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Impact of standardized monitoring for detection of atrial fibrillation in ischemic stroke (MonDAFIS)

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Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke (MonDAFIS) – Rationale and design of a prospective randomized multicenter study

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**Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke (MonDAFIS)
– Rationale and design of a prospective randomized multicenter study**

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Abstract**Background**

Atrial fibrillation (AF) is estimated to account for approximately every fifth ischemic stroke. In routine clinical practice, detection of undiagnosed, clinically silent AF represents a major diagnostic challenge, and in up to 30% of patients with ischemic stroke AF remains undetected. The MonDAFIS study has been designed to quantify the diagnostic yield and clinical relevance of systematic ECG monitoring for patients with acute ischemic stroke during the subsequent in hospital stay.

Study Design

Prospective randomized multicenter study in 3,470 patients with acute ischemic stroke or TIA and without known AF on hospital admission. Over a period of approximately 2 years patients will be enrolled in about 30 German certified stroke units and randomized 1:1 to receive either usual stroke unit diagnostic procedures for detection of AF (control group) or usual stroke unit diagnostic procedures plus standardized and centrally analyzed Holter ECG recording for up to 7 days in hospital (intervention group). Results of the ECG core lab analysis will be provided to the patients and treating physicians. All patients will be followed for treatment and cardiovascular outcomes at 6, 12, and 24 months after enrolment.

Outcomes

The primary outcome of the randomized MonDAFIS study is the proportion of patients who receive anticoagulation therapy 12 months after the index stroke. Secondary outcomes include the number of stroke patients with newly detected AF in hospital and the rate of recurrent stroke, major bleedings, myocardial infarction or death 6, 12, and 24 months after the index event. MonDAFIS will also explore patient-reported adherence to anticoagulants, the clinical relevance of short atrial tachycardia or excessive supraventricular ectopic activity as well as cost-effectiveness of prolonged, centrally analyzed ECG recordings.

Conclusion

MonDAFIS will be the largest study to date to evaluate whether a prolonged and systematic ECG monitoring during the initial in hospital stay has an impact on secondary stroke prevention. In addition, prognosis as well as adherence to medication up to two years after the index stroke will be analyzed. The primary results of the MonDAFIS study may have the potential to change the current guidelines recommendations regarding ECG work-up after ischemic stroke.

Trial registration

Clinicaltrials.gov NCT02204267

Background

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia and, as its incidence is associated with age, the absolute number of patients with AF will increase in the next years due to the ageing of the societies. AF is associated with a four- to fivefold increase of stroke risk and may account for every fifth ischemic stroke. Moreover, AF patients suffering a stroke have a poorer prognosis and a higher stroke recurrence rate than do stroke patients without AF.¹

National and international guidelines recommend long-term oral anticoagulation for ischemic stroke patients with paroxysmal, persistent or permanent AF with the highest level of evidence, while the use of antiplatelet agents does not result in a relevant stroke risk reduction in AF patients. The clinical availability of non-vitamin K antagonist oral anticoagulants (so called novel oral anticoagulants or NOACs) has overcome many of the practical difficulties of oral anticoagulation therapy, rendering anticoagulation a valid treatment option for the vast majority of stroke survivors with AF.¹⁻⁴ Detection of clinically “silent” paroxysmal AF represents a major diagnostic challenge in patients with acute ischemic stroke, and AF remains undetected in a relevant proportion of stroke patients.⁵ Prolonged ECG monitoring⁶⁻¹⁰ and systematic analysis of ECG recordings¹¹ enhances detection of non-permanent AF after ischemic stroke, but data from randomized prospective trials is limited to the subset of patients with cryptogenic stroke^{9,10} while observational data suggest that a substantial portion of non-cryptogenic stroke patients also suffers from silent AF.^{7,12} However, the ECG method of choice is still a matter of debate. While implantable cardiac-event recorders⁹ seem to solve the question of optimal duration of ECG monitoring, its invasive implantation procedure and current costs do not support routine use in unselected stroke patients. On the other hand, Holter monitoring is readily available and non-invasive, but recording time is to a certain extent limited.^{6,7,10}

Surprisingly, current stroke guidelines do not strictly recommend ECG monitoring for longer than 24 hours¹³; nor do they specify the requirements for ECG analysis in stroke survivors. Subsequently, there is no common practice or “gold standard” for ECG monitoring in most healthcare systems including the German stroke unit system¹¹, which most likely results in a substantial under-diagnosis of AF in stroke survivors and potentially the occurrence of otherwise preventable ischemic strokes.

MonDAFIS is the first large, prospective multicenter study to include a systematic assessment and a randomized comparison of the diagnostic yield and therapeutic impact of prolonged inpatient ECG monitoring for clinically silent paroxysmal AF in an unselected cohort of stroke survivors. Furthermore, this investigator initiated study will assess the clinical relevance of short atrial tachycardia as well as excessive supraventricular ectopic activity, both of which are frequently found in stroke patients.^{6,14} In addition, the prospective MonDAFIS study will assess how persistence and adherence to prescribed medication impacts on outcome after ischemic stroke.

Methods

Ethical conducts

The Charité - Universitätsmedizin Berlin is the sponsor of the investigator initiated MonDAFIS study (Clinicaltrials.gov NCT02204267). The study received primary approval from the Ethics Committee of the Charité - Universitätsmedizin Berlin, Germany (EA2/033/14) and all participating centers will procure approval from their respective ethics committees. All study procedures are carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All study patients have to give informed consent.

Sources of funding

The MonDAFIS study is supported by an unrestricted research grant to the Charité - Universitätsmedizin Berlin from Bayer Vital GmbH, Bayer HealthCare Pharmaceuticals, Germany. No sources of funding were used to support the creation of this paper. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study design

This study is based on the observations of the non-randomized “Find-AF” study⁶, which demonstrated a significantly increased detection rate of paroxysmal AF in patients with acute ischemic stroke by using a 7 day Holter ECG. Stroke patients without known AF who fulfilled the study entry criteria (**Table 1**) will be consecutively enrolled and randomized on a 1:1 basis either to undergo additional continuous Holter ECG recording for up to 7 days during the in hospital stay (“intervention group”) or to undergo no additional ECG recording (“control group”) (**Table 2**). Randomization is stratified by the participating centers. Patients and treating physicians will be aware of diagnostic procedure allocation. The rationale of including not only cryptogenic strokes but all ischemic strokes in MonDAFIS is the class I recommendation to anticoagulate AF patients with ischemic stroke, irrespective of stroke etiology.¹ Moreover, observational studies suggest that systematic ECG screening identifies so far undiagnosed paroxysmal AF in stroke patients classified as non-cryptogenic and non-cardio-embolic.⁶⁻⁷

Study centers

The stroke units chosen for participation will represent a comprehensive coverage of all levels of care. About 30 German stroke units will take part in the study. All study centers have to be certified according to the regulations of the German Stroke Society. Presently, there are more than 260 certified stroke units in Germany. At present, about 80% of all stroke patients are receiving stroke unit

care in Germany (OB; personal communication). We aim to enroll patients at “regional” stroke units, non university-based stroke centers and university-based stroke centers in a 40%: 30%: 30% ratio.

ECG monitoring

All study patients (control group as well as intervention group) will receive at least 24 hours of (monitor-based) ECG monitoring on the stroke unit (defined as usual care according to the current German Diagnosis Related Groups (DRG) system). Additional ECG recording will be performed in parallel using the portable LIFECARD CF recorder (SPACELABS, Germany). Additional Holter ECG recording in the intervention group will start as soon as possible (but at the latest 24 hours after admission at the stroke unit), and will be continued (as long as possible) until hospital discharge or for a maximum of 7 days. We estimate an average duration of 96 hours in study patients randomized to the intervention group. Study ECG data from Holter recordings will be transmitted to a cardiac core lab for analysis. Results of the core lab analysis will be communicated to the respective study patient and the patient’s physician if indicated as soon as possible but no later than three weeks after hospital discharge in a telephone follow-up performed by the enrolling study center. Moreover, the report will be sent by mail to the patient and the treating physician. Additional ECG monitoring after hospital discharge is neither intended, strictly recommended nor restricted, and will be done at the discretion of the treating physicians.

Cardiac core lab analysis

ECG data will be transmitted to the Holter ECG core lab in Birmingham, UK (coordinated by PK), analyzed by specifically trained personnel, and reviewed by a trained physician. The report will classify each Holter ECG as recording with and without AF. Each core lab report will contain the following items:

- 1) Presence or absence of AF, defined in accordance with the current ESC guideline as an absolute arrhythmia lasting ≥ 30 seconds¹. In all patients with AF, the number and duration of AF episodes will be reported.
- 2) Atrial flutter will be reported separately, and the study protocol stipulates that anticoagulation for atrial flutter must be initiated in the same way as it is for atrial fibrillation.
- 3) Underlying heart rhythm.
- 4) Minimal, maximal, and mean heart rate.
- 5) Longest pause and number of pauses.
- 6) Presence or absence of AV block including degree of AV block.
- 7) Time and duration of recording.

Incidental findings of medical relevance (e.g. ventricular tachycardia including torsade de pointes) will also be reported. Dedicated alerts will be reported when medically relevant findings are identified. We will also analyze all ECGs for atrial ectopy, short-lasting atrial arrhythmias not qualifying as AF, and other Holter ECG parameters for pre-specified exploratory analyses.

Baseline visit

Baseline assessment of all study patients will include: a detailed analysis of patient demographics, clinical characteristics (including the National Institute of Health Scale Score, the modified Rankin Scale score, the CHADS₂ and CHA₂DS₂-VASc score), vital signs, medical history, and concomitant diseases, duration, method(s) and success of inpatient ECG recording, laboratory results, imaging results (head CT/MRI, carotid ultrasound of brain-supplying arteries, echocardiography), suspected cause of stroke at hospital discharge according to TOAST criteria¹⁵, and previous symptoms probably related to undetected paroxysmal AF (such as intermittent breathlessness, palpitations, dizziness or fainting) to differentiate symptomatic from asymptomatic AF. Despite of a non-standardized monitoring and assessment of supraventricular ectopy and short atrial runs in the control group, we will collect this information by analyzing the final patient report at discharge from the respective study center.

Follow-up

Follow-up will be carried out six months, one and two year(s) after the index stroke by a central, standardized telephone interview conducted by trained study nurses at the Center for Stroke Research Berlin, Germany. The following data will be assessed: medication, recurrent ischemic stroke and other major vascular events, major bleeds, (all-cause) death, indications for the prescription of oral anticoagulation (including prescriptions unrelated to AF), the modified Rankin Scale score, the EQ-5D, the European Heart Rhythm Association (EHRA) score of atrial fibrillation as well as the Morisky Medication Adherence scale (MMAS-8; 1 year after the index stroke only) (**Table 2**). Central follow-up will be done in a blinded fashion with regard to the randomization after enrolment.

Study outcomes

The primary outcome is the difference in the proportion of study patients on oral anticoagulation (NOAC or vitamin K antagonist (VKA)) at 12 months after the index stroke, randomized either to usual in-hospital diagnostic procedures plus standardized prolonged ECG monitoring or to usual in-hospital diagnostic procedures. The primary hypothesis is that the self-reported proportion of stroke patients on oral anticoagulants 12 months after the index stroke is higher in the intervention group than in the control group. We plan to validate the accuracy of the provided information in a subgroup of patients by double-checking the prescribed medication by the treating physicians. There are no study-specific recommendations regarding the individual medical treatment for stroke prevention, which is completely at the discretion of the treating physicians. All secondary outcomes are listed in **Table 3**.

A critical event committee consisting of at least one cardiologist and one neurologist will adjudicate all serious adverse events of special interest (like recurrent stroke, myocardial infarction, major bleeding or death) as well as the primary endpoint of this study (blinded to the result of randomization). The

data safety monitoring board (DSMB) will monitor potential consequences of delayed communication of core lab results in the intervention group (i.e. hospitalization due to cardiac arrhythmia, stroke or death) as well as adverse events in the context of additional ECG monitoring in hospital (i.e. falls or skin lesions).

Statistical analysis

The sample size calculation is based on the endpoint “proportion of patients with self-reported oral anticoagulation 12 months after the index stroke”. We will test the null hypothesis that the proportion of self-reported oral anticoagulation 12 months after index stroke in patients undergoing usual ECG monitoring in hospital (control group) is equal to the proportion in patients with additional continuous ECG monitoring during the in hospital stay (intervention group). This will be tested with a two-sided Fisher’s exact test at significance level 0.05. We assume a 1:1 group proportion. According to Rizos et al.¹² we assume a proportion of 2.8% of paroxysmal AF undergoing usual stroke unit monitoring for 24 hours (control group) and 7.7% with additional continuous ECG monitoring for 3-4 days during the in-hospital stay (intervention group). We assume that 90% of patients with newly detected paroxysmal AF receive oral anticoagulation or are given a recommendation for oral anticoagulation after hospital discharge. At 12 months we assume a proportion of 65% of all patients with persistent use of oral anticoagulation according to previous studies.¹⁶ This yields a proportion of 1.64% patients on anticoagulation at 12 months in the control group and 4.50% in the intervention group. Moreover, we have to keep in mind an additional proportion of patients who receive anticoagulation in both groups for 1 year after hospital discharge due to AF detection after recurrent stroke.

By assuming an annual rate for recurrent stroke or systemic embolism of 9.16% in patients with undetected paroxysmal AF¹⁷ in up to 5.0% of patients in the intervention group and in up to 9.9% in the control group (considering a maximal proportion of 12.7% patients with paroxysmal AF⁶), we assume that an additional proportion of up to 0.91% of patients in the control group and of 0.46% in the intervention group will receive anticoagulation at 1 year due to AF detection after hospital discharge. This leads to the assumption of an overall proportion of 2.55% of patients with self-reported oral anticoagulation in the control group and of 4.96% in the intervention group. Accordingly, a sample size of $2 \times 1,388 = 2,776$ will ensure detecting a significant deviation from the null hypothesis with a power of 90%. Assuming a dropout rate of 20%, a total sample size of 3,470 patients is needed. To ensure a high external validity, we are aiming to recruit from consecutive patients enrolled in settings that are close to clinical reality. Therefore, we do not apply any major inclusion or exclusion criteria. In observational studies in health services research, a drop-out rate of 20% at one-year follow up is common^{18,19} and can generally be attributed to loss to follow-up (e.g. change of residence without notice of change of address) and to all-cause death within the first year after stroke. We would not

assume differential dropout rates between the control and the intervention group. All secondary outcomes will be evaluated using appropriate descriptive, univariate and multivariate statistical methods based on the underlying distribution of the data.

Study schedule

The first patient was enrolled in December 2014 at the Charité - Universitätsmedizin Berlin. After starting enrolment in ten sites in April 2015, we aim for a recruitment period of approximately 2 years, ending in spring 2017. With regard to the planned duration of follow-up, first patient in to last-patient out will be approximately 4.5 years. The planned duration of the entire study is five years.

Current status of recruitment

As at September 28th, 2015, 580 (16.7 %) of 3,470 patients were enrolled to the MonDAFIS study in 23 active study centers in Germany. Moreover, 3 study centers are initiated but are not yet recruiting.

Discussion

By using non-invasive, commonly available Holter monitoring, this investigator-initiated prospective randomized multicenter study will uncover the true burden of undiagnosed AF in a representative - almost unselected - sample of patients with acute ischemic stroke or TIA while they are being treated in hospital. These findings have the potential to impact on patient management, as oral anticoagulation is the secondary prevention of choice in stroke or TIA survivors when AF has been documented.^{1,3} Early optimization of secondary stroke prevention might help to minimize recurrent stroke in this cohort and further strengthen the importance of stroke unit as well as in hospital care.

Unique features of the MonDAFIS study are the very large sample size including not only cryptogenic strokes but all ischemic strokes as well as the control group, allowing us to focus on the potential impact of prolonged in-hospital ECG recording on medical secondary stroke prevention during mid-term follow-up. MonDAFIS will provide valuable new insights into the detection rate of "silent" AF in almost unselected stroke patients, thereby supplementing the available detailed information on patients with cryptogenic stroke.^{9,10} Moreover, the study ECG data will be analyzed by a cardiologist, while stroke unit monitoring in Germany rarely involves a cardiologist.¹¹ Subsequently, our data will allow us to estimate the impact of advanced diagnostic measures on the rate of cardiovascular events and patient outcome after acute ischemic stroke, as similarly reported for stroke unit treatment.²⁰ MonDAFIS therefore has the potential to impact on the so far limited guideline recommendations for ECG monitoring after stroke in hospital.¹¹ By including of approximately 30 study sites, the MonDAFIS

study will also provide important data regarding the current level of diagnostic care for AF detection on different levels of stroke units in Germany.

Besides patient persistence in taking an oral anticoagulation during clinical course, the important question of adherence to medication will be addressed. Moreover, we will explore the clinical relevance of short lasting atrial runs, which are a common finding in stroke patients^{6,8} but appear to be independently associated with a twofold higher risk of subsequent stroke according to US claims data.²¹ Furthermore, we will assess the prognostic impact of excessive supraventricular ectopic activity, also frequently found in stroke patients¹⁴ and associated with an almost threefold risk of admission for atrial fibrillation or stroke in the Copenhagen Holter Study.²² Nevertheless, there is no recommendation to use oral anticoagulants for secondary stroke prevention in patients with excessive supraventricular ectopic activity or short lasting atrial runs. Regarding the prognostic impact of excessive supraventricular ectopic activity and the rate of undetected AF in stroke patients, the awaited results of the Find-AF_{RANDOMIZED} study will add substantial information.²³ This randomized study has enrolled 400 patients with acute ischemic stroke in four German Stroke Units. By using repetitive ECG recording in the intervention group also during follow-up, the primary endpoint of Find-AF_{RANDOMIZED} is the detection of AF/atrial flutter within six months after the index stroke or before recurrence of stroke or systemic embolism.

By assessing stroke unit care in Germany, MonDAFIS might underestimate the effect of prolonged ECG monitoring in other health care systems with less intensive routine ECG work-up. Moreover, the duration and quality of additional ECG recording may be influenced by patient empowerment and the participation of nursing staff and physicians. In addition, there might be a selection bias by not including stroke patients who are not able to provide informed consent. Despite the fact that nurses and treating physicians are blinded for the results of the additional ECG recordings in the intervention group (because the ECG curve is not displayed while being recorded), the open-label design of the study might cause a bias. Study centers were, however, encouraged to avoid differences in usual diagnostic care in both study arms. While there might be a discrepancy in the quality of ECG analysis between the study arms. The control group nevertheless represents clinical routine in Germany.

Conclusion

In summary, MonDAFIS will be the largest study to date to evaluate systematic ECG monitoring in stroke survivors. The MonDAFIS study is in line with the intention of best-medical and individualized therapy. If successful, this randomized multicenter study could motivate important modifications of current diagnostic standards after acute ischemic stroke or TIA, and thus improve secondary stroke prevention in daily clinical practice.

Abbreviations

Atrial fibrillation, AF; Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke, MonDAFIS; novel oral anticoagulants, NOACs; vitamin K antagonists, VKAs.

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Conflict of interest

KGH reports speaker's honoraria, consulting fees, lecture honoraria and study grants from Bayer Healthcare, Sanofi, Pfizer and Bristol-Myers Squibb. A full list of conflicts of interest for PK is available on the home page of the ESC (www.escardio.org). PUH reports grants from Charité-Universitätsmedizin Berlin during study conduct (within MonDAFIS for biometry; member scientific board; MonDAFIS is supported by an unrestricted research grant to the Charité from Bayer); grants from BMBF, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, University Göttingen (within FIND-AF randomized for stroke adjudication; member stroke adjudication committee; Find-AF_{RANDOMIZED} is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), and University Hospital Heidelberg (within RASUNOA-prime for biometry and data management; member steering committee; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim), outside submitted work. UL reports honoraria/reimbursements for lectures, participation in studies, scientific cooperations (with Saarland University), consulting, travel, support (of colleagues) or support of scientific meetings [within the last 5 years] by ABDA, AkdÄ, Amgen, AstraZeneca, Bayer, Berlin-Chemie, Boehringer-Ingelheim, DACH, Daiichi-Sankyo, DFG, EU, i-cor, Lilly, Medtronic, MSD, Pfizer, Roche, Sanofi, Servier, Stifterverband, Synlab, Uds, UKS. OB and CB report no conflicts of interest. GT has received speaker's honoraria and consulting fees from Acandis, Bayer Healthcare, Boehringer Ingelheim, Covidien, Bristol-Myers-Squibb and Pfizer. DGN has received speaker's honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi Sankyo, Novartis and Pfizer. JR has received speaker's honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Pfizer and Astra Zeneca. RV has received speaker's honoraria, consulting fees and research support from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi Sankyo, Apoplex medical technologies, Novartis and Pfizer. ME reports lecture fees and study grants by Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Ever, Glaxo Smith Kline, MSD, Novartis and Pfizer.

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Table 1

MonDAFIS: Inclusion and exclusion criteria.

Inclusion criteria
<ul style="list-style-type: none"> • Written informed consent. • Age \geq 18 years. • Acute ischemic stroke or TIA (persisting neurological deficit on admission and / or matching brain lesion on MR imaging). • Stroke unit admission within 72 hours after onset of stroke-related symptoms. • Enrolment within 24 hours after stroke unit admission. • Start of ECG recording within 24 hours after stroke unit admission (according to randomization) • Sufficient knowledge of German. • Willingness to participate in follow-up.
Exclusion criteria
<ul style="list-style-type: none"> • Known AF before hospital admission. • AF according to 12-lead ECG on hospital admission. • AF according to inpatient ECG recording / stroke unit monitoring before enrolment. • Pre-stroke life expectancy less than 1 year. • Post-stroke life expectancy less than 1 month. • Participation in an interventional study. • Pregnancy and / or breast-feeding. • Implanted devices with the ability to record AF

Table 2

Flowchart of the MonDAFIS study.


	In hospital stay				Follow-up		
	on Ad- mission	Day 1	Day ≥2	Hospital Discharge	6 months	12 months	24 months
Past medical history	X			X	X	X	X
Current medication	X			X	X	X	X
Brain CT or MRI	X	X (if assessed)					
12-lead ECG	X	X (if assessed)					
Stroke Unit monitoring		X					
Additional ECG monitoring		<i>1:1 Randomisation</i>					
24 hour Holter		X (if assessed)					
Echocardiography	X (if assessed in clinical routine)						
NIHSS score/ mRS score	X			X	mRS	mRS	mRS
EQ-5D				X		X	
MMAS-8						X	
Laboratory assessment	X (if assessed in clinical routine)						

Table 3

Primary outcome and secondary outcomes of the MonDAFIS study.

Primary outcome of the MonDAFIS study
<ul style="list-style-type: none"> • The proportional number of study patients on oral anticoagulation (NOAC or VKA) at 12 months after the index stroke, randomized either to usual in-hospital diagnostic procedures plus standardized prolonged ECG monitoring or to usual in-hospital diagnostic procedures.
Secondary outcomes of the MonDAFIS study
<ul style="list-style-type: none"> • Number of stroke patients with AF newly detected in hospital using a standardized prolonged ECG monitoring compared to usual stroke unit diagnostic procedures alone. • Proportion of recurrent stroke, major bleeds, myocardial infarction and all-cause death (composite endpoint) within 6, 12 and 24 months after the index stroke in the intervention group or control group, respectively. • Overall costs of standardized prolonged ECG monitoring for paroxysmal AF in stroke patients. • Self-reported persistence in taking oral anticoagulation (NOAC or VKA) at 24 months after the index stroke in patients with AF. • Impact of stroke unit level (i.e. primary or comprehensive stroke center) on the rate of AF detection in in-hospital stroke in patients randomized to the intervention group. • Proportion of recurrent stroke, major bleeds, myocardial infarction and all-cause death within 6, 12 and 24 months after the index stroke in patients randomized to the intervention group with: <ul style="list-style-type: none"> (I) sinus rhythm, (II) non-permanent AF detected by usual stroke unit diagnostic procedures or by standardized prolonged continuous ECG monitoring in hospital, (III) paroxysmal short atrial tachycardia in hospital, (IV) excessive supraventricular ectopic activity in hospital.