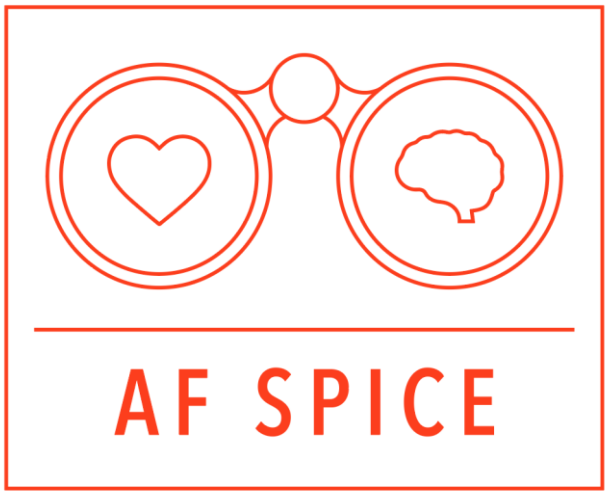

A multicenter, national, investigator-initiated, randomized, parallel-group, register based study to Compare Extended ECG monitoring Versus Standard ECG Monitoring in Elderly Patients with Ischemic Stroke or TIA.

Study protocol

Version 2.0

27 Apr 2023

AGREEMENT TO THE PROTOCOL

The investigator agrees to conduct the study as outlined in this protocol in accordance with Good Clinical Practice (ICH-GCP, https://ich.org/page/search-index-ich-guidelines) and in acoordance with the declaration of Helsinki (19): Ethical Principles for Medical Research Involving Human Subjects.

The investigator agrees, by written consent to this protocol, to fully co-operate and allowing direct access to all documentation, including source data, by regulatory authorities.

Significant changes to the protocol will be done after approval from the Swedish Ethical Review Authority.

Approved consent in writing:

Signature: 

Date: 2023-04-27

Associate professor Johan Engdahl

Sponsor, Chief Investigator

Signature:

_____ Date: _____

Local Principal Investigator

Contents

1. Trial Registration

ClinicalTrials.gov NCT05134454

2. List of abbreviations and definitions

ACE	Angiotensin Converting Enzyme
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blocker
CCB	Calcium Channel Blockers
COPD	Chronic Obstructive Pulmonary Disease
ECG	ElectroCardioGram
eGFR	estimated Glomerular Filtration Rate
GCP	Good Clincal Practice
ICD	Implantable Cardioverter Defibrillator
ICM	Insertable Cardiac Monitor
OAC	Oral Anticoagulation
PI	Principal Investigator
SmPC	Summary of product characteristics
TIA	Transitory Ischemic Attack

3. Funding

AF SPICE is funded by grants from the Swedish Research Council, the Swedish Heart & Lung Foundation, the Swedish Stroke Foundation and the Stockholm Region (ALF).

4. Roles & Responsibilities

Johan Engdahl conceived of the study and drafted the protocol. Per Wester, Kajsa Strååt, Signild Åsberg, Marie Eriksson and Eva Isaksson contributed to study design. Power calculation was performed by Karolinska Institutet Biostatics Core Facility. AF SPICE is conducted in collaboration with the Swedish Riksstroke register.

Contributor	Affiliation
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4.2 Sponsor and Funder

This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

5. Background

Ischemic stroke is one of the leading causes of mortality worldwide, and a major cause behind permanent disability in adults[1]. Despite implementation of novel treatment strategies during the latest decade, morbidity and mortality remain significant. Recurrent episodes of stroke are prevalent, despite improvement in secondary prophylaxis.

Risk factors for stroke include age, hypertension, atrial fibrillation, smoking and diabetes[2 3]. Several of these risk factors for stroke have the potential of being undetected for a long time since they in many instances are asymptomatic.

During 2019 the stroke incidence in Sweden was 349 per 100 000 and the mortality 74 per 100 000 inhabitants. In Sweden, stroke is predominantly a disease of the elderly with 74% being 70 years or older. This is not the case globally, with 2/3 of strokes occur among persons <70 years of age. Age-specific incident rates are higher in males. From 2005 to 2018, the incidence decreased in both men and women (from 293 to 223 per 100 000 men, and from 278 to 191 per 100 000 women). As a result of the larger relative decrease in women ($P<0.001$), the proportion of men in the stroke population increased from 50.9% in 2005 to 54.2% in 2018[4]. Mortality has only marginally decreased the last 15 years.

In addition to human suffering, the economic and societal burden of the disease is significant. Disability with need for long-term care and in younger patients impaired work ability entails enormous societal costs[5]. Cost-effective analyses have been made to improve the secondary prophylactic treatment and investigation after a first stroke.

Atrial fibrillation (AF) is the most prevalent permanent clinically relevant arrhythmia with a steeply increasing incidence with advancing age[6]. AF is also one of the strongest risk factors for stroke[3]. However, the increased stroke risk associated with AF can be markedly reduced by oral OAC treatment[7].

Unfortunately, AF is paroxysmal and asymptomatic in a significant proportion of stroke patients, leading to lower detection rates and a similar proportion of stroke survivors with an untreated risk factor and higher risk of stroke recurrence. Despite this, no study so far has been reported to bring evidence to the benefit of ECG AF screening in terms of reduced stroke recurrence and mortality after a stroke event.

A German multicenter study comparing 72-hour Holter with standard 24-hour workup showed an increase in AF detection from 2.9% to 4.3%[8].

Table 1 Society recommendations summary			
Society	Recommendation Summary	Year	Ref
European Stroke Organisation	In adult patients with ischaemic stroke or TIA of undetermined origin, we recommend longer duration of cardiac rhythm monitoring of more than 48 h and if feasible with ILR to increase the detection of subclinical AF.	2022	19
American Heart Association/American Stroke Association	Long-term rhythm monitoring with mobile cardiac outpatient telemetry, implantable loop recorder, or other approach is reasonable to detect intermittent AF	2021	17
European Society of Cardiology	Short-term ECG recording for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible. Long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF.	2020	16
Swedish board of health and welfare	Health care should provide long-term ECG for 24-48 h. long-term ECG for more than 48 h duration using Holter recording or inpatient telemetry ECG in selected cases.	2020	
NICE	Reveal LINQ is recommended as an option to help to detect atrial fibrillation after cryptogenic stroke only if: non-invasive electrocardiogram (ECG) monitoring has been done and a cardiac arrhythmic cause of stroke is still suspected.	2020	13
Canadian Cardiovascular Society/Canadian Heart Rhythm Society	At least 24 hours of ambulatory ECG monitoring to identify AF in patients with nonlacunar ESUS. Additional monitoring for AF detection (eg, prolonged external loop recorder or implantable cardiac monitoring, where available) be performed for selected older patients with nonlacunar ESUS in whom AF is suspected but unproven	2020	14
National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand	For patients with Embolic Stroke of Uncertain Source, longer term ECG monitoring (external or implantable) should be used.	2018	15
Royal College of Physicians	A. People with ischaemic stroke or TIA should undergo a period of prolonged (at least 12 hours) cardiac monitoring. B. Prolonged ECG monitoring (24 hours or longer), particularly if they have a pattern of cerebral ischaemia on brain imaging suggestive of cardioembolism.	2016	18

Randomised controlled trials (CRYSTAL-AF[9] and EMBRACE[10]) have shown that prolonged ECG-monitoring (insertable cardiac monitor and 30-day event-triggered loop recorder respectively) compared to standard of care (at the time 24 hr-ECG) increased detection of atrial fibrillation in cryptogenic stroke patients.

The FIND-AF$_{randomised}$ trial[11] also presented increased detection of atrial fibrillation and included a broader group of participants suggesting that prolonged ECG-monitoring should be used in all ischemic stroke patients if detection of atrial fibrillation would lead to anticoagulation therapy.

The MonDAfis study[12] was powered to evaluate the proportion of anticoagulation therapy 12 months after index stroke. Standard of care was compared to prolonged in hospital ECG-monitoring (maximum 7 days). Atrial fibrillation detection was increased in the intervention group, but this had no significant effect on the rate of anticoagulation therapy at 12 months.

AF screening post an ischemic stroke event is currently recommended by all major international societies[13-19] (table 1). The recommendations vary markedly with respect to method of screening and duration of screening, which probably reflects the lack of trials with stroke and mortality as endpoints. There are however a body of data on the proportion of AF detection using different monitoring strategies.

The development of ECG modalities and clinical practice for AF screening post ischemic stroke and TIA have evolved towards longer and more resource demanding investigations, despite the lack of data on hard clinical endpoints. Diversity within recommendations have promoted unequal care even within countries and regions. With this background, there is an urgent need for a randomized trial to investigate the efficacy of AF screening post ischemic stroke.

5.1 Choice of comparators

In many of the recommendations on AF screening post ischemic stroke from international societies, a monitoring duration of at least 24 hours of continuous ECG is recommended. In the recommendations from the Swedish Board of Health and Welfare, continuous ECG monitoring of 24-48 hours is recommended as the baseline investigation for most ischemic stroke patients, and a large share of stroke units in Sweden adhere to this recommendation. Its selection as comparator is therefore justified.

6. Study objectives

6.1 Primary Objective

To determine if extended continuous ECG screening (14+14 days) is superior to standard ECG screening (1-2 days) in the combined endpoint of stroke, death and intracranial bleeding in elderly patients with admitted for ischemic stroke or TIA.

6.2 Key Secondary Objectives

The key secondary objectives are to estimate the treatment effect in primary outcome, and determine if there are any differences between extended and standard ECG screening for:

- Ischemic stroke
- All-cause mortality

- Intracranial bleeding
- Major bleeding
- Myocardial infarction
- Pacemaker implantation
- Cost effectiveness

6.3 Other Secondary Objectives

- To study association between age and AF detection
- To study the proportion of other relevant arrhythmias detected at ECG screening
- To study predictors for AF detection
- To study signal time and signal quality achieved at ECG screening
- To study long-term adherence to OAC treatment
- To study feasibility of patients or their next-of-kin application of the second ECG patch
- To study Patient Reported Experience (PREM), collected 3 months after inclusion in the main trial
- Per protocol analysis of the primary outcome
- Win ratio analysis

7. Trial design

AF SPICE is designed as a randomized, controlled, multicenter, open-label, national, register-based study to compare two parallel groups; extended ECG monitoring (14+14 days) versus standard ECG monitoring (24-48h) in patients aged at least 70 years and admitted for ischemic stroke or TIA with the combined endpoint of recurrent stroke, all-cause mortality and intracerebral bleeding.

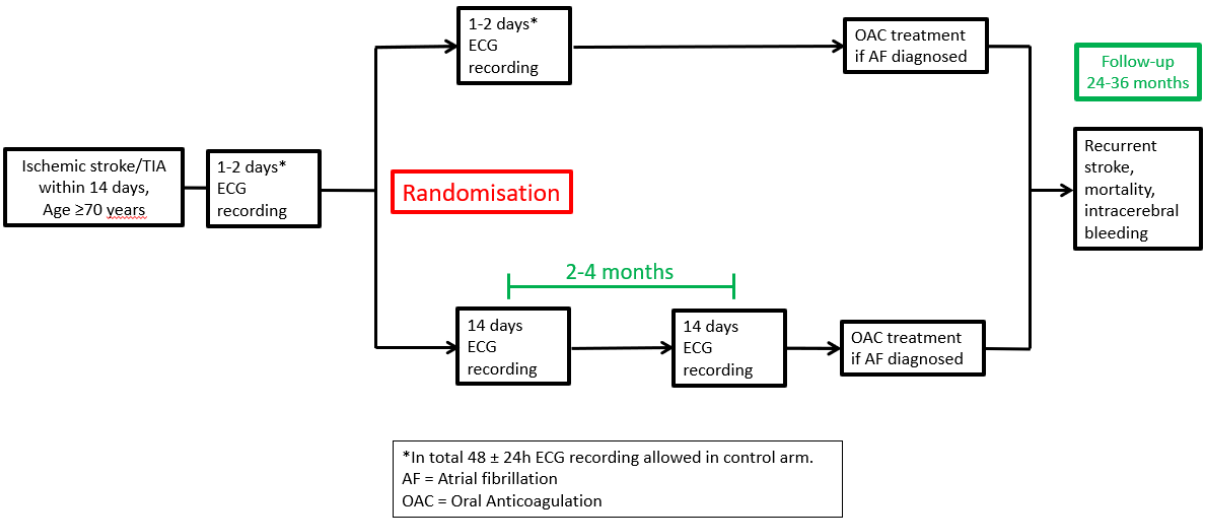

Figure 1 Trial design

8. Study setting

AF SPICE will recruit participants among admissions to stroke units in Swedish hospitals. Inclusion is also possible from non-stroke units given that they are admitted for ischemic stroke or TIA and identified by the sites PI or delegate.

A pilot study with patient inclusion from 4-6 sites started January 2022. The pilot study will evaluate inclusion rates, feasibility and adherence to ECG recorders and the administration and randomisation system. The pilot study is planned to include 300 patients and to be concluded in Q4 2022, and January 2023 will be the starting point for the main trial. During the pilot trial, the ECG investigation practice in Swedish stroke units will be investigated and the remaining sites for the main trial recruited. A list of the sites currently recruiting is available in Appendix 2.

9. Eligibility criteria

9.1 Inclusion criteria

1. Patients aged ≥ 70 years admitted with a diagnosis of ischemic stroke or TIA within 14 days from inclusion.
2. Signed informed consent.

9.2 Exclusion criteria

1. Previously diagnosed atrial fibrillation
2. Contraindication to oral anticoagulant treatment according to SmPC.
3. Indication for anticoagulant treatment other than atrial fibrillation, e.g. venous thromboembolism or mechanical heart valve prosthesis
4. Patients with pacemaker, ICD or ICM.
5. Patients who, according to the investigator, will not be able to comply with the study protocol.
6. Previous participation in the AF SPICE study

9.3 Withdrawal of patients

A patient can withdraw from the study at any time, at the discretion of the patient, or by the investigator if deemed medically indicated. If a participant refrain from completing extended ECG recording protocol, he/she will remain included in study and in the intention-to-screen data analysis. A withdrawal of consent means that no further study data will be collected, however already collected data will not be erased.

9.4 Patient log and screening of patients

All patients signing informed consent will be listed in a written log at each participating site. The log should contain personal identification number, full name, ECG device ID for patients in the intervention arm and CRF number.

11. Interventions

11.1 Extended ECG Investigation

Participants randomised to extended ECG investigation will undergo a continuous one-lead ECG-recording using the BioTel ePatch (https://www.biotel.se). The BioTel ePatch is a class IIa CE-marked Holter ECG recorder using a skin-friendly patch for skin adhesion. The ECG electrodes are embedded in the patch.

The ePatch should be applied by health care professionals at the stroke unit (visit 1) according to the manufacturer's recommendation and as soon as possible after randomisation.

The participant should be informed verbally and in writing on the limitations connected to the patch investigation, i.e. shower spray on the device or submersion into water. After completion of the 14-day ECG recording, the device should be removed by the participant or by next of kin and returned to the core facility using an envelope provided at attachment of the device. The device will then return to the BioTel core facility and uploaded to a web-accessed interpretation service (Cardiologs, https://cardiologs.com/) within 1 working day from arrival by mail.

During visit 2, participants not diagnosed with AF will have the second ePatch attached by health care professionals in connection to a scheduled follow-up visit.

The ECG recordings will be scrutinised by a core ECG reading team led by the PI.

11.1.1 Notifications following extended ECG recording

When participants are diagnosed with a new AF according to the current definition of the ESC AF guidelines, the local investigator will be notified within one working day by phone and email by the ECG reading team.

When participants are diagnosed with other arrhythmias with a prognostic implication as defined in table 2 below, the local investigator will be notified within three working days and email by the ECG reading team. If a more rapid action is deemed necessary by the ECG reading team, appropriate measures such as contacting the local investigator or delegate by phone should be undertaken.

If no AF or other prognostic arrhythmia are diagnosed after visit 1 and visit 2, participants will be notified by letter after both visits.

11.1.2 Signal quality in extended ECG recording

If the signal quality of the extended ECG recording is deemed to be of insufficient quality, the participant should be offered another attempt of patch ECG recording if possible. If this second recording have insufficient signal quality as well or if it is not possible to arrange for another patch ECG recording, a traditional Holter recording or

ECG event recording could be used as a substitute. However, it is of importance for the power of the study to achieve as long ECG recordings as possible in the intervention group. Hence, in a situation where patch ECG is not possible to perform for whatever reason, a continuous event loop recording be the first option, preferably with 14 days´duration.

At least 7 days of ECG recording should be yielded from ECG patch in connection with visit one. If less than 7 days are recorded, another recording should be offered the participant. The same minimum ECG duration of 7 days applies for ECG recording at visit 2.

If a participant randomized to intervention arm with a negative ECG recording (i.e no atrial fibrillation detected) suffers a recurrent ischemic stroke within 2 months from visit one, the second ECG patch recording (visit 2) may be started earlier than 2 months to the discretion of the local PI.

11.1.3 Initiation of OAC treatment following extended ECG recording

Patients newly diagnosed with atrial fibrillation during the long-term ECG recordings initiated in connection to randomisation should be informed by the local investigator or delegate and offered treatment with oral anticoagulation if there are no contraindications, based on the stroke risk of at least CHA_2DS_2-VASc 2 points in randomised patients.

Treatment with OAC and its long-term follow-up will be handled within standard care and according to national and international guidelines.

OAC treatment should be initiated within five working days from the reception of long-term ECG results. Long-term follow-up of OAC treatment will be using the national drug prescription registry.

All other treatments and investigations will be at the discretion of the local investigator.

Table 2. Prognostic ECG findings on extended ECG recording which should be communicated to the local investigator.
Ventricular tachycardia
Excessive ventricular extrasystoles (> 5%)
Pause > 3 seconds
AV-block type II and III
Bradycardia < 40/minute

Table 3. Members of the ECG reading team		
Name	**Title**	**Affiliation**
Christer Wredlert	Technician	Karolinska Hospital
Kajsa Stråât	MD	Danderyd Hospital
Johan Engdahl	MD	Danderyd Hospital
Adriano Atterman	MD	St Göran Hospital
Sara Själander	MD	Sundsvall Hospital

11.2 Standard care

Participants randomised to standard care should undergo 48 ±24 hours of continuous ECG monitoring, using inpatient ECG telemetry monitoring or Holter recording. The duration of the ECG recording/monitoring should be recorded by the site and noted in the eCRF.

The study will not collect any data from the standard recordings apart from the duration and containment of AF. ECG recordings of newly diagnosed AF in the standard care arm should be collected and stored by the study.

12. Outcomes

12.1 Primary outcome

Difference between the two arms in a combined endpoint of recurrent ischemic stroke, intracerebral bleeding, and all-cause mortality during at least 36 months of follow-up.

12.2 Secondary endpoints

- Individual components of the primary endpoint
- Major bleeding including Intracranial bleeding
- Myocardial infarction
- Pacemaker implantation

13. Participant timeline

13.1 Intervention arm

Participants will be screened and asked for consent during admission for ischemic stroke or TIA, within 14 days from admission. ECG investigation of 24-48h prior to randomization is allowed. For patients randomized to the intervention arm, the first 14-day ECG recording is typically commenced before discharge, and at the latest . Additional extended ECG recordings added to the first one due to shortage of analyzable ECG signal duration in the intervention arm are allowed after discharge according to 11.1. Following completion of second 14-day ECG recording, no further personal visits are made in the study.

13.2 Standard arm

Participants will be screened and asked for consent during admission for ischemic stroke or TIA, within 14 days from admission. ECG investigation of 24-48h prior to randomization is allowed. Starting or completing the ECG recording in the standard arm following discharge is allowed. The ECG recording should be performed within 3 months in this case. Following completion of the ECG investigation initiated in the standard arm, no further personal visits are made in the study.

14. Sample size

The sample size was calculated on the basis of the primary hypothesis.

The event rate of recurrent stroke, all-cause mortality and intracerebral bleeding was estimated in patients admitted for ischemic stroke or TIA. Event rate was estimated in patients with AF with and without OAC treatment and in patients without AF. A complete list of studies used for estimations in the sample size calculation is reported in appendix 4. Most studies used in this estimation reported data from patient cohorts with a lower age than expected in the AF SPICE trial. This could lead to an underestimation of event rates. Recent publications on AF status and outcomes in stroke patients in the projected age group is not available at the time of study start.

For the estimations of AF detection proportions, available studies on short-term (1-2 days) ECG recording following stroke and corresponding studies on long-term (14 days) recordings were used. A list of the AF detection studies available for this estimation is reported in appendix 5.

We estimate an AF detection proportion of 6% in the control group and 19% after two ECG recordings in the intervention group, which result in a sample size of 2718 for three years of fixed follow-up time after inclusion. Adding 20% for participant dropouts and treatment discontinuation, a total sample size of 3262 is needed, corresponding to 1631 in each arm based on three years follow-up, 80% power and double-sided significance level of 5%.

The following assumptions were applied in the sample size calculation:

Endpoint* risk in patients with AF and OAC treatment	**7,3%**
Endpoint risk in patients with AF and no OAC treatment	**17,7%**
Endpoint risk in patients without AF	**5%**
AF detection proportion in standard arm	**6%**
AF detection proportion in intervention arm	**19%**

*Endpoint including recurrent stroke, death, and intracranial bleeding.

Table 3. The total sample sample size as a function of proportion of patients with AF based on a yearly endpoint risk of 5% in patients without AF.

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.1	8536	11504	16400	25370	44652	99460	393830	-	-	-
0.11	6628	8572	11552	16470	25480	44848	99900	395590	-	-
0.12	5310	6654	8608	11600	16542	25590	45044	100340	397348	-
0.13	4360	5332	6682	8644	11650	16612	25700	45240	100780	399108
0.14	3652	4378	5352	6710	8680	11698	16682	25810	45436	101220
0.15	3110	3668	4396	5374	6738	8716	11748	16752	25922	45630
0.16	2686	3124	3682	4412	5396	6764	8752	11796	16824	26032
0.17	2346	2696	3136	3696	4430	5418	6792	8788	11846	16894
0.18	2072	2356	2708	3148	3710	4448	5440	6820	8824	11894
0.19	1844	2080	2364	2718	3160	3726	4466	5462	6848	8860
0.2	1654	1850	2086	2374	2728	3172	3740	4484	5484	6876

Proportion of patients with AF in the control group in columns, proportion of patients with AF in the intervention group in rows.

The complete sample size calculation is provided as Appendix 6.

15. Recruitment

Patients will be screened and included during stroke or TIA admissions, the majority of patients will be included in stroke units. Participating centres report ay least 200 stroke/TIA admissions yearly. With an anticipated participation of 30 sites, they need to randomize 1.1 patients weekly during two year of inclusion to fulfil the recruitment target of 3262 participants.

Patients will be screened and identified by the PI or delegate, and formally included by the PI or delegate with written permission.

16. Allocation

Participants will be randomly assigned to either control or intervention group with a 1:1 allocation as per a computer-generated randomization schedule stratified by site in the online REDCap database. The randomization code is not available until all baseline measures have been completed. Randomization will be requested by the staff member responsible for recruitment without having any insight into group allocation.

17. Blinding

Due to the nature of the intervention, neither participants nor staff will be blinded to allocation.

18. Data collection methods

18.1 Primary Outcome

The study is a randomized register-based study, primary endpoints and some baseline variables are collected from Swedish health care registers.

Primary outcome is a composite of three variables:

Variable	Coding	Source	Validity
Ischemic stroke	I63	Riksstroke	High
Stroke not specified	I64	Riksstroke	High
All-cause mortality	N/A	National register of death	Very high
Intracerebral bleeding (spontaneous)	I61	Riksstroke	High

18.2 Secondary and exploratory outcomes

Variable	Coding		Source
Myocardial infarction	I21, I22, I25.2		National inpatient register
Other Vascular Disease	I70-I74, I77-I79		
Heart Failure	I50		
Major bleeding	Gastrointestinal bleeding	K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920, K921, K922, I850, I983	
	Urogenital bleeding	N02, R319, N939, N950, N501A	
	Other bleeding	H113, H313, H356, H431, H450, H922, I312, J942, M250, R04, R58, T810, D500, D629, T792	
	Sub-, epidural and subarachnoid haemorrhages (incl traumatic)	I60, I61, I62, S064, S065, S066	
	Procedure codes for transfusion	DR029, DR033, Z513	
Atrial fibrillation/flutter	I48		
Pacemaker implantation	FPE00, FPE10, FPE20, FPE26		
OAC and antiplatelet treatment, NSAID	B01A, N02BA, M01A		National drug dispense register

18.3 Retention

At the majority of including sites, the second visit for the intervention group coincides with a outpatient follow-up visit after stroke, which will give the participant a strong motivation for attending the visit.

19. Data Collection

19.1.1 Baseline data entered at inclusion all participants

The following data are entered at baseline in **all participants**:

Variable	**Unit**
Record ID (automatically generated)	
Sex	Male/Female
Date of birth	Date
Social Security Number	Special format
Date of Stroke/TIA	Date
Age	Years
Height	cm
Weight	kg
Hemoglobin	g/l
Estimated GFR	ml/min
Site identification	Selection from list
Consent Date	Date
Randomization date	Date

19.1.2 Baseline data entered at inclusion standard care

The following data are entered at baseline in participants randomized to **standard care**:

Variable	**Unit**
ECG Telemetry used	Yes/No
Duration of ECG Telemetry	Hours
AF diagnosed during ECG Telemetry	Yes/No
Holter Recording used	Yes/No
Duration of Holter Recording	Hours
AF diagnosed during Holter	Yes/No

19.1.3 Baseline data entered at inclusion intervention arm

The following data are entered at baseline in participants randomized to **intervention arm**:

Variable	**Unit**
ePatch number 1 serial number	Integer
Date epatch number 1 recording start	Date
Additional epatch number 1 serial number	Integer
Site of application additional epatch number 1	Health care/self-application
Date for mailing out additional epatch number 1	Date
Date additional epatch number 1 recording start	Date
Reason for additional epatch	1. epatch detachment 2. Red light indicated 3. Poor signal quality 4. MRI examination 5. Other radiology 6. Thoracic/neck surgery 7. Other reason
Additional epatch number 1 serial number	Integer
Site of application additional epatch number 1	Health care/self-application
Date for mailing out additional epatch number 1	Date
Date additional epatch number 1 recording start	Date
Reason for additional epatch number 1	1. epatch detachment 2. Red light indicated 3. Poor signal quality 4. MRI examination 5. Other radiology 6. Thoracic/neck surgery 7. Other reason
Mode of application epatch number 2	Health care/self-application
Date for mailing of epatch number 2 to participant	Date
Date of application epatch number 2	Date
Epatch number 2 serial number	Integer
First additional epatch number 2 serial number	Integer
Mode of application first additional epatch number 2	Health care/self-application
Date for mailing of first additional epatch number 2 to participant	Date
Date of application of first additional epatch number 2	
Reason for first additional epatch number 2	1. epatch detachment 2. Red light indicated 3. Poor signal quality 4. MRI examination 5. Other radiology 6. Thoracic/neck surgery

	7. Other reason
Second additional epatch number 2 serial number	Integer
Mode of application second additional epatch number 2	Health care/self-application
Date for mailing of second additional epatch number 2 to participant	Date
Date of application of second additional epatch number 2	
Reason for second additional epatch number 2	1. epatch detachment 2. Red light indicated 3. Poor signal quality 4. MRI examination 5. Other radiology 6. Thoracic/neck surgery 7. Other reason
Reason for not recording epatch number 2	1. Diagnosed with AF on epatch number 1 2. Participant declines recording 3. Participant decline further participation 4. Other reason

19.2 Baseline data entered at inclusion

Baseline data from Riksstroke are listed in Appendix 3.

19.3 ECG data

There are different ECG variables for the control and intervention arms.

1. In the control arm, the PI or delegate record if ECG was recorded using ECG telemetry and/or Holter recording and the duration of each recording, and whether AF was diagnosed. ECG variables for the standard arm are listed in 19.1.2.

2. In the intervention arm, ECG data from patch recordings are stored in the patch hardware and returned by the participant using a pre-stamped envelope. Data from patch hardware are uploaded my the patch provider into the Cardiologs database. Using the Cardiologs system, patch ECG data are scrutinized by the core reading team which also enter ECG data manually into the REDCap database. In the case of insufficient amount of analyzable ECG signal time (<7 days), additional ECG patches will be offered to the participant and the reason should be entered into the REDCap database.

For the second ECG patch recording initiated 2-4 months following randomization, data is collected on whether the patch is applied within health care or by the participant. Reasons for not performing the second ECG patch recording are collected.

The following ECG variables data are collected in the intervention group:

Patch number 1	
Variable	**Unit**
Date for ECG data upload in Cardiologs	Date
Date for ECG reading	Date
Date for first additional ECG data upload in Cardiologs	Date
Date for first additional ECG reading	Date
Date for second additional ECG data upload in Cardiologs	Date
Date for second additional ECG reading	Date
Monitoring time	Hours
Analyzable time	Hours
Heart rate max	Bpm
Heart rate min	Bpm
Heart rate mean	Bpm
Proportion supraventricular ectopics	Percent
Proportion ventricular ectopics	Percent
Number of pauses > 2 seconds	Integer
Longest pause	Seconds, one decimal
AV-block II or III	Yes/No
Highest AV-block grade	1. AV-block II type 1 2. AV-block II type 2 3. AV-block III
Atrial fibrillation	Yes/No
Atrial flutter	Yes/No
Atrial fibrillation/flutter subtype	1. Paroxysmal 2. Persistant
Atrial fibrillation/ flutter heart rate max	Bpm
Atrial fibrillation/ flutter heart rate mean	Bpm
Atrial fibrillation/ flutter burden	Percent
Atrial fibrillation/ flutter longest episode	Seconds
Number of Ventricular Tachycardia (VT)	n
Duration longest episode VT	Seconds
Number of Suptraventricular Tachycardia (SVT)	n
Duration longest episode SVT	Seconds
Proportion of noise	Percent
Action triggered by recording	1. Standard statement 2. Communication with local PI within 3 working days 3. Communication with local PI within one working day 4. Further assessment following patch number 2

Patch number 2	
Variable	**Unit**
Date for ECG data upload in Cardiologs	Date
Date for ECG reading	Date
Date for first additional ECG data upload in Cardiologs	Date
Date for first additional ECG reading	Date
Date for second additional ECG data upload in Cardiologs	Date
Date for second additional ECG reading	Date
Monitoring time	Hours
Analyzable time	Hours
Heart rate max	Bpm
Heart rate min	Bpm
Heart rate mean	Bpm
Proportion supraventricular ectopics	Percent
Proportion ventricular ectopics	Percent
Number of pauses > 2 seconds	Integer
Longest pause	Seconds, one decimal
AV-block II or III	Yes/No
Highest AV-block grade	1. AV-block II type 1 2. AV-block II type 2 3. AV-block III
Atrial fibrillation	Yes/No
Atrial flutter	Yes/No
Atrial fibrillation/flutter subtype	1. Paroxysmal 2. Persistant
Atrial fibrillation/ flutter heart rate max	Bpm
Atrial fibrillation/ flutter heart rate mean	Bpm
Atrial fibrillation/ flutter burden	Percent
Atrial fibrillation/ flutter longest episode	Seconds
Number of Ventricular Tachycardia (VT)	n
Duration longest episode VT	Seconds
Number of Suptraventricular Tachycardia (SVT)	n
Duration longest episode SVT	Seconds
Proportion of noise	Percent
Action triggered by recording	1. Standard statement 2. Communication with local PI within 3 working days 3. Communication with local PI within one working day 4. Further assessment following patch number 2

19.4 Security and back-up of data

Access to the study REDCap database is restricted by passwords and IDs generated by Karolinska Institutet or SUNET edu-ID. Access to the entire database is restricted to the Chief investigator and the project managers. A complete back-up of the REDCap database is made weekly onto external hardware storage. The hardware copy is stored in a locked cabinet.

ECG data from the ECG patches in the intervention arm will be stored both as decoded recordings in the Cardiologs system archive, and as raw data (*.EFS-files) regularly transferred by the patch ECG provider. These files are stored in a storage with restricted access at the Health Care providers network and on an external hardware back-up.

Record IDs are automatically generated by the REDCap system. Numerical values entered by PI or delegate are checked for format and expected range. Categorical and dichotomous variables are entered by multiple choice forms. Forms in REDCap has to be completed before randomization can be performed. Date input are chosen from calendar input. REDCap forms are locked following data input and could only be unlocked and edited by administrator privileges. Completion of a form is color-coded and easily overviewed in REDCap.

The investigator will keep records for at least ten years from study start.

20. Statistical Methods

The primary objective of the study is to evaluate the risk of recurrent stroke, death and intracranial bleeding in patients investigated using an extended ECG recording following ischemic stroke/TIA as compared to standard of care defined as the current Swedish national guidelines on stroke care.

The primary outcome (a composite of recurrent stroke, death and intracranial bleeding) will only be analysed under the intention to treat-principle. The primary hypothesis will be tested using Log-rank test.

The cumulative incidence risk of the composite outcome in the treatment and control groups would be calculated using the Kaplan-Meier approach. The Cox hazard regressions would be used to estimate the hazard ratios of all-cause mortality of treatment group compared to the control group. The competing risk analyses would be applied to estimate the sub-hazard ratios of recurrent stroke and intracranial bleeding separately, competing of all-cause mortality risk, of treatment group compared to the control group.

21. Data Monitoring

21.1 Data Monitoring Committee

A Data Safety and Monitoring Board (DSMB) will be appointed at the start of the main study, i.e following the inclusion of the first 300 participants of the pilot phase. The Board will have a multidisciplinary composition and will be independent from the study organisers. The DSMB will have a consulting role to the steering committee. The DSMB will monitor:

1. Cumulative inclusion rate, balance in baseline characteristics, duration and yield of ECG recordings during the inclusion phase and provide statements with conclusions to the steering committee annually.

2. Event rate in the standard and intervention group annually and provide statements with conclusion to the steering committee.

22. Harms

All diagnostic tools and treatments used in the trial are approved by regulatory bodies. Any adverse events noted in connection to investigations or treatment should be reported to authorities according to practice.

23. Auditing

Monitoring of the study will focus on the match of informed consent forms to the list of included patients and the completeness of collected data. Study will follow GCP. A monitoring plan for the study has been established, with the following areas:

1. Completeness of hardcopies of study documents, investigator and delegates qualifications, delegation log

2. Written consent forms, accuracy, and completeness.

3. Subject eligibility

4. Source data entered into CRF at inclusion, accuracy and completeness
5. CRF entries in REDCap by instruments, unverified and incomplete entries by site

6. Independent reader will scrutinize 5-10% of ECG reports

24. Research Ethics Approval

24.1 Independent ethics committee

Ehical approval has been provided by the Swedish Ethical Review Authority (Dnr 2021-02770). Before entering the study, verbal and written information is given to the patient and informed consent form is signed.

24.2 Ethical conduct of the study

The study will be conducted according to the ethical principles of the declaration of Helsinki[20] and national regulatory standards.

24.3 Ethical considerations

The optimal duration of the ECG investigation following ischemic stroke/TIA is not known, since no study so far has been powered to detect differences in hard endpoints such as recurrent stroke or mortality between different ECG recording modalities, and this knowledge gap is acknowledged by the 2020 ESC AF guidelines. Because of the lack of data on hard endpoints, the recommendations for ECG recording modality and duration differ between guidelines internationally, as described in table 1.

The recommendations on AF screening after stroke/TIA from different societies are summarised in table 1.

The ethical issues in this study are partly connected to the knowledge gap of ECG monitoring duration and the clinical practice that has evolved as a result of the diversity of recommendations. For now, the minimum recommendation for ECG monitoring duration is 24-48 hours of continuous ECG recording. Several stroke units are however applying ECG monitoring protocols with longer duration. From this point of view, randomising patients to a monitoring protocol with shorter ECG screening duration than applied in clinical practice could be regarded as lowering investigation ambitions. However, since the efficacy of different ECG monitoring strategies for prevention of recurrent stroke and death is unknown, the randomisation to one of the arms in this study is considered ethically balanced against the option of continuing using monitoring strategies with unknown efficacy and unknown cost effectiveness.

The intervention arm will make two ECG recordings of 14 days duration each. As a consequence of the longer ECG monitoring duration in this arm, there could be some weeks delay from the first days of the ECG recording to the availability of ECG data. This dilemma is the same as with similar recordings in clinical practice, and ECG recording modalities with outpatient live telemetry availability are more demanding for the patient and associated with considerably higher costs.

In patients with aphasia or inability to write following stroke, it seems reasonable to collect informed consent from next of kin, i.e. a spouse or other close relative if some other mode of communication is established between the patient and the next of kin.

25. Protocol Amendments

Protocol version	Section	Description
Protocol version 2.0 issued 27 April 2023	1	Trial Registration (new section)
	4	Funding (new section)
	5	Roles & Responsibilities (new section)
	5.1	Sponsor Contact information
	5.2	Sponsor and Funder
	6	Background, last paragraph (added)
	6.1	Choice of comparator (added)
	7	Objectives (revised)
	8	Trial design (moved and revised)
	9	Study setting (new section)
	10	Eligibility criteria (moved and revised)
	11	Interventions (moved and revised)
	12	Outcomes (moved)
	13	Patient timeline (new section)
	14	Sample size (revised)

	15	Recruitment (new section)
	16	Allocation (new section)
	17	Blinding (new section)
	18	Data collection methods (revised)
	19	Data management (new section)
	20	Statistical Methods (revised)
	21	Data Monitoring (revised)
	22	Harms (new section)
	23	Auditing (new section)
	24	Research Ethics Approval (revised)
	25	Protocol Amendments
	26	Consent (new section)
	27	Confidentiality (new section)
	Appendix 4	Trials in event rates power calculation
	Appendix 5	Trials in ECG detection rate power calculation
Protocol version 1.1 Issued 28 sep 2022	6	Revision of time plan, correcting dates for start of pilot study
	6.1	Revision of study design overview
	7.2	Clarification that patients can not be included and randomised in AF SPICE more than once, added as exclusion criteria.
	8.1	Table of members of the ECG reading team
	9.1	Addition of a minimum ECG duration of 7 days at visit 1 and visit 2 respectively.
	9.1	Addition of possibility to start ECG recording earlier than 2 months in case of recurrent stroke.
	Appendix 2	Insertion of list of all centers and investigators (pp7-9)

26. Consent

Trained research nurses or investigators will introduce the study orally. Patients will receive written information about the study. Research nurses or investigators will discuss the study in light of the written information given, and patients will have an opportunity to discuss the information and ask questions about participation. Research nurses or investigators will obtain written consent from the patient or next of kin as described in 24.3.

27. Confidentiality

At the study sites, all log lists containing personal identification data will be stored securely. All study data will be stored in a REDCap database, accessible only by a password access. All actions in the REDCap database are logged. Data in the ECG reading system Cardiologs are pseudonymized and accessible with password.

28. Declaration of Interest

JE has received consultant or lecture fees from Roche Diagnostics, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Piotrode and Philips. Research grants from the Swedish Research Council, The Swedish Heart&Lung Foundation, The Swedish Innovation Agency and The Stockholm Region. KS, EI report no disclosures. ES reports consultant or lecture fees from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Johnson & Johnson, Merck Sharp & Dome. Research grants from the Swedish Research Council, The Swedish Heart&Lung Foundation, Åke Wibergs Foundation and CIMED. BN reports Data Safety Monitoring Board fees from Astra Zeneca. MvE is the chairman of Riksstroke, the Swedish Stroke Register. JOS reports no disclosures. SÅ reports lecture fees paid to the institution from Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, and is a member of the steering committee of Riksstroke, the Swedish Stroke Register. PW reports consulting fees, fee as a Clinical Events Committee member and unrestricted grants from Abbott. PW is a member of the steering committee of Riksstroke, the Swedish Stroke Register.

Appendices

Appendix 1 Steering committee

Johan Engdahl	Karolinska Institutet, Department of Clinical Sciences, Danderyds University Hospital, Stockholm, Sweden	Principal Investigator
Per Wester	Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden	Deputy principal investigator
Eva Isaksson	Karolinska Institutet, Department of Clinical Sciences, Danderyds University Hospital, Stockholm, Sweden	Study Coordinator
Marie Eriksson	Dept of Statistics, USBE, Umeå, University, Umeå, Sweden	Chief Statistician
Signild Åsberg	Dept of Medical Sciences, Uppsala University, Uppsala, Sweden	
Bo Norrving	Department of Clinical Sciences, Section IV, Lund University, Lund, Sweden	
Jakob Baianstovu-Ström	School of Medicine, Department of Neurology, Örebro University, Örebro, Sweden	
Brita Eklund	Department of Medicine, Alingsås Hospital, Alingsås, Sweden	
Elisabeth Änggårdh Rooth	Department of Neurology, Danderyd Unuiversity Hospital, Stockholm, Sweden	
Weigang Gu	Department of Neurology, South Hospital, Stockholm, Sweden	
Sara Själander	Department of Cardiology, Sundsvall Härnösand County Hospital, Sundsvall, Sweden	
Emma Svennberg	Karolinska Institutet, Dept of Medicine, Huddinge, Karolinska University Hospital, Stockholm, Sweden	
Kajsa Strååt	Karolinska Institutet, Department of Clinical Sciences, Danderyds University Hospital, Stockholm, Sweden	

Appendix 2 Study Sites

1	
Hospital	Danderyd University Hospital
Department	Department of Neurology
Primary Investigator	Elisabeth Änggårdh Rooth
Co-investigator	Maria Lantz
Co-investigator	Louise Ziegler
Co-investigator	Per Sanden
Co-investigator	Annika Lundström
Co-investigator	Anna Grünfeldt
Co-investigator	Magnus Thoren
Study nurse	Hillevi Asplund
Study nurse	Pernilla Becker
Start date	2022-01-13
Date of first randomisation	2022-01-20
REDCap designation	327

2	
Hospital	Uppsala University Hospital
Department	Department of Neurology
Primary Investigator	Signild Åsberg
Co-investigator	Erik Lundström
Co-investigator	Lars Sjöblom
Co-investigator	Jianman Lin
Co-investigator	Karl Sjölin
Study nurse	Erika Keller
Start date	2022-02-14
Date of first randomisation	2022-02-15
REDCap designation	328

3	
Hospital	Alingsås hospital
Department	Department of Medicine
Primary Investigator	Kjersti Hellqvist
Co-investigator	Brita Eklund
Co-investigator	Simona Violeta Bors
Start date	2022-02-22
Date of first randomisation	2022-04-11
REDCap designation	329

4	
Hospital	Växjö hospital
Department	Department of Medicine
Primary Investigator	Odd Almström
Co-investigator	Johan Weber
Co-investigator	Matilda Karlsson
Study nurse	Annette Borland
Study nurse	Monica Ström
Study nurs	Karin Lindberg
Start date	2022-02-24
Date of first randomisation	2022-03-08
REDCap designation	330

5	
Hospital	Örebro University Hospital
Department	Department of Neurology and Rehabilitation
Primary Investigator	Jakob Ström
Study nurse	Hanna Davidsson
Start date	2022-03-07
Date of first randomisation	2022-03-23
REDCap designation	332

6	
Hospital	Växjö hospital
Department	Department of Medicine
Primary Investigator	Odd Almström
Co-investigator	Johan Weber
Co-investigator	Matilda Karlsson
Study nurse	Annette Borland
Study nurse	Monica Ström
Study nurs	Karin Lindberg
Start date	2022-02-24
Date of first randomisation	2022-03-08
REDCap designation	330

7	
Hospital	Kungälv hospital
Department	Department of Geriatric, Neurology and rehabilitation
Primary Investigator	Margrethe Tönder
Co-investigator	Jonas Jonsson
Study nurse	Helena Engström
Start date	2022-05-23
Date of first randomisation	2022-06-07
REDCap designation	331

8	
Hospital	Sahlgrenska University Hospital
Department	Department of Neurology
Primary Investigator	Erik Lindgren
Co-investigator	Petra Redfors
Co-investigator	David Åberg
Co-investigator	Jan-Erik Karlsson
Co-investigator	Mikael Jerndal
Co-investigator	Anke Brederlau
Co-investigator	Margareta Abrahamsson
Co-investigator	Ioanna Dagiasi
Study nurse	Mathilda Errind Arvgård
Study nurse	Magdalena Hagelberg
Study nurse	Zoe Oberli
Study nurse	Susanne Nilsson
Start date	2022-06-27
Date of first randomisation	2022-06-29
REDCap designation	333

9	
Hospital	Östersund hospital
Department	Department of Medicine
Primary Investigator	Joachim Ögren
Co-investigator	Magnus Gibson
Co-investigator	Anna-Lotta Irewall
Study nurse	Linda Wiklund
Study nurse	Malin Blomkvist
Study nurse	Helena Widmark
Start date	2022-08-15
Date of first randomisation	2022-08-23
REDCap designation	407

10	
Hospital	Hässleholm hospital
Department	Department of Neurologi and Medicine
Primary Investigator	Magnus Esbjörnsson
Co-investigator	*Krzysztof* Grodon
Co-investigator	Ingar Timberg
Study nurse	Erika Snygg
Study nurse	Anna Nilsson
Study nurse	Annika Nilsson
Start date	2022-09-01
Date of first randomisation	2022-09-14
REDCap designation	408

11	
Hospital	Östra hospital
Department	Department of Medicine
Primary Investigator	Christian Alex
Study nurse	Christina Hedén Ståhl
Start date	2022-09-26
Date of first randomisation	2022-10-28
REDCap designation	409

12	
Hospital	Mölndal hospital
Department	Department of Medicine
Primary Investigator	Carolina Sixt
Study nurse	Malin Hallgren
Study nurse	Janet Moodh
Start date	2022-10-24
Date of first randomisation	2023-01-11
REDCap designation	410

13	
Hospital	Skaraborgs Hospital Skövde
Department	Department of Medicine
Primary Investigator	Alexander Johansson
Study nurse	Eva Åkerhade
Study nurse	Max Fantenberg
Start date	2022-10-24
Date of first randomisation	2022-10-31
REDCap designation	411

14	
Hospital	Malmö University Hospital
Department	Department of Neurology
Primary Investigator	Teresa Ullberg
Study nurse	Emma Rönde
Study nurse	Cecilia Johansson
Study nurse	Per Samuelsson
Co-investigator	Olof Gråhamn
Co-investigator	Conrad Drescher
Co-investigator	Eva Ask
Start date	2022-10-13
Date of first randomisation	2023-01-23
REDCap designation	412

15	
Hospital	Gävle Hospital
Department	Department of Medicine
Primary Investigator	Laith Yassen
Study nurse	Maria Smedberg
Study nurse	Helene Melin
Study nurse	Christina Andersson
Co-investigator	Ismail Zangana
Start date	2022-12-06
Date of first randomisation	2023-01-09
REDCap designation	413

16	
Hospital	Hudiksvall Hospital
Department	Department of Medicine
Primary Investigator	Anette Onkenhout
Study nurse	Isabell Sverin
Study nurse	Mina Jamali
Co-investigator	Malin Woock
Start date	2022-12-02
Date of first randomisation	2023-01-26
REDCap designation	414

Appendix 3 Baseline data collected from Riksstroke Register

Reporting Hospital	Statin treatment on admission
Date of symptom onset	Aspirin treatment on admission
Time of symptom onset	Clopidogrel treatment on admission
Level of consciousness at admission	
NIHSS at admission	Dipyridamole treatment on admission
Number of days admitted	Other antiplatelet treatment on admission
Number of days in stroke unit	Hypertension treatment on admission
	Dipyridamole treatment on admission
Diagnosis	Warfarin treatment on admission
Age at admission	Apixaban treatment on admission
Sex	Dabigatran treatment on admission
Level of assistance	Rivaroxaban treatment on admission
Living alone	Edoxaban treatment on admission
Level of dependence	
Assisted dressing	Statin treatment at discharge
Assisted personal hygiene	Aspirin treatment at discharge
Independence in locomotion	Clopidogrel treatment at discharge
	Dipyridamole treatment at discharge
Previously diagnosed AF	Warfarin treatment at discharge
AF diagnosed on arrival	Hypertension treatment at discharge
Previously or newly diagnosed diabetes	Apixaban treatment at discharge
Hypertension (treated) on admission	Dabigatran treatment at discharge
Smoking status	Rivaroxaban treatment at discharge
	Edoxaban treatment at discharge
CT brain scan performed during admission	Reason for withholding OAC treatment
MRI brain scan performed during admission	
Carotide artery ultrasound brain scan performed during admission	
CT angiography performed during admission	
Longterm ECG (at least 24 h) performed during admission	
Thrombolytic treatment administered	
Type of ward at admission	

Trials in eventrates power calculation

	AF+/OAC+			AF+/OAC-			AF-/OAC-		
	Rate	Mean Age	Reference	Rate	Mean Age	Reference	Rate	Mean Age	Reference
Stroke	2,23%	70,2	Diener[1] 2010 D110	5,30%	71,7	Diener[2] 2012	5,40%	73	Netland el al 2019
	1,91%	70,8	Diener[1] 2010 D150				5,10%	66	Amarenco[3] 2016
	2,53%	70,4	Diener[1] 2010 W				3,60%	70,1	Andersen[4] 2015
	2,39%	71,7	Diener[2] 2012 A				5,40%		Wachter[5] 2017
	2,79%	71	Hankey[6] 2012 R						
	2,96%	71	Hankey[6] 2012 W						
	2,26%	70,1	Easton[7] 2012 A						
	3,17%	70,1	Easton[7] 2012 W						
	2,44%		Rost[8] 2016 E						
All-cause mortality	3,24%	70,2	Diener[1] 2010 D110	6,86%	71,7	Diener[2] 2012	10,70%	73	Netland el al 2019
	4,39%	70,8	Diener[1] 2010 D150				1,80%	66	Amarenco[3] 2016
	4,58%	70,4	Diener[1] 2010 W				10,50%	70,1	Andersen[4] 2015
	5,78%	71,7	Diener[2] 2012 A				4,80%		Wachter[5] 2017
	4,40%	71	Hankey[6] 2012 R				10,60%		Lip[9] 2017
	4,54%	71	Hankey[6] 2012 W						
	4,22%	70,1	Easton[7] 2012 A						
	4,77%	70,1	Easton[7] 2012 W						
	4,35%		Rost[8] 2016 E						
Intracerebral bleeding	0,25%	70,2	Diener[1] 2010 D110	1,56%	71,7	Diener[2] 2012	0,40%	66	Amarenco[3] 2016
	0,53%	70,8	Diener[1] 2010 D150						
	1,28%	70,4	Diener[1] 2010 W						
	1,17%	71,7	Diener[2] 2012 A						
	0,59%	71	Hankey[6] 2012 R						
	0,80%	71	Hankey[6] 2012 W						
	0,55%	70,1	Easton[7] 2012 A						
	1,49%	70,1	Easton[7] 2012 W						
	0,62%		Rost[8] 2016 E						
Mortal bleeding	0,26%	71	Hankey[6] 2012 R						
	0,49%	71	Hankey[6] 2012 W						

AF = Atrial Fibrillation OAC = Oral Anticoagulant

Appendix 5 Trials in ECG detection rate power calculation

Publication Short-term external ECG after stroke/TIA	Detection rate (%)
Jabaudon[21] 2004	5.0
Shafqat[22] 2004	2.4
Alhadramy[23] 2010	2.5
Rizos[24] 2010	2.5
Doliwa-Sobocinski[25] 2012	2.0
Lazarro[26] 2012	6.0
Gumbinger[27] 2012	1.0
Suissa[28] 2012	2.3
Thakkar[29] 2014	5.8
Bansil[30] 2004	4.7

Publication Long-term external ECG after stroke/TIA	Detection rate (%)
Barthelemy[31] 2003	14.3
Jabadoun[21] 2004	5.7
Wallman[32] 2007	14.2
Tayal[33] 2008	5.0
Elijiovich[34] 2009	20.0
Bhatt[35] 2011	24.2
Flint[36] 2012	11.0
Higgins[37] 2013	8.0
Miller[38] 2013	17.3
Gladstone[10] 2014	16.1
Sebasigari[39] 2017	11.7

Appendix 6 Power calculation

Biostatistics
CORE FACILITY

Sample size calculation AF SPICE

Ida Hed Myrberg & Letizia Orsini

2021-10-08

Background

Sample size calculation for the AF SPICE study; a multicenter randomized register-based trail in Swedish stroke units.

Method

The function *cpower* in R package *Hmisc* is used. This is a function for calculating the power for a Cox Proportional Hazards model or log-rank test comparing two groups. The function assumes an underlying exponential distribution in both groups. To calculate the sample size needed to achieve 80% power, the function *uniroot* is used in combination with *cpower*.

How parameters are defined and calculated

In this section, it is shown how the yearly rate, and the 3-year event rate, of stroke/death/intracranial bleeding in the intervention and control group, respectively, are calculated based on the yearly rates in the three groups AF+/OAK+, AF+/OAK-, and AF-/OAK-, and on the proportions of these three groups in the intervention and control group. The proportion of AF+/OAK+, AF+/OAK-, and AF-/OAK- in the intervention and control group in Table 2 are examples, and in the next two sections they will be varied between 10-20% in the intervention group, and 3-12% in the control group. The yearly rate of stroke/death/intracranial bleeding for AF-/OAK- will be set to 5% and 8.4%, respectively, in two different scenarios.

Table 1 shows the assumed yearly rates of stroke/death/intracranial bleeding for the subgroups AF+/OAK+, AF+/OAK-, AF-/OAK-, while Table 2 shows the proportion of patients in each of the aforementioned subgroups, divided by interention and control.

Table 1: Yearly rate of stroke/death/intracranial bleeding depending on AF and treatment.

AF/treatment	Yearly rate of stroke/death/intracranial bleeding
AF+/OAK+	0.073
AF+/OAK-	0.177
AF-/OAK-	0.084

Table 2: Proportion of patients with AF and treatment in the intervention group and control group, respectively.

AF/treatment	Proportion in intervention group	Proportion in control group
AF+/OAK+	0.10	0.03
AF+/OAK-	0.00	0.07

AF/treatment	Proportion in intervention group	Proportion in control group
AF-/OAK-	0.90	0.90

The yearly rate of stroke/death/intracranial in the intervention group is calculated as 0.073 * 0.1 + 0.177 * 0 + 0.084 * 0.9 = 0.0829. The yearly rate of stroke/death/intracranial in the control group is calculated as 0.073 * 0.03 + 0.177 * 0.07 + 0.084 * 0.9 = 0.09018.

Table 3: Yearly rate of stroke/death/intracranial bleeding in the intervention group and control group, respectively.

Group	Yearly rate of stroke/death/intracranial bleeding
Intervention group	0.0829
Control group	0.0902

The minimum follow-up time is assumed to be 3 years, and the recruitment time is set to 2 years.

The 3-year event rate in the control group, denoted *mc*, i.e. the proportion expected to have experienced the event by three years, is needed for the power calculation. The proportion not having experienced the event, i.e. 1-*mc*, is calculated using the Kaplan-Meier method, and the 3-year event rate is then calculated as 1-(1-*mc*)=*mc*. The 3-year event rate in the intervention group, *mi*, is calculated in a similar way. Both *mc* and *mi* are presented in Table 4.

Table 4: 3-year rate of stroke/death/intracranial bleeding in the intervention group and control group, respectively.

Group	3-year rate of stroke/death/intracranial bleeding
Intervention group	0.2287
Control group	0.2469

The percent reduction in the 3-year event rate for the intervention group compared to the control group is given by 1-22.87/24.69=7.38%.

Results: 5% yearly rate of stroke/death/intracranial bleeding for AF-/OAK-

In this section, a yearly event rate of 5% is assumed for the AF-/OAK- group.

The sample size needed is calculated for all combination of AF proportions, ranging from 10-20% in the intervention group, and 3-12% in the control group. Table 5 shows the percent reduction in the 3-year event rate for the intervention group compared to the control group, for different combinations of AF proportions.

Table 5: Percent reduction in the 3-year event rate for the intervention group compared to the control group. Columns: AF proportions in the control group. Rows: AF proportions in the intervention group.

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.1	11.57	10.09	8.56	6.97	5.33	3.62	1.85	-	-	-
0.11	12.94	11.52	10.05	8.52	6.94	5.31	3.60	1.84	-	-

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.12	14.25	12.89	11.47	10.01	8.49	6.92	5.28	3.59	1.83	-
0.13	15.52	14.20	12.83	11.42	9.96	8.45	6.89	5.26	3.57	1.82
0.14	16.73	15.46	14.14	12.78	11.38	9.92	8.42	6.86	5.24	3.56
0.15	17.89	16.66	15.40	14.09	12.73	11.33	9.88	8.38	6.83	5.21
0.16	19.01	17.82	16.60	15.34	14.03	12.68	11.29	9.84	8.35	6.80
0.17	20.09	18.94	17.76	16.54	15.28	13.98	12.63	11.24	9.80	8.31
0.18	21.12	20.01	18.87	17.69	16.48	15.22	13.92	12.58	11.20	9.76
0.19	22.12	21.05	19.94	18.80	17.63	16.41	15.16	13.87	12.53	11.15
0.2	23.08	22.04	20.97	19.87	18.73	17.56	16.35	15.10	13.82	12.48

Table 6 shows the total sample size needed to achieve 80% power to detect a statistically significant (with alpha=0.05) difference in the 3-year event rates presented in Table 5 between the intervention group and the control group, for different combinations of AF proportions.

Table 6: Total sample size needed for different combinations of AF proportions in the intervention and control group, respectively. Columns: AF proportions in the control group. Rows: AF proportions in the intervention group.

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.1	8536	11504	16400	25370	44652	99460	393830	-	-	-
0.11	6628	8572	11552	16470	25480	44848	99900	395590	-	-
0.12	5310	6654	8608	11600	16542	25590	45044	100340	397348	-
0.13	4360	5332	6682	8644	11650	16612	25700	45240	100780	399108
0.14	3652	4378	5352	6710	8680	11698	16682	25810	45436	101220
0.15	3110	3668	4396	5374	6738	8716	11748	16752	25922	45630
0.16	2686	3124	3682	4412	5396	6764	8752	11796	16824	26032
0.17	2346	2696	3136	3696	4430	5418	6792	8788	11846	16894
0.18	2072	2356	2708	3148	3710	4448	5440	6820	8824	11894
0.19	1844	2080	2364	2718	3160	3726	4466	5462	6848	8860
0.2	1654	1850	2086	2374	2728	3172	3740	4484	5484	6876

Results: 8.4% yearly rate of stroke/death/intracranial bleeding for AF-/OAK-

In this section, a yearly event rate of 8.4% is assumed for the AF-/OAK- group.

The sample size needed is calculated for all combination of AF proportions, ranging from 10-20% in the intervention group, and 3-12% in the control group. Table 7 shows the percent reduction in the 3-year event rate for the intervention group compared to the control group, for different combinations of AF proportions.

Table 7: Percent reduction in the 3-year event rate for the intervention group compared to the control group. Columns: AF proportions in the control group. Rows: AF proportions in the intervention group.

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.1	7.38	6.40	5.40	4.37	3.32	2.24	1.13	-	-	-
0.11	8.35	7.39	6.41	5.41	4.38	3.32	2.24	1.13	-	-

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.12	9.30	8.36	7.40	6.42	5.41	4.38	3.33	2.25	1.14	-
0.13	10.23	9.31	8.37	7.41	6.43	5.42	4.39	3.33	2.25	1.14
0.14	11.14	10.24	9.32	8.38	7.42	6.44	5.43	4.39	3.34	2.25
0.15	12.04	11.16	10.26	9.34	8.40	7.43	6.45	5.44	4.40	3.34
0.16	12.91	12.05	11.17	10.27	9.35	8.41	7.44	6.45	5.44	4.41
0.17	13.78	12.93	12.07	11.19	10.28	9.36	8.42	7.45	6.46	5.45
0.18	14.62	13.79	12.95	12.08	11.20	10.30	9.37	8.43	7.46	6.47
0.19	15.45	14.64	13.81	12.96	12.10	11.22	10.31	9.39	8.44	7.47
0.2	16.26	15.47	14.66	13.83	12.98	12.12	11.23	10.33	9.40	8.45

Table 8 shows the total sample size needed to achieve 80% power to detect a statistically significant (with alpha=0.05) difference in the 3-year event rates presented in Table 5 between the intervention group and the control group, for different combinations of AF proportions.

Table 8: Total sample size needed for different combinations of AF proportions in the intervention and control group, respectively. Columns: AF proportions in the control group. Rows: AF proportions in the intervention group.

	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12
0.1	13380	18096	25892	40198	71006	158734	630838	-	-	-
0.11	10296	13362	18072	25858	40144	70910	158518	629976	-	-
0.12	8176	10282	13346	18048	25824	40090	70814	158302	629114	-
0.13	6656	8166	10270	13328	18024	25790	40036	70718	158088	628250
0.14	5530	6648	8156	10256	13310	18000	25754	39982	70622	157872
0.15	4670	5522	6640	8144	10242	13292	17976	25720	39928	70526
0.16	3998	4664	5514	6630	8134	10228	13274	17952	25686	39874
0.17	3466	3994	4658	5508	6622	8124	10216	13258	17928	25652
0.18	3034	3460	3988	4652	5500	6614	8112	10202	13240	17904
0.19	2680	3030	3456	3984	4646	5494	6604	8102	10188	13222
0.2	2386	2676	3026	3452	3978	4640	5486	6596	8092	10174

Selected sample size

To calculate the expected cases in the intervention group and the control group, the function *cpower* was run with the following parameters:

- accrual time 2 years;
- follow-up time 3 years;
- aplha 0.05;
- power 0.8;
- 5% yearly rate of stroke/death/intracranial bleeding for AF-/OAK-;
- 19% AF proportions in the intervention group;
- 6% AF proportions in the control group.

The result of *cpower* is:

```
Accrual duration: 2 y  Minimum follow-up: 3 y
```

Biostatistics
CORE FACILITY

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Total sample size: 2718

Alpha= 0.05

3-year Mortalities
     Control Intervention
   0.1901558    0.1544025

Hazard Rates
     Control Intervention
  0.07030447   0.05590393

Probabilities of an Event During Study
     Control Intervention
   0.2445141    0.1999611

Expected Number of Events
     Control Intervention
       332.3        271.7

Hazard ratio: 0.7951689
Standard deviation of log hazard ratio: 0.08178795
    Power
0.8002227
```

In the first two years, you have to enroll uniformly over time 1359 patients in the control group and 1359 in the intervention group. After the first two years, you have to follow them up for another three years. At least five years after the start of the study, you must check the observed cases in the control group and in the intervention group. If the study did not reach 333 cases in the control group and 272 in the intervention group, the follow-up can be extended until these are reached. This minimum number of cases guarantees a power of 80%.

References

1. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021;20(10):795-820. [published Online First: 2021/09/07]
2. Hankey GJ. Stroke. *Lancet* 2017;389(10069):641-54. [published Online First: 2016/09/18]
3. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogosova N, Weimar C, Iqbal R, Diaz R, Yusoff K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388(10046):761-75. [published Online First: 2016/07/20]
4. Eriksson M, Åsberg S, Sunnerhagen KS, von Euler M. Sex Differences in Stroke Care and Outcome 2005-2018: Observations From the Swedish Stroke Register. *Stroke* 2021:Strokeaha120033893. [published Online First: 2021/07/01]
5. Mukundan G, Seidenwurm DJ. Economic and Societal Aspects of Stroke Management. *Neuroimaging Clin N Am* 2018;28(4):683-89. [published Online First: 2018/10/17]
6. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke* 2013;44(11):3103-8. [published Online First: 2013/08/29]
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857-67.
8. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Kohrmann M, Wachter R, Rosin L, Kirchhof P. Improved Detection of Silent Atrial Fibrillation Using 72-Hour Holter ECG in Patients With Ischemic Stroke: A Prospective Multicenter Cohort Study. *Stroke* 2013;44(12):3357-64. [published Online First: 2013/10/17]
9. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370(26):2478-86. [published Online First: 2014/06/26]
10. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370(26):2467-77. [published Online First: 2014/06/26]
11. Wachter R, Groschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jurries F, Messerschmid A, Behnke N, Groschel S, Uphaus T, Grings A, Ibis

T, Klimpe S, Wagner-Heck M, Arnold M, Protsenko E, Heuschmann PU, Conen D, Weber-Kruger M, Find AFI, Coordinators. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. *Lancet Neurol* 2017;16(4):282-90. [published Online First: 2017/02/12]

12. Haeusler KG, Kirchhof P, Kunze C, Tütüncü S, Fiessler C, Malsch C, Olma MC, Jawad-Ul-Qamar M, Krämer M, Wachter R, Michalski D, Kraft A, Rizos T, Gröschel K, Thomalla G, Nabavi DG, Röther J, Laufs U, Veltkamp R, Heuschmann PU, Endres M. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, multicentre study. *Lancet Neurol* 2021;20(6):426-36. [published Online First: 2021/05/23]
13. NICE AF post stroke Guidelines 2023 [Available from: https://www.nice.org.uk/guidance/dg41/ accessed 2023-01-15.
14. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, Cox JL, Dorian P, Gladstone DJ, Healey JS, Khairy P, Leblanc K, McMurtry MS, Mitchell LB, Nair GM, Nattel S, Parkash R, Pilote L, Sandhu RK, Sarrazin JF, Sharma M, Skanes AC, Talajic M, Tsang TSM, Verma A, Verma S, Whitlock R, Wyse DG, Macle L. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020;36(12):1847-948. [published Online First: 2020/11/17]
15. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Heart, lung & circulation* 2018;27(10):1209-66. [published Online First: 2018/08/06]
16. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42(5):373-498. [published Online First: 2020/08/30]
17. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, Lennon O, Meschia JF, Nguyen TN, Pollak PM, Santangeli P, Sharrief AZ, Smith SC, Jr., Turan TN, Williams LS. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;52(7):e364-e467. [published Online First: 2021/05/25]
18. Physicians Rco. National guideline for stroke London2016 [Fifth edition:[Available from: https://www.strokeaudit.org/Guideline/Full-Guideline.aspx accessed 2023-01-15
19. Rubiera M, Aires A, Antonenko K, Lémeret S, Nolte CH, Putaala J, Schnabel RB, Tuladhar AM, Werring DJ, Zeraatkar D, Paciaroni M. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient

ischaemic attack of undetermined origin. *Eur Stroke J* 2022;7(3):Vi. [published Online First: 2022/09/10]
20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013;310(20):2191-4. [published Online First: 2013/10/22]
21. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke* 2004;35(7):1647-51.
22. Shafqat S, Kelly PJ, Furie KL. Holter monitoring in the diagnosis of stroke mechanism. *Intern Med J* 2004;34(6):305-9.
23. Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and predictors of paroxysmal atrial fibrillation on Holter monitor in patients with stroke or transient ischemic attack. *Stroke* 2010;41(11):2596-600. [published Online First: 2010/10/16]
24. Rizos T, Rasch C, Jenetzky E, Hametner C, Kathoefer S, Reinhardt R, Hepp T, Hacke W, Veltkamp R. Detection of paroxysmal atrial fibrillation in acute stroke patients. *Cerebrovasc Dis* 2010;30(4):410-7. [published Online First: 2010/08/20]
25. Doliwa Sobocinski P, Anggardh Rooth E, Frykman Kull V, von Arbin M, Wallen H, Rosenqvist M. Improved screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2012;14(8):1112-6. [published Online First: 2012/02/07]
26. Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis* 2012;21(2):89-93. [published Online First: 2010/07/27]
27. Gumbinger C, Krumsdorf U, Veltkamp R, Hacke W, Ringleb P. Continuous monitoring versus HOLTER ECG for detection of atrial fibrillation in patients with stroke. *Eur J Neurol* 2012;19(2):253-7. [published Online First: 2011/09/08]
28. Suissa L, Lachaud S, Mahagne MH. Optimal Timing and Duration of Continuous Electrocardiographic Monitoring for Detecting Atrial Fibrillation in Stroke Patients. *J Stroke Cerebrovasc Dis* 2012 [published Online First: 2012/02/22]
29. Thakkar S, Bagarhatta R. Detection of paroxysmal atrial fibrillation or flutter in patients with acute ischemic stroke or transient ischemic attack by Holter monitoring. *Indian Heart J* 2014;66(2):188-92. [published Online First: 2014/05/13]
30. Bansil S, Karim H. Detection of atrial fibrillation in patients with acute stroke. *J Stroke Cerebrovasc Dis* 2004;13(1):12-5. [published Online First: 2007/10/02]
31. Barthelemy JC, Feasson-Gerard S, Garnier P, Gaspoz JM, Da Costa A, Michel D, Roche F. Automatic cardiac event recorders reveal paroxysmal atrial fibrillation after unexplained strokes or transient ischemic attacks. *Ann Noninvasive Electrocardiol* 2003;8(3):194-9. [published Online First: 2003/09/27]
32. Wallmann D, Tuller D, Wustmann K, Meier P, Isenegger J, Arnold M, Mattle HP, Delacretaz E. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. *Stroke* 2007;38(8):2292-4. [published Online First: 2007/06/23]
33. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, Jarouse J, Brillman J, Murali S, Gupta R. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology* 2008;71(21):1696-701. [published Online First: 2008/09/26]

34. Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis* 2009;18(3):185-9. [published Online First: 2009/05/12]
35. Bhatt A, Majid A, Razak A, Kassab M, Hussain S, Safdar A. Predictors of occult paroxysmal atrial fibrillation in cryptogenic strokes detected by long-term noninvasive cardiac monitoring. *Stroke Res Treat* 2011;2011:172074. [published Online First: 2011/03/23]
36. Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke* 2012;43(10):2788-90. [published Online First: 2012/08/09]
37. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. *Stroke* 2013;44(9):2525-31. [published Online First: 2013/08/01]
38. Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN, Mitsias PD. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. *J Neurol Sci* 2013;324(1-2):57-61. [published Online First: 2012/10/30]
39. Sebasigari D, Merkler A, Guo Y, Gialdini G, Kummer B, Hemendinger M, Song C, Chu A, Cutting S, Silver B, Elkind MSV, Kamel H, Furie KL, Yaghi S. Biomarkers of Atrial Cardiopathy and Atrial Fibrillation Detection on Mobile Outpatient Continuous Telemetry After Embolic Stroke of Undetermined Source. *J Stroke Cerebrovasc Dis* 2017;26(6):1249-53. [published Online First: 2017/02/27]