people with previously unrecognized AF, this study may contribute to change the approach to screening for AF in the community. Consequently, the study may prevent stroke in the future.

The results from the study may also contribute to improved interaction between the specialist health care and the primary care physician in treatment of patients with AF, and patients at risk of developing AF and stroke.

The study results will be published in international scientific journals and have possibility to influence new European guidelines. The results will also be of great interest for national and international patient organizations.

5 User involvement

- Patients: Participants who participate in the project will be consulted by a co-worker in the project group and their feedback will be used to adjust the study procedure and the project outline. A Participant Advisory Committee consisting of three participants will be established. The committee will contribute to evaluation of the practical performance of the project and modifications of it within the protocol frames.
- Patient organizations: The users represented by the patient organization The National Association for Heart and Lung Disease have been active in the development of the research protocol and will contribute throughout the project to ensure appropriate application of research results.
- General population: Communication to the general population about the results from the project. The patient organization will use their broad network to disseminate the results from the project both in Norway and internationally.
- Health personnel and students: Results will be implemented in lectures for medical students, nurses and residents within the field of cardiology.
- Health authorities: Knowledge derived from our project may be used as a basis for new National Guidelines.

6 Ethical considerations

Participation in the study will depend on informed consent by the participants. Participation is voluntarily, and the participant´s decision will not influence further treatment. A request for approval by the Regional Committee for Medical and Health Research Ethics has been submitted.

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