Subclinical atrial fibrillation in patients with recent transient ischemic attack

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54.8% of first time ICD recipients were candidates for S-ICD.¹

REFERENCE
Subclinical atrial fibrillation in patients with recent transient ischemic attack

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Abstract

BACKGROUND: Atrial fibrillation (AF) is a major risk factor of stroke, but the association between AF and transient ischemic attack (TIA) is less clear. Despite this, patients with TIA are included in stroke trials.
AIMS: To determine the one-year incidence of AF in TIA patients using an insertable cardiac monitor (ICM); second, to determine factors associated with incident AF in these patients.

METHODS: Prospective cohort study of patients with TIA with normal standard ECG and 72h Holter monitoring (HM). Exclusion criteria: Age <18 or >81 years; prior AF/stroke; ongoing oral anticoagulation therapy or contraindication for it; significant carotid artery stenosis; uncertain TIA diagnosis. Eligible patients received an ICM and were followed for 12 months.

RESULTS: From November 2013 to October 2015, 809 patients were diagnosed with TIA. In total, 235 patients were eligible. Nine (3.8%) of these had AF on standard ECG or HM. Of the remaining patients, 121 refused ICM implantation. In total, 105 patients (median age 65.4 (range 27.1-80.8) years, 46% males) received an ICM, which revealed AF in seven (6.7%). Factors associated with new-onset AF were a history of recurrent TIA (Odds ratio (OR) 11.5, 95% confidence interval (CI) 2.1-63.6) and heart failure (OR 12.7, 95% CI 1.71-96.83).

CONCLUSIONS: The one-year incidence of AF in TIA patients with normal ECG and HM was 6.7% using an ICM. Factors associated with development of AF were recurrent TIA and heart failure.

Keywords
transient ischemic attack, atrial fibrillation, cardiac monitoring, implantable cardiac monitor, stroke

Introduction

Atrial fibrillation (AF) is a major cause of stroke [1], and oral anticoagulants are superior to conventional antiplatelet treatment in reducing the risk of stroke in patients with AF [2,3]. However, AF episodes are often asymptomatic and paroxysmal and therefore difficult to detect with conventional monitoring strategies such as serial ECGs or Holter-monitoring (HM). In recent years, insertable cardiac monitors (ICMs) for long-term ECG monitoring have been shown to increase the detection rate of AF in patients with stroke and transient ischemic attack (TIA) compared to
conventional noninvasive methods [4-8]. These episodes of AF which would otherwise remain
undetected are termed subclinical AF.

Numerous publications have investigated the incidence of subclinical AF in patients after acute
ischemic stroke or TIA, but primarily included patients with ischemic stroke and only a minority with
TIA [9]. While stroke is diagnosed from brain imaging and ongoing neurological deficits, the diagnosis
of TIA relies on clinical signs supported by cerebrovascular risk factors [10]. Several conditions such
as migraine, hypoglycemia, syncope, and stress can mimic TIA [11], and it is estimated that 50% of all
patients initially referred with suspected TIA had TIA mimics [12].

These observations call the inclusion of TIA patients in stroke trials into question. Very few studies
have investigated the incidence of new-onset AF (NOAF) exclusively in TIA patients. A recent
systematic review and meta-analysis by Korompoki et al. [13] found that the detection rate of NOAF
in TIA patients was lower than in mixed populations with stroke or TIA, but prospective studies
exclusively investigating TIA patients and focusing on detection of NOAF using long-term continuous
ECG monitoring with an ICM are lacking.

The primary aim of this study was to investigate whether continuous cardiac rhythm monitoring
(CRM) for one year with an ICM increases the detection rate of NOAF in patients with recent TIA
compared to standard care with ECG and 72-hour HM. The secondary aim was to identify factors
associated with NOAF.

Methods

Study design

We performed a prospective, single-center cohort study in consecutive patients with acute TIA, who
were admitted to the Department of Neurology, Odense University Hospital (OUH), Denmark. In a
sample size calculation made prior to study start, we estimated that 125 patients were needed to
detect AF in at least 4.5% of the patients with a significance level of 5% and a power of 0.9. TIA was defined as an episode of neurologic deficit presumably caused by cerebrovascular ischemia and with full remission of symptoms within 24 hours regardless of signs of infarction on brain imaging [14]. We regarded TIA as a clinical diagnosis based upon the discretion of the clinician. Exclusion criteria were: age <18 or >81 years, a history of AF or stroke, ongoing oral anticoagulation (OAC) therapy or contraindication for OAC, severe dementia or mental illness, life expectancy <12 months, thrombolysis, and carotid artery stenosis requiring endarterectomy.

Patients with a suspected TIA episode within the last 24 hours were hospitalized, whereas those with episodes occurring more than 24 hours ago were mainly seen at the TIA outpatient clinic. All patients were examined by an experienced neurologist. The work-up included a detailed history and physical examination, 12-lead ECG, carotid ultrasound if appropriate, and brain imaging using either computed tomography (CT) or magnetic resonance imaging (MRI). To avoid inclusion of TIA mimics all eligible patients were independently reevaluated by a second neurologist before inclusion in the study. This evaluation was made on a case-by-case basis and took into consideration the type of symptoms, their duration and CT/MR-findings and the presence of risk factors.

Cardiac evaluation

All patients with a suspected TIA underwent ECG and 72-hour HM. An echocardiography was done in patients with suspected heart disease (heart valve murmur, signs of congestive heart failure) or patients <65 years according to national guidelines [15]. All patients who received device implantation underwent a thorough transthoracic echocardiography (TTE). We performed transesophageal echocardiography (TEE) if cardiac source of embolism was suspected on TTE.

If admission ECG and 72-hour HM were without AF and echocardiography did not show any cardiac source of embolus, patients were offered ICM implantation (Reveal® XT or Reveal LINQ™, Medtronic Inc., USA).
Device implantation and follow up

The device was implanted subcutaneously under local anesthesia. All patients were monitored using a secure online database (CareLink® Network, Medtronic Inc., USA). Patients with the Reveal® XT performed transmissions at 1, 3, 6, 9 and 12 months, whereas those with the Reveal LINQ™ made automatic daily transmissions. All patients were monitored for 12 months after device implantation regardless of findings on ICM.

The device was programmed to detect AF episodes ≥ 2 minutes and store the electrograms for review. A minimum AF episode duration of 2 minutes is required by the device to detect AF with a high sensitivity [16]. AF was defined as irregularly irregular heart rhythm with the absence of p-waves. Other clinically relevant arrhythmias were also stored. AF detected on HM lasted at least 30 seconds [17]. Suspected AF and other arrhythmias were independently adjudicated by two experienced senior electrophysiologists.

Ethics

The study was approved by the Ethical Committee in the Region of Southern Denmark (registration number S-20130027) and the Danish Data Protection Agency and complies with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (NCT02011256).

Statistical analysis

Data were analyzed using STATA 14 (Statacorp LP, College Station, USA). Continuous variables following a normal distribution were reported as means ± standard deviation (SD). Test for significance was done using Student’s t-test. Non-normally distributed data was reported as median (total range or interquartile range) and significance was tested with the Wilcoxon rank-sum test. Binary variables were tested for significance using Fischer’s exact test. Univariate logistic regression with AF as the dependent variable was presented as Odds ratio (OR) with a 95% confidence interval.
(CI). Time from device implantation to event was analyzed with the Kaplan-Meier curve. Difference between time to first AF episode and time to first arrhythmia episode other than AF was calculated using the log-rank test. A two-sided $P$-value < 0.05 was considered significant.

**Results**

From November 2013 to December 2015 a total of 809 patients were admitted with TIA. We excluded 413 patients, mainly because of age, known AF or previous stroke. TIA diagnosis was not confirmed in 161, leaving 235 patients eligible for inclusion, of which nine had AF on either ECG or 72-hour HM. One-hundred and twenty-one patients subsequently declined ICM implantation, leaving 105 patients in the final study population (figure 1), which was below the intended sample size.

The patients had a median age of 65.4 (range 27.1-80.8) years, and 46% were males. ICM implantation was performed with a median of 113 days (range 30-294) after the index event. Patients were monitored for a median of 381 (25-75% interquartile range 371-390) days. The device was explanted in two patients due to infection or pain. A third patient had a superficial skin infection requiring treatment with antibiotics but not device removal. During 12 months follow-up 7 patients (6.7%) had NOAF. There were no differences in most parameters between patients with or without NOAF on CRM (Table 1). However, significantly more patients with NOAF had a history of recurrent TIA (42.6% vs. 6.1%, $P = 0.0131$) and a history of heart failure (28.6% vs. 3.1%, $P = 0.0348$).

Patients with NOAF had median episode duration of first AF episode of 8 minutes (total range 2-1284). The median time to first AF episode was 21 days (total range 5-146) while the median time to the first arrhythmia other than AF was 233 days (total range 0-486). In 6 out of 7 patients (85.7%) AF was detected within the first 67 days. The corresponding Kaplan-Meier curves are presented in figure 2 A-D. There was a significant difference in time to first device detected AF episode compared with first arrhythmia episode other than AF (log-rank test, $P = 0.0058$). The most common other
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AF and we found the same association in this study [20]. Rare paroxysms of AF could cause recurrent TIAs, but recurrent TIAs could also indicate higher-risk patients who might be more prone to AF.

Detection of atrial fibrillation in patients with TIA

In the present study, the incidence of NOAF found during one year of monitoring was lower compared to the AF-incidence found in similar studies with mixed populations of stroke and TIA. In the randomized CRYS-TAL-AF study NOAF was found in 12.4% of patients with cryptogenic stroke during one year of CRM (n = 221). In a similar group of patients who did not undergo device implantation (n = 220) only 2% had AF. In a subpopulation of 40 TIA patients, NOAF was found in 20% [4]. However, in CRYS-TAL-AF only TIA patients with visible lesions on brain imaging that fitted the symptoms were included, whereas our study utilized the time-based definition of TIA. Only a minority in this study had signs of acute infarction on brain imaging. Evidence of acute infarction is known to have prognostic value and is associated with increased risk of stroke in patients with TIA [21,22]. Focal ischemic abnormalities on brain MRI can cause autonomic imbalance that can predispose to AF (neurogenic AF) [23], which could explain the higher detection rate of AF in TIA-patients in the CRYS-TAL AF study. Other studies in small TIA sub-populations undergoing prolonged monitoring with an ICM found AF in 15% after two years of monitoring and no AF after 14 months of monitoring, respectively [24,7].

Reasons for low incidence of atrial fibrillation in patients with TIA

This and other studies confirm the lower incidence of AF in patients with TIA compared to patients with stroke. The diagnosis of TIA is often subject to some degree of uncertainty, because it is a clinical diagnosis and symptoms are often completely remitted at initial presentation to the health care system. Even after evaluation by a neurologist, several conditions can be misinterpreted as TIA (mimics). Even though all patients in our study were evaluated by two independent expert neurologists, inclusion of TIA mimics cannot completely be ruled out. A common condition that can
mimic TIA is syncope or near-syncope [25]. Five patients in our study had pacemaker implantation due to complete AV block or sick sinus syndrome. Some patients reported that symptoms during near-syncope during ICM monitoring were similar to the symptoms leading to admission for TIA.

In the present study, the median time from TIA-event to device implantation was 113 days, why we could have missed AF episodes caused by transient causes such as autonomic dysfunction and inflammation.

Patient selection criteria are important for AF detection rate in TIA patients [13]. In our study we excluded patients above 81 years of age and patients with severe disability (i.e., previous stroke), both known risk factors for AF, because (1) we found it unethical to implant devices in patients with severe disability and (2) elderly patients might not complete follow-up and might lack the technical skills needed to send transmissions from home. We might have seen a higher AF incidence if elderly and patients with prior stroke had not been excluded. We also excluded patients already on OAC treatment or with a contraindication for OAC treatment, because they would not benefit from AF detection, and those patients could potentially also have a higher risk for AF.

It is also possible, that the devices used in this study might have missed AF episodes, as detection requires an episode duration of at least 2 minutes. Regular data transmissions ensured that episodes were not overwritten, but some patients with the Reveal® XT did not regularly transmit due to poor compliance. However, the overall risk of episode deletion was regarded as low as patients were contacted regularly if a transmission was missed. The reported device sensitivity of 96.1% ensured that almost all possible AF episodes were stored and reviewed [16].

Finally, it is possible that TIA patients with ischemic lesions were diagnosed with stroke instead. This selection bias may arise if TIA patients with alarming symptoms received more a thorough evaluation that might result in a change in diagnosis from TIA to stroke. Removing these high-risk patients from our study sample could result in lower AF detection rate.
Optimal monitoring duration

Current European stroke guidelines recommend a 12-lead ECG on admission and 24 hours of continuous ECG monitoring, whereas the American Stroke Organization recommends 30 days of prolonged rhythm monitoring if there is no other apparent cause of stroke [3,2]. The European Society of Cardiology currently recommends long-term monitoring for at least 72 hours. In our study 85.7% of all AF episodes were detected within 67 days. The maximal monitoring is limited by the battery life of the ICM, which is estimated at approximately 3 years for the devices used in this study. The CRYSTAL AF study found a progressively increasing AF incidence throughout the monitoring period and after 3 years 30% had been diagnosed with AF [26]. Though AF found after 3 years still warrants OAC treatment, establishing causality between initial event and AF is difficult. In this present study the time to first AF episode was significantly lower than the time to first non-AF arrhythmia, which might indicate a temporal relationship. However, it might also just indicate that TIA-patients with NOAF have had paroxysmal episodes that remained undetected during the initial diagnostic work-up with ECG and HM.

Limitations

This study has some important limitations. The recently ASSERT-2 and REVEAL-AF studies reported AF detection rates of 34.4% after 12 months and 40% by 30 months, respectively, in patients at high risk of AF, but without recent stroke or TIA [27,28]. Therefore, it would have been optimal to have a matched control group of patients without TIA to determine if TIA-patients are at higher risk of having AF than patients without TIA. Comparing ASSERT-2 and REVEAL-AF with the present study, we had a similar mean CHA²DS²-VASc score, but our study patients were at lower risk than those in ASSERT-2 and REVEAL-AF with a lower mean age, less presence of heart failure, hypertension, coronary artery disease, diabetes and, previous stroke/TIA.
Another important limitation was that we did not reach the expected number of study participants due to difficulties in patient recruitment and time constraints. Because of the small study size and low event rate the results of the univariate logistic regression analysis must be interpreted with caution, and we decided not to do a multivariate analysis. The estimated ORs for recurrent TIA and heart failure have large CIs, which makes it difficult to determine, how strong their predictive value for AF is. Additionally, more than half of all eligible patients declined participation, primarily due to concerns about the implantation procedure, which introduces participation bias. Due to ethical guidelines, follow up and analysis of those patients who declined participation is not possible. During the inclusion period we switched from Reveal® XT to Reveal LINQ™, which is substantially smaller and easier to insert, which might enhance patient participation in later studies. We might have missed possible AF episodes in this study, because we had a significant delay from event to device implantation. Ethical considerations were the main reasons for this delay as patients were given considerable time to give their informed consent. Patients also had to complete our standard monitoring regime with 72h HM after discharge before device implantation. Patients were examined with TTE but only a minority with TEE, why we could have missed potential cardiac source of embolism in some patients.

Conclusions

Addition of CRM with an ICM for one year detected NOAF in 6.7% of TIA patients with normal ECG and 72-hour HM. Factors associated with AF were a history of recurrent TIA and heart failure. We found that 85.7% of all AF episodes were detected after 67 days.

References

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Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 105)</th>
<th>No NOAF (n = 98)</th>
<th>NOAF-group (n = 7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.4 (27.1-80.8)</td>
<td>64.7 (27.1-80.8)</td>
<td>68.6 (45.3-75.5)</td>
<td>0.2583</td>
</tr>
<tr>
<td>Male sex</td>
<td>48 (45.7)</td>
<td>46 (46.9)</td>
<td>2 (28.6)</td>
<td>0.4497</td>
</tr>
<tr>
<td></td>
<td>BMI*, kg/m²</td>
<td>Index event</td>
<td>Admission type</td>
<td>Event length &lt;1 hour</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td></td>
<td>26.7 (4)</td>
<td>93 (88.6)</td>
<td>74 (70.5)</td>
<td>62 (59.1%)</td>
</tr>
<tr>
<td></td>
<td>26.8 (4)</td>
<td>87 (88.8)</td>
<td>69 (70.4)</td>
<td>56 (57.1)</td>
</tr>
<tr>
<td></td>
<td>25.2 (4)</td>
<td>6 (85.8)</td>
<td>69 (71.4)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3901</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>Blood pressure*</th>
<th>Platelet therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>- systolic, mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- diastolic, mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>137 (18.6)</td>
<td>32 (30.5)</td>
</tr>
<tr>
<td></td>
<td>138 (18)</td>
<td>29 (29.6)</td>
</tr>
<tr>
<td></td>
<td>125 (20)</td>
<td>3 (42.8)</td>
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<tr>
<td></td>
<td>0.0928</td>
<td>0.4333</td>
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<tr>
<td></td>
<td>0.0963</td>
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<table>
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<tr>
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<th>CHA²DS₂VASc-score</th>
<th>Platelet therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>4 (2-7)</td>
<td>32 (30.5)</td>
</tr>
<tr>
<td></td>
<td>4 (2-7)</td>
<td>29 (29.6)</td>
</tr>
<tr>
<td></td>
<td>5 (2-7)</td>
<td>3 (42.8)</td>
</tr>
<tr>
<td></td>
<td>0.094</td>
<td>0.4333</td>
</tr>
</tbody>
</table>
Baseline Characteristics of study participants. All continuous variables are expressed as median (total range) unless marked with * where it is reported as mean (± standard deviation). Categorical variables are expressed as numbers (percent). BMI, Body Mass Index; TIA, Transient Ischemic Attack; SD, Standard Deviation; n, number; CT, computed tomography; MRI, magnetic resonance imaging. The P value listed represents the comparison between the NOAF and no NOAF group.

### Table 2. Detected arrhythmias and cardiovascular events during one year of follow-up.

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Number of patients (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Complete atrio-ventricular block</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Sick sinus node</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>
Cardiovascular events | Total number of events (n = 13)
---|---
TIA recurrence | 7 (53.8)
Stroke | 3 (23.1)
Myocardial infarction | 2 (15.4)
 Decompensated heart failure | 1 (7.7)

The detected arrhythmias made with one year of ICM-monitoring and the observed cardiovascular events during monitoring. Numbers in parenthesis is the percentage of the total number of patients and events for arrhythmias and cardiovascular events, respectively. One patient experienced two cardiovascular events.

**Table 3. Univariate logistic regression analysis.**

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (0.96-1.13)</td>
<td>0.304</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.45 (0.084-2.44)</td>
<td>0.357</td>
</tr>
<tr>
<td>Index event retinal TIA</td>
<td>1.32 (0.15-12)</td>
<td>0.806</td>
</tr>
<tr>
<td>Admission type TIA clinic</td>
<td>0.95 (0.18-5.19)</td>
<td>0.954</td>
</tr>
<tr>
<td>Recurrent TIA</td>
<td>11.5 (2.1-63.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.13 (0.24-5.32)</td>
<td>0.875</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.32 (0.15-12)</td>
<td>0.806</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>1.55 (0.33-7.33)</td>
<td>0.583</td>
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<tr>
<td>Coronary artery disease</td>
<td>4.5 (0.75-27)</td>
<td>0.100</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12.7 (1.71-96.83)</td>
<td>0.013</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.04 (0.22-4.91)</td>
<td>0.958</td>
</tr>
<tr>
<td>Systolic Blood pressure</td>
<td>0.96 (0.91-1.00)</td>
<td>0.097</td>
</tr>
<tr>
<td>CHA2DS2VASc</td>
<td>1.68 (0.92-3.1)</td>
<td>0.094</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>1.78 (0.38-8.48)</td>
<td>0.466</td>
</tr>
</tbody>
</table>
Univariate logistic regression analysis for predictors for atrial fibrillation after one year of continuous cardiac monitoring with an implantable loop recorder (n = 105). OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack; CT computed tomography; MRI, magnetic resonance imaging.