Atrial fibrillation detected with outpatient cardiac rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause

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ABSTRACT

Objectives: Guidelines advise cardiac rhythm monitoring for 3 up to 30 days for detecting atrial fibrillation (AF) in patients with ischemic stroke of undetermined cause. However, the optimal monitoring duration is unknown. We aimed to determine the AF detection rate during 7-day outpatient cardiac rhythm monitoring in this patient group.

Methods: Participants from a large tertiary hospital in a prospective observational study (ATTEST) underwent outpatient cardiac rhythm monitoring after a negative standard diagnostic evaluation (i.e., 12-lead electrocardiogram and in-hospital telemetry). Primary outcome was the rate of newly detected AF.

Results: We examined 373 patients [age: 67.8±11.6 years; women: 166(44.5%); stroke: 278(74.5%)]. Median monitoring duration was 7 days (Inter Quartile Range (IQR) 7-7), performed after median of 36 days (IQR 27-47). AF was newly detected in 17(4.6%) patients, 5.4% of patients with ischemic stroke and 2.1% of patients with TIA. 53% of AF was detected on day-1, after day-3 73% of new AF was found. First AF episodes were detected up to day-7. Diabetes and increasing age were independent predictors of new AF.

Conclusion: After ischemic stroke or TIA of undetermined cause, 7-day outpatient cardiac rhythm monitoring detected new AF in 4.6%. Patients with AF had significantly more cardiovascular risk factors. Although about 50% of first AF episodes occurred during the first day of monitoring, new AF was detected up to day-7, implying that the recommended minimum of 3 days cardiac rhythm monitoring after ischemic stroke of undetermined cause is insufficient. Subsequent long-term rhythm monitoring should be considered in selected patients.

Introduction

Atrial fibrillation or atrial flutter (AF, both) is one of the most prevalent causes of embolic ischemic stroke. Oral anticoagulation therapy reduces the risk of recurrent stroke, and it is therefore very relevant to diagnose AF in patients previously unknown with AF.[1] AF can occur not only as persistent or permanent, but also as paroxysmal AF. As patients are often asymptomatic, detection of AF can be difficult.

In ischemic stroke patients, several strategies are applied to find AF. On admission, a 12-lead electrocardiogram (ECG) detects AF in about 7.7% of patients without previously known AF.[2] Subsequent in-hospital cardiac monitoring that currently is guideline-recommended for at least 24 hours[3] detects AF in another 3–5 %.[2] In many tertiary hospitals, initial assessment and treatment of patients with ischemic stroke or TIA is performed or coordinated by a dedicated Stroke Unit.

For patients with ischemic stroke or TIA of undetermined cause, who

after the in-hospital diagnostic work-up still have no determined cause of ischemic stroke, longer cardiac rhythm monitoring is warranted. The European Society of Cardiology recommends AF screening for at least 3 days, and consideration of additional long-term monitoring (either non-invasive or invasive) in selected patients deemed at risk of developing AF or with characteristics suggestive of embolic stroke.[1] The American Heart Association/American Stroke Association and the European Stroke Organisation both suggest prolonged rhythm monitoring up to 30 days.[3,4] In addition, the American College of Cardiology/American Heart Association/Heart Rhythm Society guideline considers implantation of a cardiac monitor in patients with ischemic stroke of undetermined cause in whom external ambulatory monitoring is inconclusive to be reasonable.[5] These recommendations are Class IIa, level B. A recent meta-analysis in patients with ischemic stroke of undetermined cause reported an overall AF detection rate –a pooled rate based on all non-invasive monitoring strategies– of 9.5 % after 3 weeks and 13.7% after 4 weeks.[6] Invasive monitoring with implantable loop recorders (ILR) can further increase the detection rate. Still, pre-selection of ischemic stroke patients with the highest risk for having AF is crucial.[7]

Several prediction scores have been developed to stratify stroke patients according to the risk of having AF, and might be used to optimize AF detection strategies in patients with ischemic stroke of undetermined cause.[8,9] Yet, the optimal strategy for monitoring duration and patient selection is unknown, as reflected in the underuse of ECG monitoring in ischemic stroke patients.[10,11]

In the present study, we assessed AF detection rates and the time of the first-detected episode with non-invasive,7-day outpatient cardiac rhythm monitoring, in patients with ischemic stroke or TIA of undetermined cause in a real-world setting. In addition, we aimed to gain insights into the AF patients' characteristics.

Methods

For this study, we used data from our large tertiary hospital of patients included in the ATTEST (The optimal Approach of TransThoracic Echocardiography in ischemic Stroke or TIA of undetermined cause) study, a cross-sectional study that mainly aimed to determine the prevalence of major cardioembolic sources detected with transthoracic echocardiography (TTE) in patients with ischemic stroke or TIA of undetermined cause. Between March 2018 and October 2020, patients were enrolled from both inpatient and outpatient clinics of a tertiary hospital. Patients had ischemic stroke or TIA of undetermined cause after standard diagnostic evaluation according to the TOAST criteria.[12] The initial evaluation included a 12-lead ECG, and in case of hospital admission at least 24 hours of in-hospital telemetry. Further details of inclusion criteria and the extent of diagnostic evaluation have been published elsewhere.[13] Patients then underwent a cardiac assessment that –in the population of the present study– comprised non-invasive AF monitoring of at least 3 days in total (i.e., in-hospital telemetry plus ambulatory screening). The study was reviewed by the Medical Ethical Committee Twente in Enschede, the Netherlands. According to Dutch law, the study was not considered subject to the Medical Research Involving Human Subjects Act (WMO). According to the Dutch General Data Protection Regulation (AVG), informed consent for participation in the main ATTEST study was obtained where appropriate.

AF monitoring strategies

Our local standard strategy was monitoring for 7 days with an external loop recorder (ELR), but a small number of patients were monitored for 4 to 6 days. These patients were included in the analysis, if they had cardiac rhythm monitoring for at least 3 days (i.e., sum of in-hospital and outpatient telemetry). A few patients who only underwent 24-hour Holter monitoring were not included in the current analysis. If a patient had more than one distinct outpatient cardiac monitoring period, only the first period was included in the analysis.

Monitoring results were available for remote assessment while the registration was running; although not routinely analyzed during recording, registrations could be reviewed before the planned end of monitoring, if required. Usually, monitoring registrations were evaluated after the ELR was disconnected. If monitoring was discontinued before completing the intended monitoring period due to remote signaling of AF detection, the initially intended duration of monitoring was used for analyses. If the monitoring period was shorter than intended due to other reasons (e.g., technical issues), the actual monitoring duration was used. Atrial fibrillation was defined as a sequence of at least 30 seconds of irregular R-R intervals in the absence of distinct repeating P waves but presence of irregular atrial activity,[1] and atrial flutter was defined as an ECG pattern of regular tachycardia with a minimal heart rate of 240 beats per minute, lacking an isoelectric baseline between deflections.[14]

Statistical analysis

Primary outcome measure was the proportion of patients with newly detected AF. The secondary outcome measure was the time between the start of monitoring and AF detection. All outcome measures were calculated with 95% confidence intervals (CI). Data were presented as numbers and frequencies, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. Differences in baseline characteristics between patients with and without AF were calculated using an independent T-test, Mann-Whitney U-test, Chi-square test, or Fisher exact test, as appropriate. A significance level of 0.05 was used. For exploration of associations between baseline characteristics in patients with and without newly detected AF, variables with a significance of $p < 0.15$ were included in a stepwise multivariable logistic regression model with forward selection. All statistical analyses were performed with SPSS, Version 24 (IBM Corp., Armonk, NY, USA).

Results

Details of the patient inclusion are presented in the flow chart of Fig. 1. In brief, of 2138 patients who were examined in our hospital for ischemic stroke or TIA, 1430 were diagnosed with a determined cause of ischemia. Notably, of 726 patients who prior to ECG and/or telemetry had no determined cause of ischemia, 57 (7.9%) were diagnosed with newly detected AF based on information from submission ECGs and in-hospital telemetry combined. Of all 669 patients with undetermined cause of ischemia despite complete in-hospital work-up, 475 were eligible for inclusion in the ATTEST study and provided an informed consent. Ultimately, 373 (78.5%) of these study participants underwent non-invasive AF monitoring for at least 3 days and were eligible for assessment in the present analysis, representing the current study population. Demographics and other characteristics of the study population are presented in Table 1.

In 291 patients (78.0%), prior to outpatient cardiac rhythm monitoring, in-hospital telemetry was performed with a median duration of 1 day (IQR 1-1). Median time interval between ischemic event and start of the outpatient cardiac rhythm monitoring was 36 days (IQR 27-47), and median duration of the outpatient monitoring was 7 days (IQR 7-7); only in 15 patients outpatient monitoring was shorter than 7 days for technical or logistic reasons: 3 patients had 4 days of monitoring, 5 patients had 5 days of monitoring and 7 patients had 6 days of monitoring.

Of all 373 patients with outpatient cardiac rhythm monitoring, 17 (4.6%; 95% CI 2.8-7.1 %) had newly detected AF. These patients were older and more often had diabetes and hypertension. 12 (70.6%) AF patients had ≥2 risk factors [diabetes; hypertension; age >65 years]. Median time from start of monitoring to the first AF episode (available for 15/17 patients) was 8 hours (IQR 1-81). In about half of the patients (n=8, 53.3 %) AF was discovered early during the first day of cardiac rhythm monitoring, but in a few patients (n=4, 26.7 %) AF was first
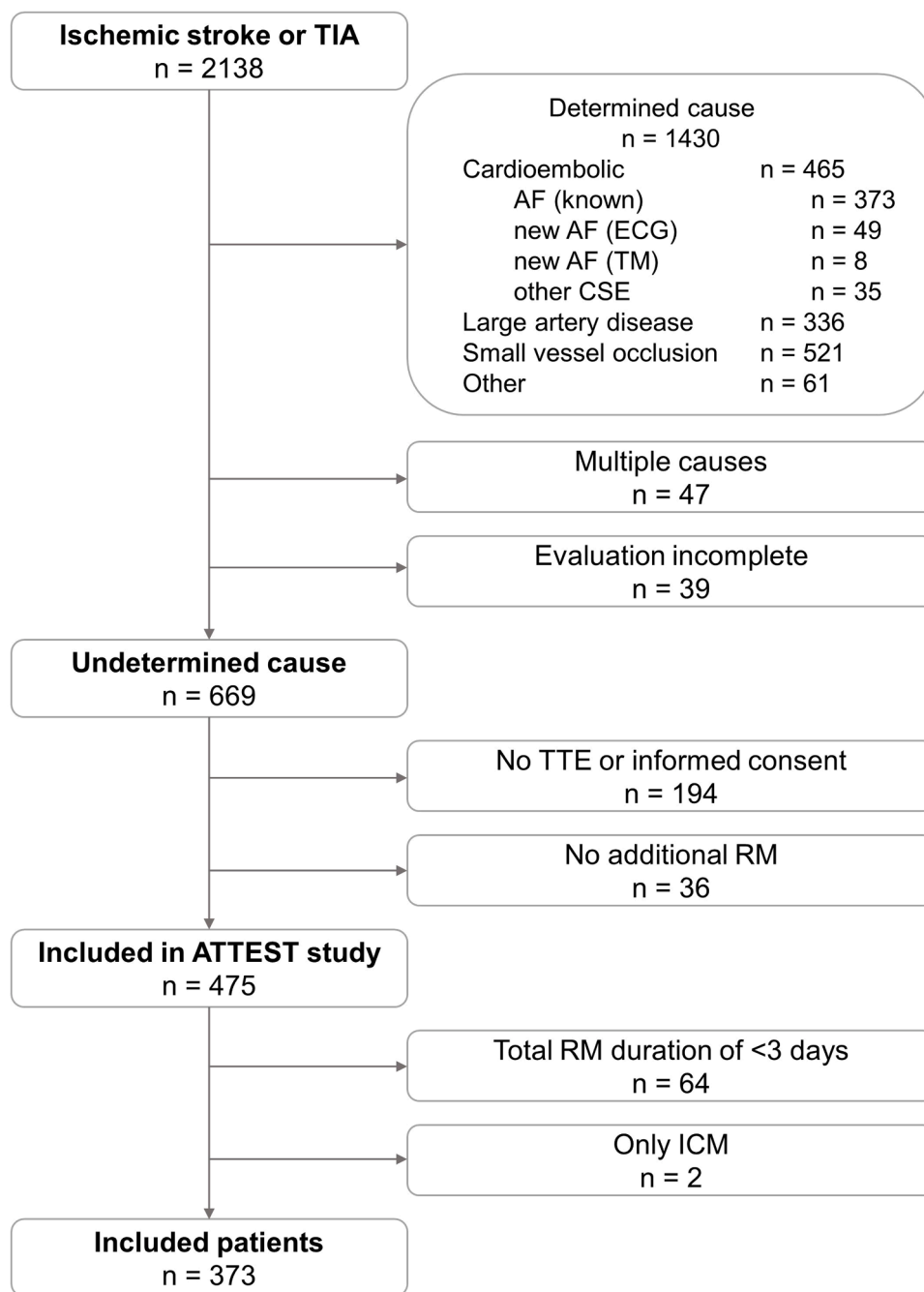
Fig. 1. Flowchart of patient inclusion.
AF = atrial fibrillation, CSE = cardiac source of embolism, ECG = electrocardiogram, ICM = implantable cardiac monitor, RM = rhythm monitoring, TIA = transient ischemic attack, TM = telemetry, TTE = transthoracic echocardiography.

detected on monitoring day four to seven (Fig. 2).

Out of the total study population of 373 patients, 95 patients (25.5 %) had a TIA. In the subpopulation of 17 patients with AF, 2 patients (11.8%) had a TIA, and in the subpopulation of 356 patients without AF, 93 patients (26.1%) had a TIA (p=0.258). Conversely, in the subpopulation of 278 patients with ischemic stroke, 15 patients (5,4%) had AF, and in de subpopulation of 95 patients with a TIA, 2 patients (2,1 %) had AF (p=0.258).

Variables that were used in the stepwise multivariable logistic regression analysis were age, sex, diabetes mellitus, hypertension, and a history of cardiac disease. The analysis showed that both diabetes (adjusted OR 4.58 (95% CI 1.67-12.59)) and increasing age (adjusted OR 1.07 for each additional year (95% CI 1.01-1.13)) were independent

predictors of newly discovered AF.

Discussion

In patients with ischemic stroke or TIA of undetermined cause, 7 days of outpatient cardiac rhythm monitoring (beyond routine ECG and 24-hour in-hospital telemetry) detected new AF in 4.6%. About 50% of the first new AF episodes occurred during the first day of monitoring, and about 75% during the first 3 days. Yet, about 1 out of 4 patients with newly detected AF had their first AF episode on days four to seven. Thus, the minimum recommended monitoring period of three days seems insufficient. Patients with AF had significantly more cardiovascular risk factors for AF[15] and 12 (70.6%) AF patients had ≥2 risk factors.

Table 1

Baseline characteristics of study population and patients with and without AF detection during outpatient monitoring.

	Total N = 373	AF n = 17	No AF n = 356	p**
Male	207 (55.5%)	6 (35.3%)	201 (56.5%)	0.086
Age	67.8 ± 11.6	75.2 ± 5.7	67.5 ± 11.7	<0.001
Age >65	232 (62.1%)	215 (60.4%)	16 (94.1%)	0.005
Cardiovascular risk factors				
BMI	27.1 ± 4.4	27.3 ± 4.8	27.0 ± 4.4	0.818
Diabetes mellitus	66 (17.7%)	9 (52.9%)	57 (16.0%)	0.001
Dyslipidemia	116 (31.1%)	7 (41.2%)	109 (30.6%)	0.358
Hypertension	169 (45.3%)	12 (70.6%)	157 (44.1%)	0.032
Smoking	75 (20.1%)	5 (29.4%)	70 (19.7%)	0.353
History of				
Ischemic stroke	59 (15.8%)	4 (23.5%)	55 (15.5%)	0.324
Cardiac disease	73 (19.6%)	6 (35.3%)	67 (18.8%)	0.115
Type of event				
TIA	95 (25.5%)	2 (11.8%)	93 (26.1%)	0.258
Ischemic stroke	278 (74.5%)	15 (88.2%)	263 (73.9%)	
Acute treatment	70 (18.8%)	5 (29.4%)	65 (18.3%)	0.335
rtPA	66 (17.7%)	5 (29.4%)	61 (17.1%)	0.197
Endovascular	12 (3.2%)	1 (5.9%)	11 (3.1%)	0.434
Baseline NIHSS	2 (1-4)*	2 (0-6)*	2 (1-4)*	0.848
Localization				0.545
Cortical	180 (50.6%)	8 (47.1%)	188 (50.4%)	
Subcortical	90 (25.3%)	4 (23.5%)	94 (25.2%)	
Cerebellar/ brainstem	64 (18.0%)	4 (23.5%)	68 (18.2%)	
Multiple locations	16 (4.5%)	0 (0.0%)	16 (4.3%)	
Uncertain	6 (1.7%)	1 (5.9%)	7 (1.9%)	
Interval between hospital admission and start monitoring (days)	36 (27-47)	34 (28.5-42)	37 (27-48)	0.449

Data are presented as n (%) except for age [mean (±SD)], NIHSS (National Institute of Health Stroke Scale) [median (Inter Quartile Range)], and interval between hospital admission and start of monitoring (Inter Quartile Range)].

* Patients with TIA excluded

** p value of AF versus No AF

AF = atrial fibrillation or atrial flutter, TIA = transient ischemic attack, rtPA = recombinant tissue plasminogen activator

The AF detection rate of the current study is lower than that reported by a meta-analysis of 1- and 7-day ambulatory Holter-monitoring (10.7%) in all ischemic stroke patients.[2] Yet, when only considering five studies in patients with ischemic stroke of undetermined cause, AF detection rates ranged from 1.7 to 26.5%. The result of our present study falls within that range. These five previous studies had smaller sample sizes than the present study. Also, they applied different definitions of ischemic stroke of undetermined cause and of AF (i.e., different for minimum AF duration cut-offs),[16-19] which renders comparison with our findings difficult. In addition, the study with the lowest rate of new AF detection (1.7%) did not perform continuous cardiac rhythm monitoring but performed ECG recordings of 7 minutes on 7 consecutive days.[19] Furthermore, ambulatory monitoring was often started earlier, which may have increased the AF detection rate.[20]

The ambulatory detection rate of new AF may also depend on the proportion of patients in whom new AF has already been detected earlier in the diagnostic process (i.e., during in-hospital work-up). In our study, of all patients who prior to in-hospital work-up at the Stroke Unit had no determined cause of ischemia, about 8% were diagnosed with newly detected AF, based on information from submission ECG and in-hospital telemetry combined. Previous studies generally did not provide comparable information.

A more recent meta-analysis –specifically in patients with ischemic stroke of undetermined cause– concluded that non-invasive ambulatory monitoring resulted in a 13.7% AF detection rate after 4 weeks.[6] However, in these studies, the monitoring phase was substantially longer than the 1-week monitoring in our study. In that meta-analysis, only a single study[18] had applied monitoring for less than 3 weeks. It is a well-established fact that longer periods of non-invasive monitoring result in higher AF detection rates.[21,22] Additional invasive monitoring with ILR leads to significantly more AF detection in patients with ischemic stroke of undetermined cause.[6,23] In patients with stroke attributed to large- or small-vessel disease ILR also detects more AF compared with usual care.[24]

Studies assessing predictors for AF in stroke patients found that several patient characteristics are associated with a higher risk of developing AF, including increasing age and presence of vascular risk factors reflected in higher CHA_2DS_2VASc score.[25] In line with these findings, older age and diabetes were independent predictors of having AF in our study. Combinations of these and additional predictors, such as echocardiographic characteristics, electrocardiographic features and brain imaging results, have been used to propose several different prediction scores,[8,9] that might be used to select candidates for prolonged cardiac rhythm monitoring. Still, the robustness needs confirmation in prospective studies.

The detection of new AF is essential, as it has major therapeutic consequences. In patients with embolic stroke of undetermined source, empirical use of direct oral anticoagulants (i.e., without demonstrated AF or other cardiac source of embolism) was shown to have no benefit regarding the prevention of recurrent stroke.[26,27] However, rivaroxaban was associated with a higher risk of major bleeding compared with aspirin,[26] while on the other hand, a subanalysis showed that in patients qualifying for a lower dose of dabigatran, the risk of recurrent stroke was lower with dabigatran compared with aspirin.[33] Long-term monitoring of the cardiac rhythm will increase the detection rates of both AF and short-lasting subclinical AF. In addition, longer cardiac rhythm monitoring strategies are likely to increase healthcare costs. Extended ambulatory cardiac rhythm monitoring in patients with ischemic stroke of undetermined cause may be cost-effective, but no conclusion could yet be drawn regarding the most favorable duration of monitoring.[28] Furthermore, the use of ILR carries a small risk of complications.[29] Non-invasive ECG-recording with smartwatch applications might represent a less costly alternative that is investigated by studies such as MOBILE-AF.[30] Finally, even if short-lasting subclinical AF is detected, it is yet unknown whether this requires the initiation of oral anticoagulation therapy.[31] The results of ongoing randomized trials comparing the prescription of direct oral anticoagulants and aspirin after device-detected subclinical AF may help us make future treatment decisions in this particular clinical setting.[32]

Limitations

Our study has several limitations. It presents data obtained at a single medical center. Nevertheless, the findings may be of substantial interest, as they reflect the real-world clinical practice of outpatient cardiac rhythm monitoring in patients with ischemic stroke of undetermined cause, as performed in one of the largest tertiary hospitals in the Netherlands. In addition, the time interval between the index ischemic event and the start of cardiac rhythm monitoring was quite long, which might have lowered the AF detection rate. Furthermore, from 2 of all 17
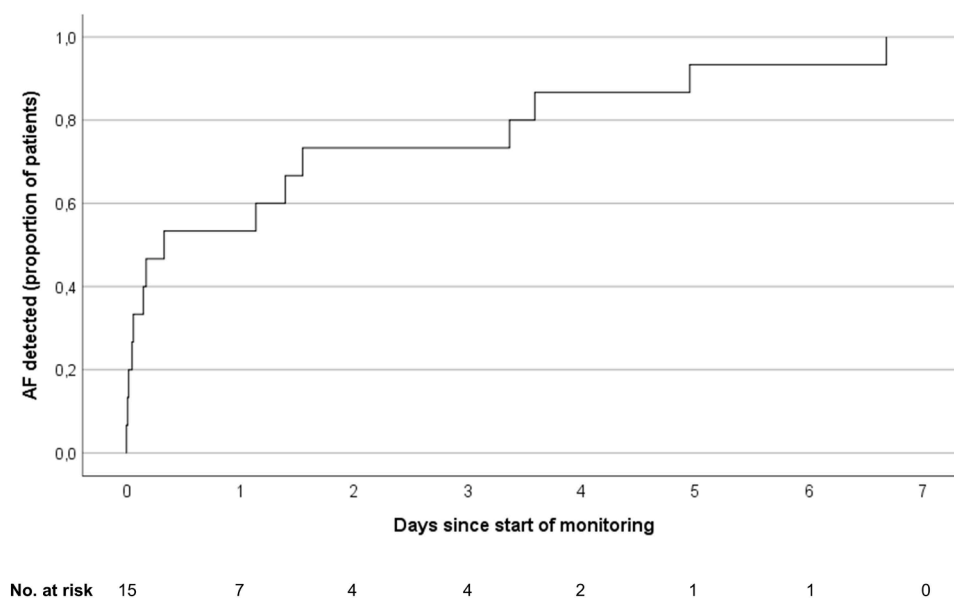
Fig. 2. Timing of AF detection in patients with 7-day external loop recorder monitoring.
Kaplan-Meier curve of time from the start of monitoring to the first new AF detection in 15/17 patients with newly detected AF (2 patients were excluded from this analysis as the exact time of their first AF detection was unknown). On day one, 8 patients (53%) showed new AF and after three days, 11 out of 15 patients (73%) had at least one episode of AF.
AF = atrial fibrillation, ELR = external loop recorder.

patients with newly detected AF, no detailed data on exactly the first moment of AF detection could be obtained. Consequently, both patients were excluded from the analysis of time intervals between the ischemic index event, the onset of cardiac rhythm monitoring, and the first detection of AF.

Conclusion

In our study population of patients with ischemic stroke or TIA of undetermined cause, 7 days of outpatient cardiac rhythm monitoring detected new AF in 4.6%. Patients with AF had significantly more cardiovascular risk factors. On day one, AF was detected in about 50%, and after three days in about 75%. Still, new AF was detected up to day 7. These data show that the recommended minimum of 3 days of cardiac rhythm monitoring after ischemic stroke of undetermined cause is insufficient, and should be prolonged. Subsequent long-term rhythm monitoring might be considered in selected patient groups. Our data show that diabetes and increasing age were independent predictors of finding new AF. These data, in combination with the results of previous and future studies, could be used to improve approaches for AF detection in similar patient populations.

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Declaration of Competing Interest

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