

# Improved screening for silent atrial fibrillation after ischaemic stroke

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## Objectives

To what extent silent paroxysmal atrial fibrillation (AF) is present in ischaemic stroke patients has not been established. We hypothesized that brief intermittent long-term electrocardiogram (ECG) recordings at regular time intervals are more effective than short-term continuous ECG monitoring in detecting silent AF episodes.

## Methods and Results

Consecutive patients who had suffered an ischaemic stroke/transient ischaemic attack (TIA) and were without known AF underwent a 24 h continuous ECG recording and performed 10 s rhythm registrations using a hand-held ECG recorder twice daily for 30 days and when arrhythmia symptoms occurred. Two hundred and forty-nine stroke patients were included. Mean National Institute of Health Stroke Scale (NIHSS) score was 0.9 (0–10). In total, 17 patients were diagnosed with AF. One hundred and eight AF episodes were diagnosed in 15 patients using intermittent recording, out of which 22% were unscheduled symptom triggered episodes. In three patients AF was diagnosed with both methods and in two patients AF was detected exclusively with 24 h Holter monitoring. A significant difference in favour of the hand-held ECG was shown between the two methods ( $P = 0.013$ ). The total prevalence of AF was 6.8% and increased to 11.8% in patients  $\geq 75$  years. No AF was found in patients  $< 65$  years.

## Conclusions

Prolonged brief intermittent arrhythmia screening substantially improves the detection of silent paroxysmal AF in patients with a recent ischaemic stroke/TIA, and thus facilitates the detection of patients who should receive oral anticoagulant treatment.

## Keywords

Paroxysmal atrial fibrillation • Stroke • Telemedicine

## Background

Atrial fibrillation (AF) is a major risk factor for ischaemic stroke.<sup>1–3</sup> A previous stroke in a patient with AF indicates an increased risk for a renewed stroke. In patients with ischaemic stroke without known cardioembolic source, routine investigations such as electrocardiogram (ECG), echocardiography, 24–48 h continuous ECG recordings, and carotid artery ultrasound examinations in search of thromboembolic sources often reveal normal findings. In the presence of AF, oral anticoagulation treatment is indicated.<sup>4,5</sup>

Prolonged continuous monitoring reveals increased number of previously undiagnosed episodes of AF in patients after an ischaemic stroke.<sup>6,7</sup> Since long-term continuous ECG monitoring might

be associated with lower compliance and diagnostic accuracy, alternate methods needs to be explored. Whether intermittent monitoring over a long time period may improve AF detection remains to be determined in a clinical setting.

We hypothesized that brief intermittent ECG monitoring over a long time period (30 days) compared with 24 h of continuous ECG monitoring would be a more efficient method for detection of silent AF in patients with a recent stroke.

## Method

Patients with a recent ischaemic stroke/transient ischaemic attack (TIA) and without previously diagnosed AF were recruited from

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the stroke units (SUs) at three hospitals in Sweden. Medical records were scrutinized and renewed patient interviews were performed to exclude previously diagnosed AF and to determine risk factors for thromboembolic events according to the CHADS2 scoring system. Patients who were diagnosed with AF during hospitalization before enrolment using, for example, continuous ECG recording due to recurrent TIAs were excluded and were considered to have previously known AF. All participating patients were Warfarin naïve except for three patients due to clinical suspicion of previous cerebral emboli ( $n = 1$ ), known carotid artery stenosis with recurrent stroke ( $n = 1$ ), and previous surgical heart valve replacement ( $n = 1$ ).

The inclusion criteria consisted of a diagnosed ischaemic stroke/TIA in the SU based on clinical signs and a computed tomography with findings consistent with a recent ischaemic stroke/TIA. Study inclusion was to be within 14 days from the index event. Exclusion criteria were haemorrhagic stroke, inability to perform recordings such as dementia, grave neurological deficit, presence of a continuous pacemaker rhythm, age  $<70$  years according to a study amendment halfway through the inclusion period, and an index event surpassing 14 days.

Stroke severity was classified according to the National Institute of Health Stroke Scale (NIHSS): 0 points indicating normal and 42 points worst possible symptoms. Patients performed an ambulatory continuous 24 h ECG recording (Braemar DL700 analysed by Aspect 3.81R3a; GE Healthcare) before or within the first few days after hospital discharge. The majority of patients initiated the continuous recording within 24 h from admission to the SU. Concomitantly, patients were equipped with a hand-held ECG recorder (Zenicor-EKG<sup>®</sup>; Zenicor Medical Systems AB) and instructed to perform 10 s rhythm recordings once in the morning and once in the evening for 30 days. In addition, patients were instructed to perform recordings in case of any arrhythmia symptoms.

The device, for intermittent ECG recordings, is a  $110 \times 80 \times 15$  mm rectangular plastic box weighing 100 g. A display indicates whether a correct registration has been performed. The device is equipped with two thumb sensors providing bipolar extremities ECG lead I. The patient's thumbs are applied onto the sensors for 10 s for rhythm registration. The ECG recording is transferred sonically via mobile phone to a centralized, secure socket layer encrypted digital ECG database on the Internet and is then available for evaluation at the investigators discretion at a web address.

A more complete technical description of the intermittent ECG device with an assessment of sensitivity and specificity for AF detection has been previously published.<sup>8</sup>

The two methods were compared against each other to determine which method diagnosed the most AF episodes. As the intermittent ECG recorder only has a 10 s memory capacity, the definition of an AF episode for both methods was irregular ventricular rhythm without visible P-waves for a minimum of 10 s. Only AF diagnosis set by one of these methods during the study period was considered relevant.

Initially, no age limit was set, but due to an initial overrepresentation of patients under the age of 65, a study amendment was made halfway through the study with a lower age limit of 70 years in order to receive a more balanced age representation.

In addition to heart rhythm recordings, patients also underwent blood chemistry, ECG, transthoracic echocardiography, and a carotid artery ultrasound as part of a general risk stratification programme. Carotid ultrasound findings were divided into normal, unspecified atherosclerotic changes, significant stenosis (70–99% vessel lumen occlusion), and complete carotid artery occlusion.

Echocardiographic parameters were evaluated by experienced echocardiographers. Left ventricular ejection fraction (LVEF) was determined using either a visual estimate or the Simpson biplane method where a median was established based on three<sup>1–4</sup> separate measurements. Results were divided according to local practice into LVEF normal ( $\geq 50\%$ ) or depressed ( $< 50\%$ ). Left atrial size estimation was based on a measurement of the anterior posterior diameter of the left atrium in a parasternal long-axis view of the heart. Left atrial size was divided into normal ( $\leq 42$  mm) or enlarged ( $> 42$  mm).

The study was approved by the Regional Ethics Committee and was registered at ClinicalTrials.gov, ID number: NCT01160406. All participating patients gave written informed consent.

## Statistical methods

To test the hypothesis that intermittent ECG recordings are superior to 24 h continuous monitoring, we used McNemar's test for paired proportions. The criterion for significance ( $\alpha$ ) was 0.05 (two-tailed test).

The study was dimensioned to detect clinically relevant discrepancies between the two methods based on the following population effect size: In 80% of the patients, both methods will classify a patient as negative AF and in another 5% both methods will classify a patient as positive. A discrepancy between the two methods was assumed in the population as follows: in 4% of all patients only one test will show an outcome of positive, while 11% of all patients will show an outcome of positive AF for the other method. We needed 222 patients to yield a power of 80% with a statistically significant result with an  $\alpha$  of 0.05 (two tailed). Calculating with a drop out rate of 10%  $\sim 240$  patients needed to be included; the power calculation was performed in SamplePower 2.0. The statistical analysis was performed in SPSS version 17.

## Results

### Study population

Between 2007 and 2010, 290 patients were enrolled in the study. Forty-one patients were excluded. Reasons for exclusion were compliance problems (29 patients) attributed to patient-related technical problems with the intermittent ECG device and patients decisions to end study participation prematurely, misdiagnosis (7 patients), and too young age according to the study protocol amendment (5 patients, see above).

Two-hundred and forty-nine patients, with ischaemic strokes/TIA without known cardioembolic source, fulfilled the study. Patients had a high prevalence of hypertension (65%) and low NIHSS scores on admission to the hospital, mean 0.9 (range 0–10); the latter was required at the time of inclusion for the intermittent ECG recorder handling (further demographics are shown in Table 1).

**Table 1** Patient characteristics

Parameter	All	Non-AF	AF
Number of patients	249	232	17
Gender male (%)	57	58	47
Age (years)	72 (39–91)	72 (39–91)	75 (66–84)
Diabetes mellitus (%)	16	16	12
Congestive heart failure (%)	4	4	0
Previous stroke/TIA <sup>a</sup> (%)	25	25	35
Ischaemic heart disease (%)	20	20	12
Hypertension (%)	65	65	65
Previous palpitations (%)	15	13	35
Mean NIHSS <sup>b</sup> on admission	0.9 (0–10)	0.9 (0–10)	0.7 (0–3)
CHADS2 mean at study inclusion	3 (5–2)	3 (5–2)	3 (5–2)
Carotid duplex examination (%)	92	94	89
Pathologic (%)	61	57	35
Significant stenosis (>70%) (%)	6	7	0
Complete carotid artery occlusion (%)	3	3	0
LVEF <sup>c</sup> depression (%)	6	6	6
Left atrial enlargement (%)	13	13	24

<sup>a</sup>Before current ischaemic incident.

<sup>b</sup>National Institute of Health Stroke Scale.

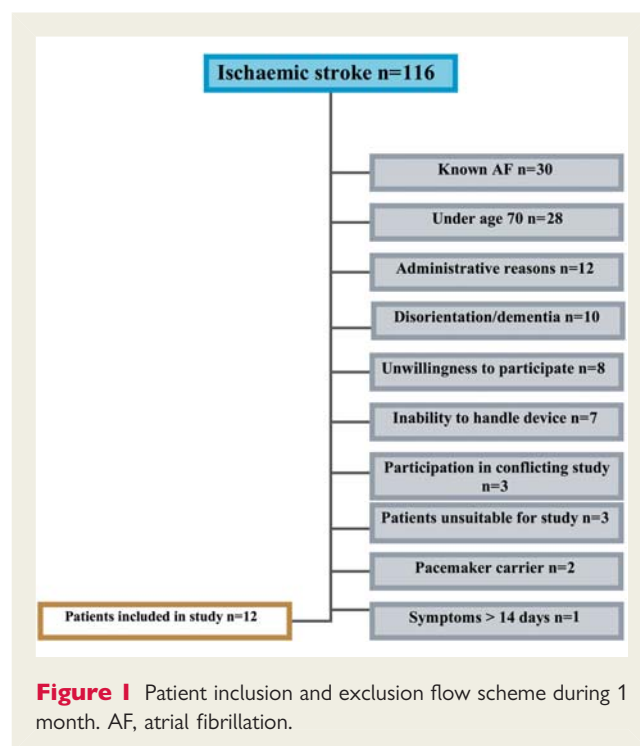
<sup>c</sup>Left ventricular ejection fraction.

During 1 month, a log was kept over all patients admitted at one of the SUs to give an approximation of the amount of patients who actually fulfilled inclusion criteria. During this period 257 patients were treated in the SU, out of which 141 patients had other diagnoses than ischaemic stroke or TIA. Atrial fibrillation was previously known or diagnosed during the hospital stay prior to study inclusion in 30 patients and 28 patients did not fulfil the age criteria. Out of the remaining 58 patients who fulfilled inclusion criteria, 12 patients were included in the study. Reasons for exclusion were disorientation/dementia, unwillingness to participate, pacemaker carrier, inability to handle the intermittent ECG device, index stroke symptoms >14 days ago, participation in conflicting clinical trials, administrative reasons, and patients not found suitable for participation due to psychiatric illness, terminal disease, and blindness. See [Figure 1](#).

### Atrial fibrillation detection

A total of 15 864 brief intermittent ECG recordings were recorded. Each patient contributed a mean of 59 (range 10–89) recordings. The mean recording time with the 24 h continuous ECG was 22.6 h.

Atrial fibrillation was diagnosed in 17 patients, of whom 12 were diagnosed with intermittent recordings only. In two patients AF



**Figure 1** Patient inclusion and exclusion flow scheme during 1 month. AF, atrial fibrillation.

was detected by 24 h continuous recordings only. One hundred and eight episodes of AF were diagnosed in the 15 patients using intermittent recordings. Of the recorded AF episodes 78% were seen as scheduled recordings and 22% as symptom-triggered recordings.

The statistical analysis according to McNemar's test for paired proportions showed a significant difference between the two methods in favour of brief intermittent ECG recordings with regard to the ability to detect AF ( $P = 0.013$ ).

The majority (94%) of all AF episodes was detected within the first 20 days using intermittent ECG recordings.

The number of diagnosed AF episodes ranged from 1 to 23 with a median of 5 episodes per patient ([Table 2](#)).

Atrial fibrillation was diagnosed exclusively in the elderly patients ([Figure 2](#)). Mean age among those with AF was 75 (range 66–84 years) with a slight female overrepresentation (53%).

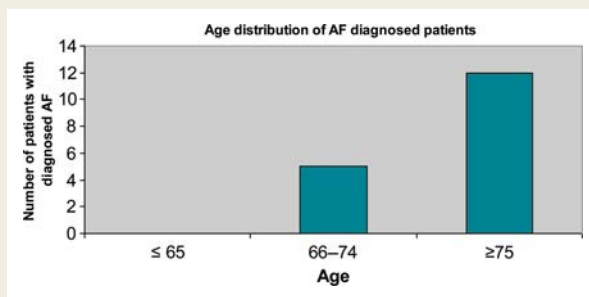
### Carotid artery ultrasound and echocardiography

Carotid artery ultrasound was done in 92% of the patients and showed less pathological findings in AF diagnosed patients (35%) compared with non-AF patients (57%). The pathology observed consisted mainly of unspecified atherosclerotic changes. No significant stenoses of the carotid arteries were seen in the AF group as compared with 7% in the non-AF group.

Echocardiographic investigations were performed in 90% of the patients. Depressed LVEF was seen in 6% of all patients, with identical findings within the AF patient group. Enlarged left atrium was found in 13% of the whole patient population, in contrast to the AF patients where it was 24%.

**Table 2** Atrial fibrillation diagnostics comparing continuous and intermittent electrocardiogram screening

Method	Intermittent ECG positive	Intermittent ECG negative	Added results
24 h continuous ECG positive	3	2	5
24 h continuous ECG negative	12	232	244
Added results	15	234	Total: 249

**Figure 2** Age distribution of patients diagnosed with AF.

## Discussion

The major findings of this study is that brief intermittent ECG screening over a long time period seems to be a more efficient method to detect silent paroxysmal AF compared with continuous short-term recordings in patients with ischaemic stroke/TIA without known cardioembolic source. Silent AF is common (>10%) in stroke patients over 75 years without a history of AF.

Our stroke and TIA population was similar with respect to basic clinical demography as compared with other large stroke cohorts of patients with ischaemic stroke and TIA without cardioembolic source.<sup>9</sup> The observation that AF is more common among the elderly is in accordance with previous findings.<sup>10</sup> The observation that AF was diagnosed in >10% of elderly stroke patients with less severe symptoms is however interesting and indicates an even higher incidence if, in addition, stroke patients with more severe symptoms were to be screened for silent AF. It further indicates the necessity of an extensive arrhythmia screening in all ischaemic stroke/TIA patients without known AF and cardioembolic source, irrespective of symptoms, particularly in the elderly. A larger proportion of the AF patients were found to have enlarged atria in comparison with the study population, a finding in accordance with previous studies.<sup>11</sup> Interestingly, the AF patients had no signs of significant carotid disease compared with 7% in the non-AF group, indicating that the strokes in the AF patients were more likely to be of a cardioembolic source.

## Detection of atrial fibrillation

The optimal fashion for screening of atrial fibrillation non-invasively has not been fully evaluated, as a meta-analysis of several AF screening studies in stroke populations revealed various results irrespective of method and monitoring time.<sup>12</sup> It seems clear, however, that longer recording periods detect more AF episodes. Longer recordings might, however, be demanding from a patient perspective and increase the risk for poor technical quality as seen in the Stahrenberg study where only 69% of patients had evaluable material of at least 5 out of 7 days.<sup>13</sup> Furthermore, since there is poor correlation between patient symptoms of palpitations and actual AF occurrence,<sup>14,15</sup> intermittent screening needs to be performed at fixed time intervals rather than patient symptom guided to improve AF detection frequency. In our study most patients only performed recordings at scheduled hours and less frequently at unscheduled symptom triggered recordings. Out of the registered AF episodes, 78% were detected at scheduled times and only 22% at unscheduled symptom-triggered recordings which underline AFs often asymptomatic character. This demands a more thorough and expanded screening period in order to confirm or rule out its presence, making a strategy of spot checks at certain time intervals, besides symptom-guided registrations more effective. Our findings that 94% of all AF episodes were detected within the first 20 days from study start might hint towards the time period necessary to establish whether AF is present or not. Whether such a time period is optimal for continuous ECG recordings still has to be established.

The fact that all episodes of AF were detected in individuals older than 65 years indicates that age is important when selecting patients for screening.

An alternative method to detect episodes of asymptomatic silent atrial fibrillation is implantable loop recorders, which provide extensive arrhythmia monitoring over extended time periods. Ziegler *et al.*<sup>16</sup> showed continuous monitoring with an implanted device to be significantly reliable in assessing AF burden compared with intermittent monitoring.

However, such a strategy is invasive and implies a high up-front cost.

## Atrial fibrillation burden

It is from this study not possible to quantify the AF burden. In the TRENDS study a high AF burden as detected by an implanted pacemaker was associated with a high risk for stroke within a short timeframe.<sup>17</sup> However, it has been further shown that patients with short AF bursts or even increased number of supra-ventricular complexes also have an increased risk of ischaemic stroke.<sup>18</sup> This finding might diminish the importance of AF burden in respect of stroke risk. Several patients who did not fulfil the 10 s duration criteria for AF diagnosis presented with shorter irregular supraventricular runs. In these and the AF diagnosed patients, these runs might have been surrogate markers for longer AF runs predating the ischaemic stroke. If this is the case or if very short supraventricular runs are able to cause stroke is speculative and still has to be investigated. Observed absolute stroke rates for non-anticoagulated AF patients with single independent risk factors are ~6–9% per year for prior stroke/

TIA.<sup>19</sup> As modern oral anticoagulation treatment can reduce the risk for stroke with 70%, detection of AF of any duration is of importance. According to a consensus statement from the Heart Rhythm Society,<sup>20</sup> AF episodes after catheter ablation for AF are considered to be significant if lasting 30 s or longer. This patient group seldom discontinues anticoagulant medication and it is further documented that short AF bursts commonly occur early after such procedures when screening for recurrence is usually performed. Such an arbitrary time duration limit is inherently thus due to a risk–benefit ratio, with regard to new procedures. The screened stroke population on the other hand has already suffered a feared AF complication, where it becomes difficult to disregard even short AF runs and withhold oral anticoagulant treatment in order to prevent further complications.

## Limitations

Since the ECG monitoring device required technical compliance, not always achievable in patients with severe neurological deficit, our study has a selection bias with inclusion of patients with less disabling symptoms only, reflected by the comparatively low NIHSS points of our study population. However, one might propose that this patient group is the one who may benefit the most from a thorough investigation and, if needed, oral anticoagulant treatment, in order to prevent a new ischaemic stroke with more disabling symptoms. Current AF consensus statements and guidelines, and Calkins *et al.*<sup>20</sup> and Camm *et al.*<sup>21</sup> deem AF episodes of 30 s or longer to be clinically relevant. Recordings of this duration were not possible to achieve in this study due to technical limitations pertaining to the intermittent ECG device which makes an assessment of the actual AF duration not possible and may further raise suspicion of AF oversensing. The median number of registered AF episodes per patient was five on the other hand and often seen on subsequent registrations, which adds strength to the diagnosis by the number of registrations. The small number of patients diagnosed with AF in the study is also a limitation and might be a source of uncertainty. The studied population, on the other hand, was quite healthy with low percentage of other risk co-morbidities apart from hypertension. The study was further a Swedish cohort and it remains to be proven whether these results may be generalized to other similar patient populations.

## Conclusion

Intermittent ECG recordings, time fixed in combination with symptom activated, over a longer time period in ischaemic stroke/TIA patients seems to be a more efficient method in detecting silent paroxysmal AF, in comparison with shorter continuous ECG recordings. Atrial fibrillation is common in elderly patients with ischaemic stroke/TIA and minor neurologic deficits. Intermittent ECG recordings seem to be a plausible alternative in stroke patients with less disabling symptoms where implantable devices are not always plausible due to cost issues.

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**Conflict of interest:** M.R. works pro bono as a consultant for Zenacor Medical Systems AB. None of the authors has economic interests in the company.

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