Creating a continuum of care : smart technology in patients with cardiovascular disease

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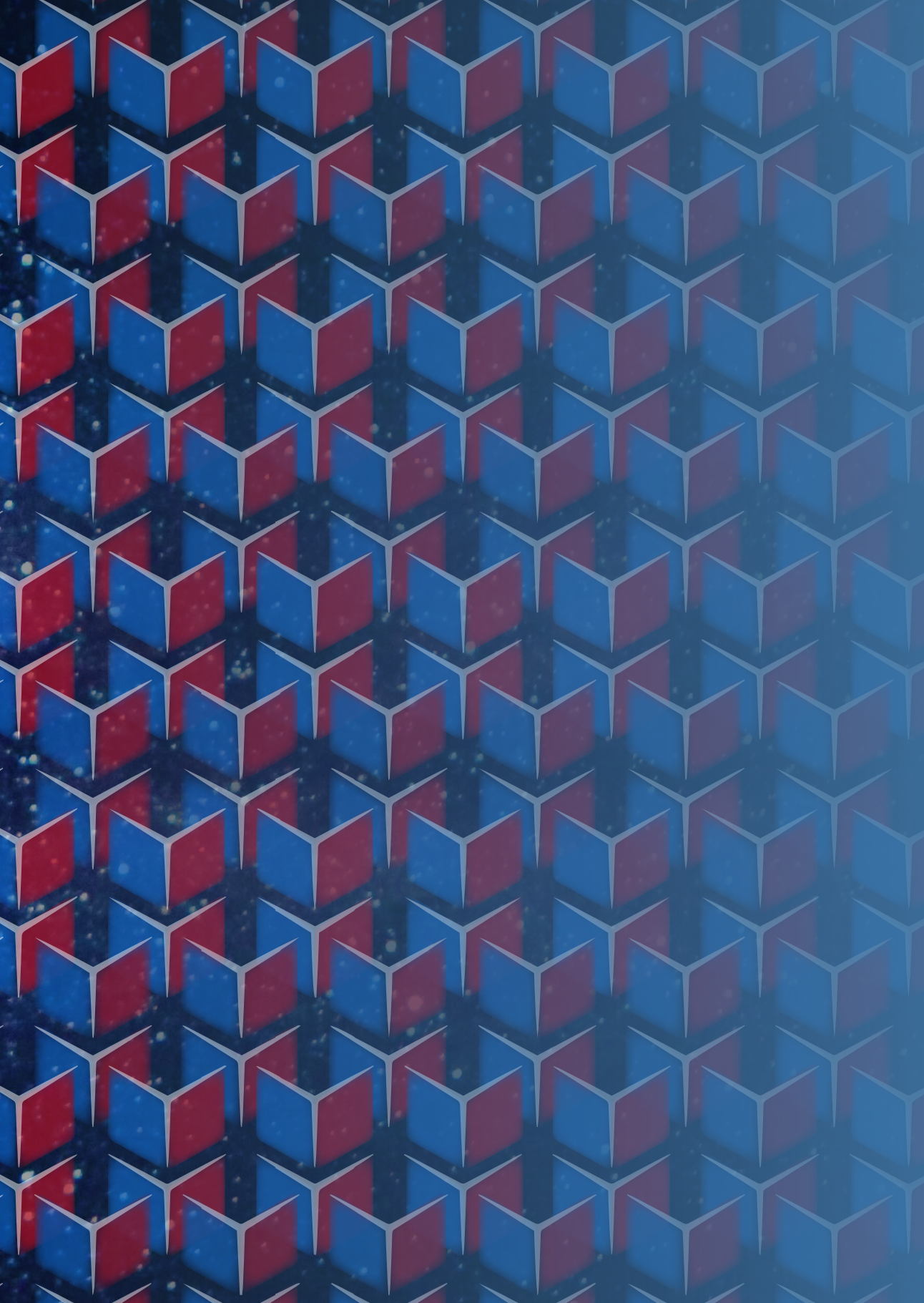

CHAPTER 5

Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF): design and rationale

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Abstract

Background

Recently published randomized clinical trials indicate that prolonged ECG monitoring might enhance detection of paroxysmal atrial fibrillation (AF) in cryptogenic stroke or TIA patients. A device that might be suitable for prolonged ECG monitoring is a smartphone compatible ECG device (Kardia Mobile, Alivecor, San Francisco, CA) that allows the patient to record a single lead ECG without the presence of trained healthcare staff. The MOBILE-AF trial will investigate the effectiveness of the ECG device for AF detection in patients with cryptogenic stroke or TIA. In this paper, the rationale and design of the MOBILE-AF trial is presented.

Methods

For this international multicentre trial, 200 patients with cryptogenic stroke or TIA will be randomized. 100 patients will receive the ECG device and will be asked to record their ECG twice daily during a period of one year. 100 patients will receive a 7-Day Holter monitor.

Discussion

The primary outcome of this study is the percentage of patients in which AF is detected in the first year after the index ischaemic stroke or TIA. Secondary outcomes include markers for AF prediction, oral anticoagulation therapy changes, as well as incidence of recurrent stroke and major bleedings. First results can be expected mid-2019.

Trial registration

Number NCT02507986 in ClinicalTrials.gov. Registered in July 2015.

Background

In approximately 30% of all patients with ischaemic stroke or transient ischaemic attack (TIA), no cause can be determined after standard evaluation. These strokes and TIAs are referred to as cryptogenic.(1) One of the known risk-factors for ischaemic stroke is atrial fibrillation (AF).(2) Current guidelines state that oral anticoagulation therapy (OAC) should be prescribed in case AF of any duration above 30 seconds is detected after ischaemic stroke/TIA on a 12-lead ECG or lasting at least 30 seconds(3) on a 24-hour Holter monitor.(3, 4) However, as AF is often asymptomatic and paroxysmal,(5) the detection of AF with the currently advised standard work-up using a 24-hour Holter recording is low.(6, 7)

Consequently, recently published research indicates that AF episodes may be missed using this standard evaluation. In the CRYSTAL-AF(6) and EMBRACE trials,(7) it was demonstrated that prolonged ECG monitoring yielded significantly higher percentages of detected AF in patients with cryptogenic stroke or TIA.(6, 7)

It has been discussed that it is uncertain if subclinical AF, especially short episodes, require anticoagulation in patients with cryptogenic stroke.(8) Several trials (NCT02313909, NCT02427126 and NCT02239120) started to randomize patients with cryptogenic stroke between non-vitamin K oral anticoagulants (NOACs) and aspirin. Pending the results of these trials, the diagnosis of AF after cryptogenic stroke remains to have therapeutic consequences.(3) The diagnostic method therefore remains important.

In the CRYSTAL-AF trial, an implantable cardiac monitor (ICM) showed significantly higher detection rates of AF after 6-months follow-up in patients with cryptogenic stroke. However, placement of an ICM is costly and has some limitations, as it brings in the risk of pocket infection.(6)

In the EMBRACE trial, a 30-day event-triggered loop recorder showed significantly higher rates of AF after 90-days of follow-up. However, the device was moderately tolerated as 60% of all participants completed the full month of wearing the device. (7)

In the past five years, smartphone-connected ECG devices have been developed. One of these devices is the Kardia Mobile (Alivecor, Inc., San Francisco, CA, USA). This a handheld ECG device that transmits and stores a single lead ECG on a smartphone. It is cleared by the United States Food And Drug Administration (FDA) and has received a European Union CE mark for the detection of AF.(9) The device is easy-to-use, non-invasive, electrically safe and can be used on demand. It does not bring in the risk of pocket-infection, does not have to be worn on the body and is cheaper than an ICM.(10, 11) It furthermore does not, in contrast with an ICM, necessitate trained healthcare staff or a dedicated hospital room to hand the device to the patient.(11, 12) Therefore, the Kardia Mobile may be a more feasible alternative for prolonged ECG monitoring in cryptogenic stroke patients. However,

the clinical effectiveness of the Kardia Mobile in detecting AF in cryptogenic stroke patients has not been investigated before.

Therefore, the Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs to detect Atrial Fibrillation (MOBILE AF) trial is designed to investigate the effectiveness of the Kardia Mobile device for AF detection in patients with cryptogenic stroke or TIA and to compare this with the effectiveness of regular follow-up for AF detection.

In this paper the design and rationale of the study are presented.

Methods

Patient population

For this study, patients with cryptogenic stroke or TIA that have been treated at one of the participating centers (see list Appendix A) will be asked to participate. Ischaemic stroke will be defined as an episode of neurological dysfunction caused by focal brain or retinal ischaemia with recent (hours to days) infarction on cerebral imaging.(13) TIA is defined as a transient episode of neurologic dysfunction lasting less than one hour caused by focal brain or retinal ischaemia without recent infarction on cerebral imaging.(14)

A stroke or TIA is defined as cryptogenic if no cause can be determined after standard work-up, consisting of at least:

1. Computed Tomography (CT) of the brain
2. Computed Tomography Angiography (CTA) of head and neck arteries or Echo Doppler of the carotid arteries
3. Transthoracic echocardiography followed by transoesophageal echocardiography when indicated
4. 12-lead 10-second electrocardiography
5. 24-hour ECG monitoring
6. Laboratory tests
    a. Complete blood count
    b. Prothrombin time
    c. Partial thromboplastin time
    d. Serum electrolytes
    e. C-reactive protein
    f. Hepatic and renal chemical analysis
    g. Erythrocyte sedimentation rate

If a stroke or TIA is considered to be cryptogenic, a patient will be evaluated with the described in-, and exclusion criteria. These criteria are listed in Table 1. Generally, adult patients who suffer from a cryptogenic stroke or TIA who are willing to sign informed consent, and are in possession of a smartphone with Android OS or iOS can participate. A maximum duration of six months between diagnosis of the index event and study inclusion is allowed.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Admitted to the stroke unit of participating centres with an ischaemic stroke or TIA
Exclusion criteria
Known aetiology of TIA or ischaemic stroke
TIA or stroke caused by spinal ischaemia
TIA is only present with non-localising symptoms(25)
Uncertainty about the diagnosis of TIA because of unclear clinical symptoms
Myocardial infarction <1 month before stroke
Coronary Artery Bypass Grafting <1 month before stroke
Surgery indicated valvular heart disease
Documented history of AF or atrial flutter
Left ventricular aneurysm on echocardiography
Intracardiac Thrombus on echocardiography
Renal dysfunction (creatinine clearance <30 mL/min/1.73m2)
Patient is not able or willing to sign the informed consent form
Patient is <18 years of age
Patient is considered an incapacitated adult
Patient is not in possession of a smartphone or tablet with Android Operating (OS) System or iOS and is unwilling to arrange one

The Kardia Mobile

The Kardia Mobile device is a handheld smartphone compatible device which contains two electrodes. The Kardia Mobile device is battery powered and electrically safe. The Kardia Mobile device communicates with the Kardia Mobile app, which can be downloaded on smartphones running Android OS or iOS. The device records a 30 sec ECG from the fingers of both hands. A single lead ECG is instantly shown on the smartphone screen. The recording of an ECG does not require the presence of healthcare staff.

An automated algorithm on the Kardia Mobile app checks the ECG for R-R wave irregularity. It delivers a diagnosis citing either “no abnormalities detected”, “possible atrial fibrillation” or “this ECG could not be interpreted”. This is a validated, FDA approved algorithm with a 97% sensitivity and 98% specificity for AF detection.(10)

After the diagnosis, the Kardia Mobile app offers the possibility to take notes. Patients are explicitly asked to take notes of their symptoms, if present, at the time of the recording.
If the diagnosis “possible atrial fibrillation” or “this ECG could not be interpreted” is delivered, the ECG is assessed for the presence of AF on the same or next working day by a PhD student with ample training and experience at the Holter department, who is not blinded to patient data. In case of any uncertainty about the diagnosis, the ECG is evaluated by an experienced cardiologist/electrophysiologist, who is blinded to the patient data. The ECG is saved in a secured cloud environment. ECGs in PDF can be automatically send to and checked by the study supervisors after patients’ consent. An example of such a PDF showing sinus rhythm is presented in Figure 1. An example of such a PDF showing atrial fibrillation is presented in Figure 2.

The Kardia mobile can be discontinued on patient’s request. In case of non-adherence (defined as not having sent a single lead ECG for two consecutive days), patients will first receive a standardized e-mail asking if there are any technical problems. If patients do not send ECGs for another two consecutive days, patients will receive a phone call asking for the reason. Technical issues will be addressed immediately. In case of loss of the Kardia device, a new device will be provided free-of-charge. If patients wish to discontinue their recordings, they will be considered lost to follow-up.

7-Day Holter monitor
For this study, H3+ recorders (Mortara Instrument, Milwaukee, WI, USA) are deployed. All Holter recorders are battery powered and electrically safe. The Holter recorders have a CE mark. The H3+ recorder records three ECG channels continuously. A total of 5 electrodes are applied to the patient’s chest and abdomen. ECG data will be downloaded and analysed using the H-Scribe Holter Analysis System (Mortara Instrument, Milwaukee, WI, USA). This software package analyses the ECG for R-R wave irregularities and automatically detects possible abnormalities such as premature atrial contractions, premature ventricular contractions, supraventricular arrhythmias and ventricular arrhythmias. All Holters are checked by a PhD-Student (who is not blinded to patient data) with ample training and experience at the Holter department, supervised by an experienced senior observer, who is blinded to the patient data. The 7-Day Holter monitor can be discontinued on patient’s request or in case of serious allergic reactions to the patches.

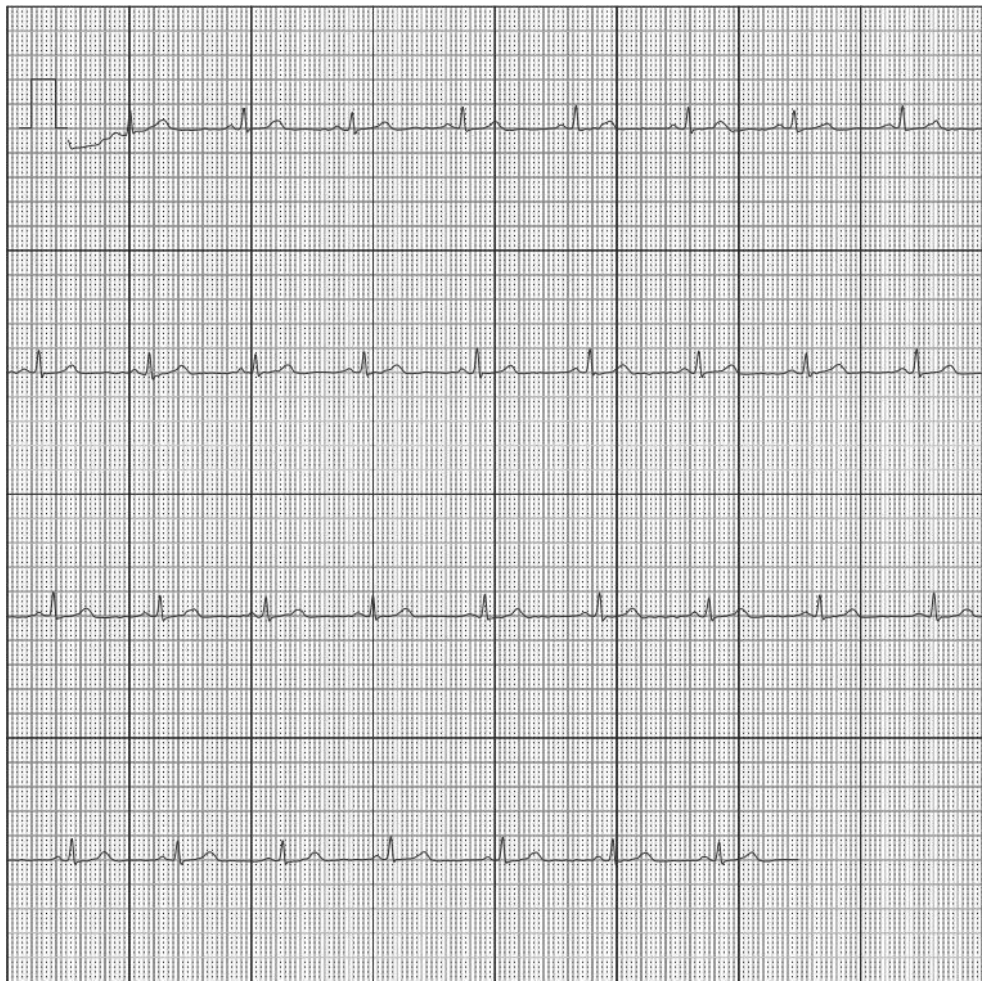

Figure 1. An electrocardiogram (ECG) recorded by the AliveCor device showing sinus rhythm.

Study design, randomization and follow-up

The Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection trial (MOBILE-AF) is an international multicentre (a list of the six participating centres can be found in Appendix A) randomized open clinical trial, registered under clinical trial numbers NCT02507986 (www.clinicaltrials.gov) and NL54103.058.15 (www.toetsingonline.nl), in accordance with the SPIRIT guidelines (in Appendix B). A flow-chart of the study design is given in Figure 3. It randomizes patients, after inclusion, to follow-up with either the Kardia Mobile (intervention group) or the 7-Day Holter monitor (control group). Block randomization will be performed. Randomization will be stratified per centre and per diagnosis (TIA or

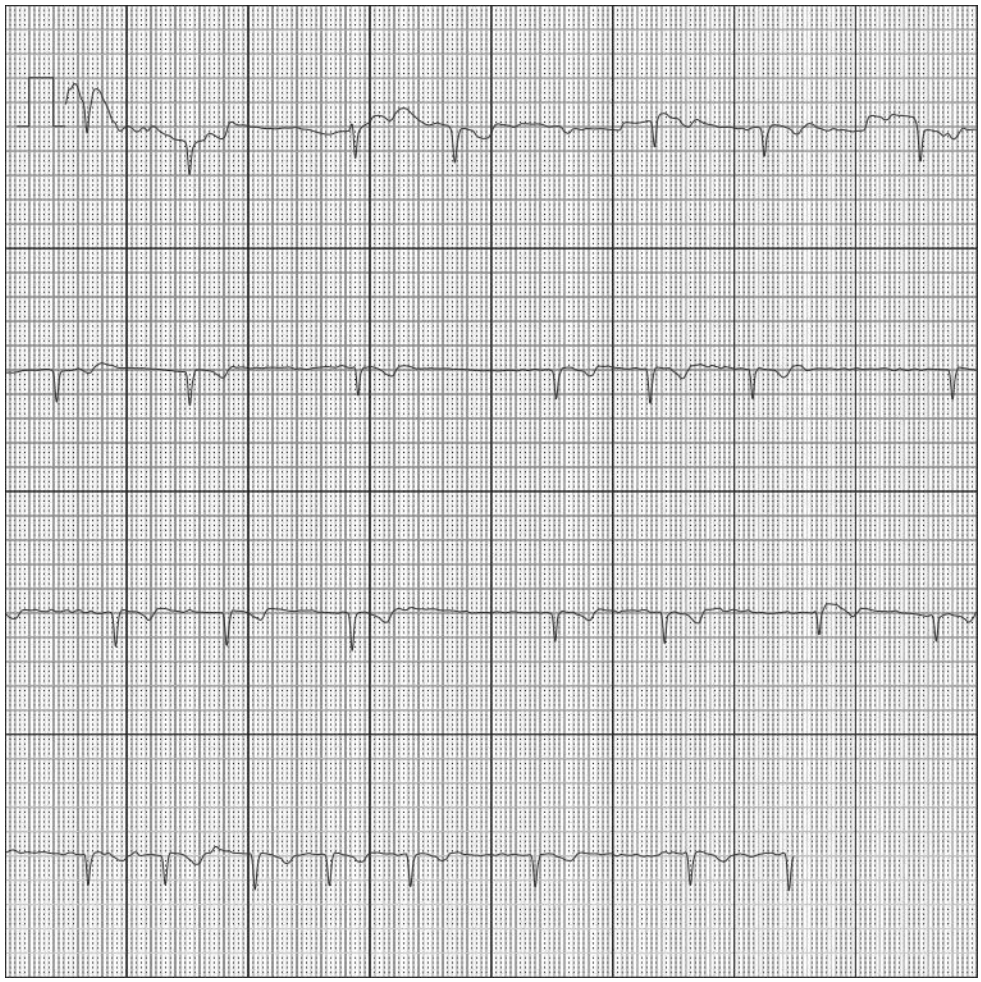

Figure 2. An electrocardiogram (ECG) recorded by the AliveCor device showing atrial fibrillation.

ischaemic stroke). The allocation sequence will be generated using a website (www.randomizer.org) and stored in an Excel (Microsoft, Redmond, Washington, United States of America). The document is only accessible for a PhD-student who is not otherwise involved in the trial. Patients will be approached and randomized by a project dedicated PhD-Student. This PhD-Student will not have access to the allocation sequence.

When randomized to the intervention group, patients will receive the Kardia Mobile device. Patients will receive this device immediately after randomization. Patients will be instructed by a dedicated PhD-Student about the usage of the Kardia Mobile,

including downloading the app, setting up an account and recording an ECG with the Kardia Mobile device.
Patients are requested to record an ECG at least twice daily, with the two measurements separated by at least 6 hours. Furthermore, patients are urged to record an ECG in case of any symptoms of possible cardiac origin, as judged by the patient.

When randomized to the control group, patients' heart rhythm will be recorded for 7 consecutive days (24 hours per day), using the 7-Day Holter monitor. This will be done directly after randomization. After 7 days, patients are referred to regular follow-up after ischaemic stroke or TIA. Regular follow-up usually consists of a referral to the general practitioner who will see patients only in case of symptoms. However, patients might also be followed-up at the site of referral, in which case a patient might have one more scheduled visit to the cardiologist. This is left to the discretion of the treating cardiologist.

In case AF is detected, the recording is sent to the treating cardiologist. The treatment options, including the decision to change anticoagulation treatment, will be left to the discretion of the treating cardiologist.
Patients will continue to participate in the trial, even though AF is documented. Each ECG that shows AF will be sent to the treating cardiologist of the patient.
All patients will continue to receive regular follow-up after cryptogenic stroke or TIA. All study actions are additional to regular follow-up. For both groups at 12 months, a phone call will be scheduled including a standardized interview (Appendix B). If a patient has been admitted to another hospital than the participating centre, the patient and hospital will be asked to share all relevant health information.

Study outcomes
The primary outcome of this study is the percentage of patients in which AF is detected in the first year after the index ischaemic stroke or TIA. The primary outcome will be assessed by two cardiologists who will be blinded to patient data. Both will be working independent from each other. Any disagreements will be solved by consensus. AF is defined as a rhythm with completely irregular RR intervals and no distinct P-waves on the surface ECG.(15)

Secondary outcomes are
1. Pro-BNP levels in all patients within 24 hours after cryptogenic stroke
2. Percentages of atrial ectopy detected on the 24-hour Holter monitor
3. Left atrial diameter and volume on 2D-echocardiography

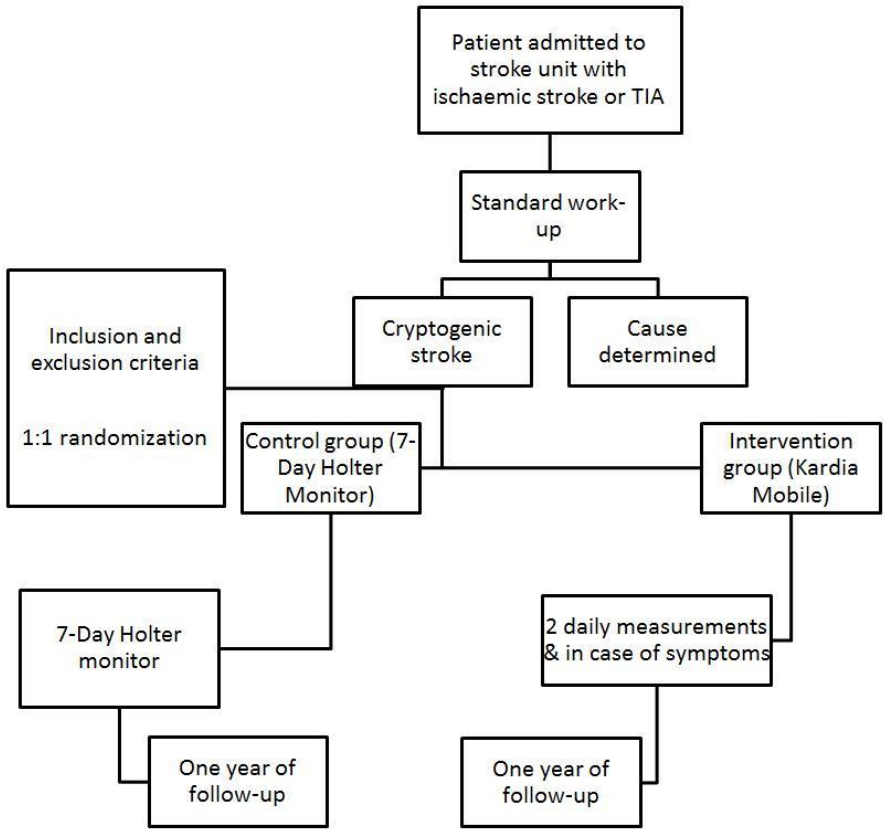

Figure 3. Flowchart of study design

4. Percentage of patients on oral anticoagulation therapy at the beginning and at the end of the study.
5. The incidence of recurrent ischaemic stroke or TIA. Ischaemic stroke will be defined as an episode of neurological dysfunction caused by focal brain or retinal ischaemia with recent infarction on cerebral imaging.(13) TIA is defined as a transient episode of neurologic dysfunction lasting less than one hour caused by focal brain or retinal ischaemia without recent infarction on cerebral imaging.(14) All recurrent ischaemic strokes and TIAs will be evaluated by two neurologists based on information noted in the electronic health records, working independently of each other. Any disagreements will be solved by consensus.
6. Major bleeding (defined as: any bleeding that needs medical treatment or hospital admission/prolongation of admission)
7. Number of single lead ECGs taken per patient, as a measure of compliance

8. Number of Holter studies (either 24-hours, 48-hours or 7-day) done after randomization in both groups (in which the 7-day Holter monitor that is done as part of the trial protocol is not included)
9. Time (in days) between randomization and detection of first AF episode.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT**	0	0	1 week	1 year	1 year
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
7-Day Holter monitor			x		x
ECG device (Kardia Mobile)			X	X	x
ASSESSMENTS:					
Prior stroke, prior TIA, primary diagnosis, gender, hypertension, diabetes, smoking status, alcohol, previous bleeding, drug abuse, abnormal liver function, abnormal renal function	X	X			
AF, recurrent stroke, major bleeding, Pro-BNP, atrial ectopy on Holter, change in therapeutic regimen			x	x	X

Figure 4. Standard protocol items: recommendations for interventional trials (SPIRIT) Figure: schedule of enrolment, interventions and assessments.

Statistical analysis

The power calculation was done in PASS (Hintze J. (2008). PASS 2008. NCSS, LLC. Kaysville, Utah, CO. www.ncss.com) and is based on a comparison of two proportions of patients with diagnosed AF in a two by two table with a chi-squared statistic or odds ratio calculated. The underlying assumption is that in 2.0% of the 7-Day Holter monitor group AF will occur. This proportion is assumed to be 12.4% in the Kardia

Mobile group. These percentages are based on the results of the CRYSTAL-AF trial. (6) A sample size of 200 patients was calculated with an alfa level of 0.05 and a power of 0.85. Patients will be 1:1 randomized.
Data will be analysed according to the intention-to-treat principle. After completion of the inclusion of study patients, the proportion of patients with AF will be compared with a Chi-squared test or rate ratio (RR). Causes of missing data will be tabulated. Because of the expected low percentage of missing data, complete case analysis will be done. Analysis will be based on the missing-at-random assumption. In case of serious imbalances of baseline variables after randomization, additional Poisson regression might follow with correction for potential confounding variables at baseline.

Ethical conduct

The study will be conducted according to the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice. Potential study subjects will be approached by a project dedicated PhD-Student who is not involved in their treatment. Written informed consent will be obtained from all study participants before randomization. For this study, no data monitoring committee is installed, because both devices are battery powered an electrically safe. They do not bring risks to patients safety. The absence of a DMC is approved by the hospital's MEC. All devices used bear a CE mark and are approved by the United States Food and Drug Administration (FDA). No manufacturer of any devices used in this study is involved in study design, data collection, data analysis, data interpretation or writing of the report. No financial support or any other form of support is received for this study from any manufacturer. If the protocol changes as such that it affects participants who are already participating in the trial, they will be notified by telephone or e-mail by a project dedicated PhD-Student. It is our intention to publish the results of the trial in a peer-reviewed scientific journal.

Data safety

Data Collection Forms, Case Report Forms, Informed Consent Forms and all other study documentation containing subject information will be stored under locked conditions when not in use. Computers and all storage devices containing study data will be password-protected. Data stored on the computer will use an numeric code to identify the subject. Personal information will be kept in a password protected, separate document. Access to data is restricted to study personnel and when required the MEC or the Healthcare Inspectorate as required by Dutch law. No personnel of any manufacturer of any device involved in the study will have access to the study data.

Timeline

The sample size is 200 patients. Our trial started on July 29th, 2016. Our proposed end date is July 1st, 2019. Currently, 6 hospitals are referring patients for the trial. Each center has an estimated sixty patients per year that are eligible for this study. In case of slow recruitment (less than eighty patients in one year), more hospitals will be approached to refer patients for participation in the trial. This will be communicated via clinicaltrials.gov. A final list of centers that referred patients for the trial will be published when the final results of the trial are available.

Discussion

The MOBILE-AF trial is an international multicentre randomized clinical trial that evaluates the efficacy of the Kardia Mobile device in the detection of AF in cryptogenic stroke and TIA patients. To our knowledge, this is the first and only clinical trial that uses the Kardia Mobile for this indication. The Kardia Mobile is a validated device that is non-invasive and easy-to-use. Because of its negligible burden on the patient, its low cost and the fact that it can be used by patients on demand, without the presence of trained health care staff, to our opinion it has potential to improve the yield and cost-effectiveness of AF detection in this population.

Subclinical AF after cryptogenic stroke and subsequent risk of recurrent stroke

Currently, there is scientific uncertainty about the causal relationship between subclinical paroxysmal AF following cryptogenic stroke and the subsequent risk of recurrent stroke.(8, 16-19) In contrast, clinical AF has been a long known independent risk factor for ischaemic stroke.(2) More recent trials in patients without prior ischaemic stroke and implanted pacemakers or ICDs demonstrated that also subclinical paroxysmal AF increased ischaemic stroke risk.(20, 21) One of these trials, the ASSERT trial, found a 2.5 fold increased risk in patients who experienced episodes of subclinical AF lasting more than six minutes. This risk tended to increase in patients who experienced longer or more frequent episodes of subclinical paroxysmal AF. However, the authors noted that the study was underpowered to draw conclusions about this particular question.(20)

Detecting subclinical AF after cryptogenic stroke

In the CRYSTAL-AF trial, 12.4% of paroxysmal AF was found after 12 months in patients wearing an ICM. Of these episodes, 79% were asymptomatic. The median value of maximum duration of an AF episode was 11.2 hours. A total of 61% of all AF episodes was longer than 6 hours.(6) In the EMBRACE trial no data on AF symptoms are given. Of the 284 patients randomized to the 30-day ECG monitoring, 56 (19.7%) had AF of any duration. A total of 44 patients (15.5%) had at least one

episode which lasted longer than 30 seconds. A total of 28 patients (9.9%) had at least one episode which lasted longer than 2.5 minutes.(7)
The Kardia Mobile produces a PDF in which 30 seconds of measurement are shown. Therefore, the duration of an paroxysmal AF episode cannot be adequately determined by the Kardia Mobile. However, we consider it likely that a 30-second recording of AF on the Kardia Mobile will be part of a longer during episode of AF. In comparison, in the CRYSTAL-AF trial 61% of patients with detected AF had episodes which lasted longer than 6 hours.(6) As we expect that most patients will perform a Kardia Mobile measurement twice daily, the chances that the Kardia Mobile will detect sporadically occurring AF episodes lasting only several minutes are low.

Prevention of recurrent stroke
Determining the percentage of anticoagulants users, the percentage of recurrent strokes and the percentages of major bleedings are secondary objectives of the MOBILE-AF trial. At the end of the CRYSTAL-AF TRIAL, 10.1% in the ICM group and 4.6% of all control group patients used OAC. Recurrent stroke occurred in 5.2% in the ICM group and 8.6% in the control group. These results may indicate that OAC in patients with subclinical AF indeed lowers the risk of recurrent stroke. However, no data were shown about the relationship between duration or frequency of AF episodes and recurrent stroke. Furthermore, the study was underpowered to draw conclusions about this specific relation.(6) It therefore remains unclear whether subclinical AF in cryptogenic stroke is of clinical importance. For this reason, we leave the decision to start OAC to the discretion of the patient's treating cardiologist. We will however carefully monitor percentages of patients in which OAC was described, as well as the main effect (stroke recurrence) and side effect (major bleedings) and therefore included these in our secondary objectives.

Prediction of AF occurrence
There are a number of publications available about prediction of the occurrence of mainly paroxysmal AF after cryptogenic stroke or TIA. One is a paper by Rodriguez-Yanez et al., who evaluated 372 patients with cryptogenic stroke. Pro-BNP levels were determined within 24 hours of stroke onset. Patients were followed-up for 2 years for the development of AF. The authors concluded that a pro-BNP≥360 pg/mL had a negative predictive value of 98.6%. Overall, 5.6% of all stroke patients was found to have AF.(22) This is a relatively low percentage, compared with the CRYSTAL-AF (12.4% after one year) and EMBRACE (16.2% after 90-days).(6, 7) This might be explained by the frequency of monitoring: follow-up was done by taking elective 12-lead 10-seconds ECGs. No continuous monitoring was applied.(22) Therefore, as our trial involves more frequent ECG monitoring, we would like to corroborate that a pro-BNP≥360 pg/mL has indeed a high negative predictive value.

A second is a paper by Gladstone et al., who evaluated 237 patients with cryptogenic stroke or TIA. They assessed the amount of atrial premature beats (ABP) on the 24-hour Holter monitoring which was part of the standard work-up of cryptogenic stroke. They found that the amount of ABPs was strongly and independently associated with the development of subclinical AF within 90 days after cryptogenic stroke.(23) We would like to also confirm these findings in our population.
A third is a paper by Tsang et al.(24), who investigated the relationship between left atrial diameter and volume and the development of AF. They found that an increase in left atrial volume was independently associated with the development of AF. Although this study was not performed in patients who had experienced a cryptogenic stroke, we believe this might also be true for our population. We therefore would like to verify the study's findings in our population.(24)
To our knowledge, these three predictors have not been combined into a prediction score yet. We would like to combine the three predictors and develop a prediction score for the occurrence of paroxysmal AF after cryptogenic stroke or TIA, in order to individualize monitoring strategies for these patients.

Summarizing, we present a study that is designed to investigate the effectiveness of the Kardia Mobile to detect AF in patients with cryptogenic stroke. The Kardia Mobile is a device with serious potential to improve clinical and cost-effectiveness. The first results can be expected end 2018.

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