Original Paper

Low Incidence of Atrial Fibrillation in Patients with Transient Ischemic Attack

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Abstract
Background: Atrial fibrillation (AF) is a major cause of stroke. Therefore, all patients with ischemic stroke or transient ischemic attack (TIA) should be examined with 12-lead electrocardiogram (ECG) and continuous monitoring to detect AF. Current guidelines recommend at least 24 h continuous ECG monitoring, which is primarily based on studies investigating patients with ischemic stroke. The aim of our study was to investigate the diagnostic yield of 12-lead ECG and Holter monitoring in patients with TIA. *Methods:* We retrospectively investigated all patients diagnosed with TIA at Odense University Hospital, Denmark, from January 1, 2014 to December 31, 2014. TIA was a clinical diagnosis according to the WHO definition. Patients received admission ECG and 72-hour Holter monitoring after discharge. *Results:* 171 patients without known AF were diagnosed with TIA. Four (2.3%) were diagnosed with AF on admission ECG. Another 2 (1.2%) were diagnosed with AF on Holter monitoring. In total, 6 patients (3.5%) were diagnosed with AF. Patients with AF were significantly older (mean age 79.4 [95% CI 65.1–93.6] years) than patients without AF (mean age 67.6 [95% CI 65.6–69.5] years) but otherwise showed no difference in baseline characteristics. *Conclusion:* In this retrospective study, patients with TIA had a low incidence of AF detected with ECG and 72-hour Holter monitoring. Prospective studies are needed to confirm these findings.

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Introduction

Atrial fibrillation (AF) is the most frequent cardiac source of emboli and a major cause of stroke [1, 2]. Therefore, efforts should be made to detect AF, so that patients with prior stroke or transient ischemic attack (TIA), who per se are at high thromboembolic risk, can be treated appropriately with oral anticoagulants to reduce this risk [3]. If AF is persistent, the diagnosis will easily be made by taking a 12-lead electrocardiogram (ECG). Unfortunately, AF often is paroxysmal and can only be detected by long-term ECG monitoring. Current guidelines recommend 24-hour Holter monitoring (HM) if cardiac arrhythmias are suspected or if the cause of stroke is unknown [4].

During recent years, a lot of studies have investigated different ECG monitoring strategies in patients with stroke or TIA. In a meta-analysis, Sposato et al. [5] analyzed 50 studies including 11,658 patients and found new-onset AF in 12.2% diagnosed during the in-hospital stay by admission ECG, serial ECGs, continuous cardiac telemetry, and in-hospital HM. Admission ECG alone yielded 7.7%. Another 10.7% of patients were diagnosed with AF by ambulatory HM after discharge. The vast majority of the studies in this meta-analysis predominantly included stroke patients, whereas patients with TIA were either excluded or constituted only a minority of up to 20% of the total number of included patients. Moreover, one can speculate whether the same monitoring strategies used in stroke patients might also be suitable for patients with TIA.

Thus, the aim of this study was to determine the detection rate of previously undiagnosed AF in patients with TIA using 12-lead ECG on admission and 72-hour HM after discharge and then compare our findings with other studies investigating pure cohorts of TIA patients.

Methods

We retrospectively assessed all consecutive patients diagnosed with TIA or retinal TIA (amaurosis fugax) (ICD10, G45.9, and G45.3) at the Department of Neurology, Odense University Hospital from January 1, 2014 to December 31, 2014. Although there also were data available for the end of 2013 and the beginning of 2015, we chose only to include those admitted in 2014 to avoid influence of the seasonal variation in AF incidence [6, 7]. The study was approved by the Regional Scientific Ethical Committees for Southern Denmark and the Danish Data Protection Agency.

Clinical Management

Both in- and outpatients were included. Patients with suspected TIA with symptom onset <24 h were usually referred to acute hospital admission, whereas those with symptom onset >24 h were referred to the TIA outpatient clinic. Patients were referred to the hospital by either primary care physicians or emergency physicians/paramedics, if they suspected ischemic stroke. The emergency department or other medical specialties such as ophthalmologists also referred patients with suspected TIA. The initial investigation, regardless of admission type, included a consultation with a neurologist, a physical examination, blood samples, brain CT or MRI, 12-lead ECG, and carotid ultrasound.

Diagnosis of Transient Ischemic Attack

TIA was a clinical diagnosis and based on the definition by The World Health Organization as "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting less than 24 h, with no apparent non-vascular cause" [8], regardless of findings on brain imaging. Patients who received systemic thrombolysis or other revascularization

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procedures were excluded. Patients diagnosed with TIA but not living in the catchment area of Odense University Hospital were excluded as well, since these patients underwent further examinations at their local hospital and therefore we were unable to access the results.

After a thorough investigation, the neurologist classified the patient as having a TIA or a TIA mimic. This study only focuses on those patients who were classified as having TIA or retinal TIA. Patients with a confirmed diagnosis received antiplatelet therapy and were referred for HM and further cardiac evaluation.

Referral for Cardiac Evaluation

Patients without previously known AF or without AF on standard ECG were referred to 72-hour HM. The Holter monitor (Lifecard CF, Spacelabs Healthcare) was connected with 4 electrodes, which were attached to the chest surface. A continuous two-channel ECG was stored on a CompactFlash card with a maximum capacity of 7 days. All Holter recordings were analyzed by trained personnel using a dedicated software (Pathfinder SL, Spacelabs Healthcare), and the reports were reviewed by an experienced electrophysiologist. Transthoracic echocardiography was performed if patients were <65 years of age or if the referring physician suspected a cardiac source of embolism or heart disease. Transesophageal echocardiography was done if a suspected cardiac source of embolism was found on transthoracic echocardiography. Smaller atrial septal defects and patent foramen ovale were not considered cardiac sources of embolism, as their role in embolic stroke or TIA remains unclear [9, 10].

AF was defined as irregularly irregular heart rhythm with the absence of P waves and/or presence of F waves either on admission ECG or HM. An experienced cardiologist confirmed all diagnoses of AF regardless of monitoring type.

Patient Characteristics

Hypertension was defined as receiving antihypertensive treatment. Hyperlipidemia was defined as treatment with statins or other cholesterol-lowering drugs on admission or having a total cholesterol >5 mmol/L or LDL cholesterol >3 mmol/L. Diabetes was defined as treatment with antidiabetics on admission or HbA_{1c} >48 mmol/mol. Previous stroke was defined as a prior diagnosis of stroke due to focal neurologic symptoms with typical findings on brain imaging with or without residual symptoms. Smoking was defined as a history of current or former tobacco use. Ischemic heart disease was defined as prior myocardial infarction, prior CABG/PCI, or prior coronary angiography or other imaging techniques demonstrating coronary artery disease.

Data Acquisition, Validity, and Statistical Analysis

Data were obtained from the patients' electronic medical records. Prior to data collection, a report defined how each variable should be obtained. All data were entered into a database (Access 2010, Microsoft Corporation, Redmond, WA, USA) and subsequently analyzed using STATA 14 (StataCorp LP, College Station, TX, USA).

Continuous variables were reported as mean with 95% confidence interval if data followed a normal distribution. Significance was tested using Students t test. Non-normal continuous data were reported as median and range. Significance was tested using Wilcoxon Mann-Whitney U test. Binary variables were reported as percentages and analyzed using Fisher's exact test. A two-sided p value <0.05 was considered statistically significant.

Identifying other Transient Ischemic Attack Studies

To compare our results with similar studies, we conducted a literature search in PubMed, Embase, and The Cochrane Library for studies reporting the detection rate of AF in a TIA population. We included only prospective studies, as these had predefined patient inclusion
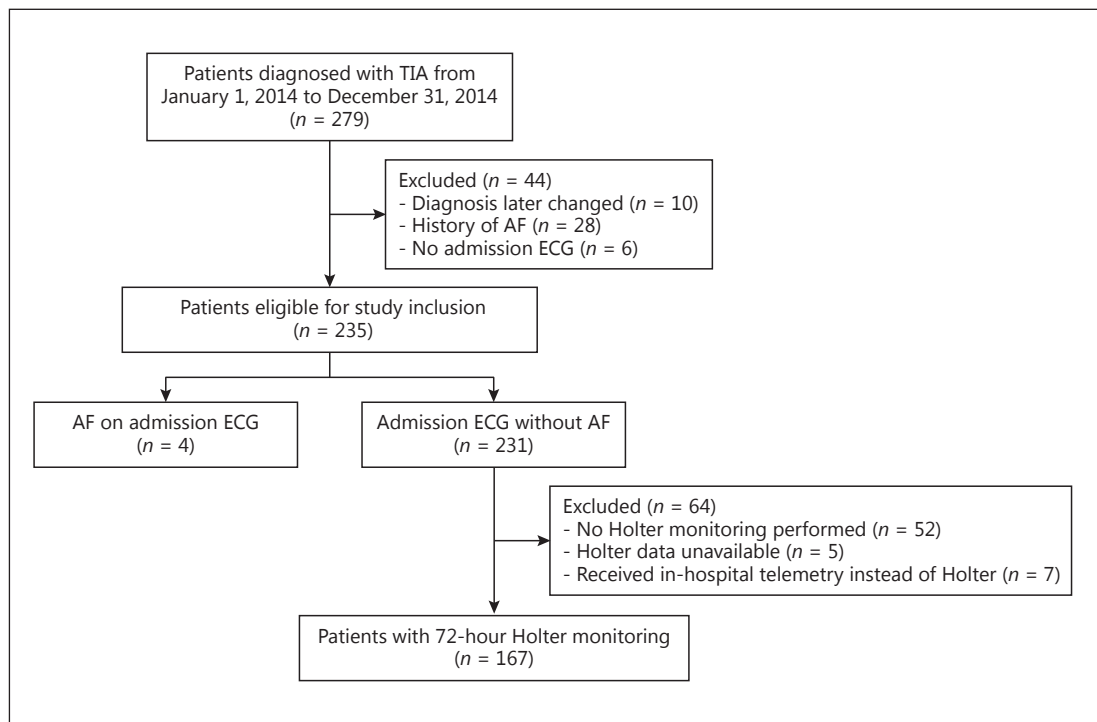
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Fig. 1. Flowchart highlighting the patient selection process. TIA, transient ischemic attack; AF, atrial fibrillation; ECG, electrocardiogram.

criteria, and we wanted to avoid a possibly high incidence of AF due to selection bias. Studies regardless of language or publication date were eligible.

Results

Between January 1, 2014 and December 31, 2014, 279 patients were diagnosed with TIA. In total, 44 patients were excluded because they were later characterized as TIA mimics (n = 10), had a history of AF (n = 28), or had no ECG taken on admission (n = 6), leaving 235 patients eligible for study inclusion (Fig. 1). An additional 64 patients were excluded, as they had no HM (n = 52), Holter recording was unavailable for review (n = 5), or they received in-hospital telemetry (n = 7). In-hospital telemetry was rarely and inconsistently used throughout the study inclusion period and excluded because ECG data were unavailable for review.

Table 1 shows the baseline characteristics of the entire cohort, patients with newly diagnosed AF (AF group), and those without AF (non-AF group), respectively. Patients in the AF group were significantly older with a mean age of 79.4 (95% confidence interval 65.1–93.6) years compared with 67.6 (95% confidence interval 65.6–69.5) years in the non-AF group (p = 0.0276). There was no statistically significant difference regarding the other baseline characteristics. TIA constituted the majority of patients, as less than 10% had retinal TIA. Fifty-eight percent were treated in-hospital, while the remaining patients were later seen in the TIA outpatient clinic after a median delay of 4.5 days.

Table 1. Baseline characteristics of the study subjects

	All patients (n = 171)	Non-AF group (n = 165)	AF group (n = 6)	p
Male gender	89 (52)	87 (52.7)	2 (33)	0.4284
Mean age, years	68 (66.1–70)	67.6 (65.6–69.5)	79.4 (65.1–93.6)	0.0276
Mean BMI	26.3 (25.7–26.9)	26.4 (25.7–27)	25.4 (21.8–29.1)	0.5649
Mean blood pressure, mm Hg	147/83	147/83	157/80	0.29/0.62
Index event				
TIA	158 (92.7)	153 (92.7)	5 (83.3)	0.3823
Retinal TIA	13 (7.3)	12 (7.3)	1 (16.7)	0.3823
Admission type				
In-patient	99 (58)	95 (57.6)	4 (66.7)	1
TIA clinic	72 (42)	70 (42.4)	2 (33.3)	1
Median delay to TIA clinic, days	4.5 [1–153]	4.5 [1–153]	27 [4–50]	0.28
Medical history				
Hypertension	93 (54.4)	88 (53.3)	5 (83.3)	0.221
Diabetes	19 (11.1)	18 (10.9)	1 (16.7)	0.512
Hyperlipidemia	63 (36.8)	60 (36.4)	3 (50)	0.671
Previous stroke	31 (18.1)	31 (18.8)	0 (0)	0.5932
Ischemic heart disease	19 (11.1)	19 (11.5)	0 (0)	1
Smoking	90 (52.6)	86 (52.1)	4 (66.7)	0.392
Antiplatelet treatment at admission	59 (34.5)	59 (35.8)	0 (0)	0.094
OAC treatment at admission	3 (1.8)	3 (1.8)	0 (0)	1
Blood samples				
Mean cholesterol, mmol/L	5.2 (5–5.4)	5.2 (5–5.4)	5.1 (3.6–6.6)	0.8421
Mean LDL, mmol/L	3.2 (3–3.4)	3.2 (3–3.4)	3.4 (2–4.8)	0.7273
Mean HbA_{1c}, mmol/mol	38 [23–85]	37.5 [23–85]	38 [34–49]	0.7350

Values in parentheses are percentages or 95% confidence intervals, and values in square brackets are ranges. BMI, body mass index; AF, atrial fibrillation; TIA, transient ischemic attack; OAC, oral anticoagulation therapy.

Detection of Atrial Fibrillation

New AF on admission ECG was found in 4 patients out of the initial 235 patients (1.7%). HM was done in 167 patients, and AF was found in 2 patients (1.2%). Excluding all patients not undergoing HM, we ended up with 171 patients. Six of them (3.5%) were diagnosed with AF by using ECG and 72-hour HM.

Holter Monitoring

The median duration of HM was 71.7 h with a median delay from admission to HM of 48 days. In general, all HM showed a good quality with a median percentage of unreadable data of 0.2% (Table 2).

HM was not performed in 52 patients (22.5%), mainly because patients did not show up, but some also had previous HM close to the event, which was why it was not deemed necessary to perform a new one. Some patients with dementia or nursing home residents with low functional level were not offered HM because of inability to participate.

Significant arrhythmias other than AF requiring either admission or further examinations were found in 15 patients (9%), of which the most common was non-sustained ventricular tachycardia (n = 12).

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Table 2. Holter monitoring data

	Patients with Holter monitoring (n = 167)
Atrial fibrillation found on Holter, any duration	2 (1.2)
Atrial fibrillation found on Holter, ≥30 s	1 (0.6)
Mean delay from admission to Holter, days	48 (43–54)
Median time from Holter to final analysis and patient information, days	13 [4–116]
Median length of Holter monitoring, h	71.7 [45.7–116]
Median percentage of unreadable Holter data	0.2 [0–37.6]
Median number of premature ventricular complexes	66 [0–123,366]
Median number of supraventricular extrasystoles	55 [0–21,533]
Median number of supraventricular tachycardias (not atrial fibrillation) <30 s	1 [0–208]
Significant arrhythmias	15 (8.8)
Sinus arrest	1 (0.6)
Second-degree atrioventricular block	2 (1.2)
Non-sustained ventricular tachycardia	12 (7.2)

Values in parentheses are percentages or 95% confidence intervals, and values in square brackets are ranges.

Table 3. Diagnostic procedures

	Study sample (n = 171)	Non-AF group (n = 165)	AF group (n = 6)	p
Cranial CT	165 (94.5)	159 (96.4)	6 (100)	1
Cranial MRI	67 (39.2)	66 (40)	1 (16.7)	0.406
Evidence of acute or old infarction on CT or MRI	63 (36.8)	60 (36.4)	3 (50)	0.671
Carotid ultrasound	164 (95.9)	159 (96.4)	5 (83.3)	0.2248
Significant carotid stenosis	9 (5.5)	8 (5.5)	1 (20)	0.2486
Carotid endarterectomy	6 (3)	5 (3)	1 (20)	0.1955
Thrombophilia	1 (0.6)	4 (0.6)	0 (0)	1
TTE	112 (65.5)	107 (64.8)	5 (83.3)	0.6656
TOE	7 (4.1)	7 (4.2)	0 (0)	1
Cardiac source of embolus found on TTE/TOE	0 (0)	0 (0)	0 (0)	1
Cardiac CT	4 (2.3)	4 (2.4)	0 (0)	1
Myocardial perfusion scintigraphy	2 (1.2)	2 (1.2)	0 (0)	1
Coronary angiography	6 (3.5)	6 (3.6)	0 (0)	1

Values are expressed as numbers with percentages in parentheses. CT, computed tomography; MRI, magnetic resonance imaging; TTE, transthoracic echocardiography; TOE; transesophageal echocardiography.

Cerebrovascular and Cardiac Diagnostic Imaging

Brain imaging was done in all patients. Brain CT was done in 165 patients (94.5%) and brain MRI in 67 patients (39.2%) (Table 3). Carotid artery ultrasound was performed in 164 patients (95.9%). Six of these patients (3.7%) had a significant carotid artery stenosis requiring carotid endarterectomy. Transthoracic echocardiography was performed in 112 patients (65.5%) and did not reveal any thrombi or other cardiac source of emboli.

In 7%, coronary angiography, cardiac computed tomography, or myocardial perfusion imaging was performed. The main reason for the examinations was non-sustained ventricular tachycardia detected on Holter monitoring or suspected angina pectoris.

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Table 4. Prospective studies with TIA patients

First author [Ref.]	Year	*n*	Age, years	History of AF, *n* (%)	New AF, *n* (%)	Combined AF, *n* (%)	Monitoring methods
Al-Khaled [15]	2014	2,200	70.6	381 (17.3)	–	–	–
Sheehan [14]	2010	443	70			112 (25.3)	ECG and/or CM
von Weitzel-Mudersbach [13]	2012	203	66.3	18 (8.9)	–	–	–
Perry [12]	2014	3,906	68	349 (9.2)	53 (1.5)	402 (10.3)	ECG
Inoue [11]	2004	1,084	69.2	–	–	186 (17.2)	ECG and/or 24HM

AF, atrial fibrillation; ECG, electrocardiography; CM, continuous ECG monitoring; 24HM, 24-hour Holter monitoring.

Literature Search of Similar Studies

Searching the online literature databases, we found five prospective studies focusing on patients with TIA (Table 4) [11–15]. A total of 7,837 patients with a mean age of 69.2 years were included in these studies. All studies used the WHO definition of TIA. However, the methods of reporting the percentage of AF were largely differing. Three studies reported the percentage of patients with a history of AF prior to TIA being 17.3, 8.9, and 9.2%, respectively. Two other studies reported the total number of patients with AF including both history of AF and new AF being 25.7 and 17.2%, respectively. Perry et al. [12] also reported the percentage of new AF (1.5%). In some of the studies, patients underwent continuous monitoring, but the type or duration was not always specified. None of the studies reported a definition of AF or who made the diagnosis.

Discussion

In our study of 171 patients with TIA and no history of AF, we found 4 patients (2.3%) with new AF on admission ECG. AF was afterwards found in another 2 (1.2%) out of the remaining 167 patients undergoing HM. In total, 6 patients (3.5%) were diagnosed with new AF. Looking at the entire population screened and excluding TIA mimics (*n* = 269), 28 patients (10.4%) had a history of AF.

The proportion of patients with a history of AF is similar to those in the TIA studies by Perry et al. [12] and von Weitzel-Mudersbach et al. [13], who reported a known AF percentage of 9.2 and 8.9%, respectively. Perry et al. [12] found 1.5% of their patient population having new AF using admission ECG, which is similar to our results. Interestingly, we found only 2 patients with AF in the 167 patients undergoing HM.

Comparing our results with a mixed population of ischemic stroke and TIA patients in the meta-analysis by Sposato et al. [5], we found fewer patients with new AF on admission ECG (2.3 vs. 7.7%) and fewer patients with new AF on ambulatory monitoring (1.2 vs. 10.2%). There could be several possible explanations for these findings.

Differences in Study Populations

The studies in the meta-analysis by Sposato et al. [5] primarily included patients with ischemic stroke, although some had a minor proportion of patients with TIA as well. AF is known to cause severe ischemic strokes [16] and the underlying pathophysiological mechanism is believed to be thrombus formation due to blood stasis, hypercoagulability, and endothelial dysfunction in the left atrial appendage and subsequent embolization of the thrombus to the brain [17].

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In theory, TIA could be caused by micro-embolization from such a thrombus, but our data suggest that AF might be less common in patients with TIA and therefore less likely to be the cause. Even in ischemic stroke patients it is still being discussed whether or not AF is the cause of thrombus formation per se or just a marker of an underlying atrial pathology predisposing to thrombus formation [18]. The only statistically significant difference between the AF and non-AF group in our study was age, which is also known to be the single most important risk factor for developing AF [19].

Diagnosing Atrial Fibrillation

Another important factor to consider when comparing the low diagnostic yield of cardiac monitoring in our study population with other studies is the validity of the AF diagnosis. In our study, all ECGs and HMs were analyzed by an experienced electrophysiologist. An episode of AF on HM was defined as an episode with irregularly irregular rhythm regardless of length, although current guidelines [20] recommend a minimum AF duration of 30 s. We chose to consider all AF episodes regardless of their duration because there is currently no convincing evidence that shorter episodes of AF are less dangerous than longer episodes in a population at high risk of stroke [21].

None of the five prospective studies we identified from the literature had a clear definition of AF, and they did not state who made the diagnosis. AF is easy to diagnose on ECG, but it requires trained staff to distinguish AF from other atrial arrhythmias such as ectopic atrial tachycardia, sinus arrhythmia, and frequent premature atrial complexes. Oral anticoagulant treatment in patients with ischemic stroke/TIA and AF reduces the risk of recurrent stroke, but if AF is misdiagnosed, however, the treatment could be potentially dangerous, putting the patients at unnecessary risk of hemorrhage. If AF is suspected, efforts should be made to confirm the diagnosis by consulting a cardiologist.

Validity of Diagnosing Transient Ischemic Attack

Our low detection rate of AF could also be due to differences in the diagnostic criteria of TIA. It is estimated that around 50% of all patients with suspected TIA have "TIA mimics" [22]. In our study, we only included patients with a final diagnosis of TIA, and only in a few, the diagnosis was later changed. We do not have data from the patients with suspected TIA who were finally diagnosed with TIA mimics. However, the majority of patients were seen by an experienced senior neurologist, which limits the possibility of including an excessive number of patients with TIA mimics in this study.

Definition of Transient Ischemic Attack

At our institution, we use the WHO definition of TIA, which is a clinical diagnosis primarily based on a description of the symptoms as the neurological deficit often disappears before admission. A tissue-based definition of TIA is not routinely used, because the brain MRI capacity at our institution is a limiting factor. Patients with signs of new infarction on brain imaging could have been included in our study because their symptoms resolved within 24 h. On the other hand, we cannot rule out that some of these patients were diagnosed with stroke instead of TIA because brain MRI showed signs of infarction. There is no clear pattern which patients received brain MRI, brain CT, or both, but one could suspect that younger patients and patients with severe or longer-lasting neurological deficits were offered a brain MRI. If some of these patients were categorized as stroke and, therefore, not included in the study, this could be a possible cause of selection bias, which could explain our low incidence of AF.

We identified our study population on the basis of a final clinical diagnosis of TIA or retinal TIA, and did not review all patients diagnosed with ischemic stroke to see whether or not the episode length was <24 h.

The American Heart Association and American Stroke Association published a scientific statement regarding TIA in 2009 [23]. They argued for a revision of the diagnostic criteria for TIA to include brain imaging, preferably brain MRI, to categorize all patients with signs of acute brain infarctions as ischemic stroke regardless of time criteria. This would simplify the diagnostic process and make a diagnosis of TIA more accurate. It was not possible in this study to use brain imaging for the selection of study participants because brain MRI was not systematically used throughout the study inclusion period.

Atrial Fibrillation: Cause or Consequence?

It has been hypothesized that AF after stroke and TIA could be due to imbalance in the autonomic nervous system caused by cerebral ischemia [24]. In other words, is AF the cause or the consequence of stroke or TIA? This hypothesis of neurogenically mediated AF could explain the low incidence of AF in patients with TIA compared to stroke. Stroke patients suffer more severe brain damage than patients with TIA resulting in autonomic imbalance which can affect the heart. In addition, the delay in our study from event to HM was 48 days. We could have missed AF episodes occurring shortly after TIA onset, especially if AF was triggered by a temporary risk factor such as infection at the time of TIA or if AF was caused by autonomic imbalance caused by transient ischemia.

Conclusion

In our study of 171 patients with TIA or retinal TIA with no history of AF, we found new AF in 3.5% by using admission ECG and 72-hour HM. The percentage of patients with a history of AF prior to the event was similar to other studies with the same population but markedly lower compared to patients with stroke. Clinicians should be aware that the incidence of AF is lower in patients with TIA than in those with stroke. The reason for low AF incidence could be due to AF and TIA diagnostic criteria, but also because all ECGs in our study were reviewed by a cardiologist to avoid misdiagnosing AF. The theory of neurogenically mediated AF could explain the low incidence of AF in patients with TIA, but prospective studies with clear definitions of TIA and AF are needed to confirm our results and test the hypothesis. In the meantime, all patients with confirmed AF and TIA should be treated with oral anticoagulants regardless of AF duration.

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Disclosure Statement

The authors have no conflict of interest to declare.

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