Occult Atrial Fibrillation in Cryptogenic Stroke
Detection by 7-Day Electrocardiogram Versus Implantable Cardiac Monitors

Martin A. Ritter, MD*; Simon Kochhäuser, MD*; Thomas Duning, MD; Florian Reinke, MD; Christian Pott, MD; Dirk G. Dechering, MD; Lars Eckardt, MD; E. Bernd Ringelstein, MD

Background and Purpose—A significant number of patients with cryptogenic stroke suffer from intermittent atrial fibrillation (iAF) which was not detected during the standard diagnostic procedures. We investigated whether implantation of an insertable cardiac monitor (ICM) is feasible in patients with cryptogenic stroke, and compared the iAF detection rate of the ICM with 7-day Holter monitoring.

Methods—Sixty patients (median age 63; interquartile range, 48.5–72 years) with acute cryptogenic stroke were included. ICM was implanted 13 days (interquartile range; 10–65 days) after the qualifying event. Seven-day Holter was performed after the ICM was implanted.

Results—The iAF was detected by the ICM in 10 patients (17%; 95% CI, 7% to 26%). Only 1 patient (1.7%; 95% CI, 0% to 5%) had iAF during 7-day Holter monitoring as well (P=0.0077). Episodes of iAF lasting 2 minutes or more were detected 64 (range, 1–556) days after implantation. There were no recurrent strokes during the observation period. The implantation procedure was well tolerated with no adverse events; the daily data transmission protocol was easy to handle by the patients.

Conclusions—ICM implantation for the detection of iAF during outpatient follow-up is feasible in patients with cryptogenic stroke. ICMs offer a much higher diagnostic yield than 7-day Holter monitoring. (Stroke. 2013;44:1449-1452.)

Key Words: 7-day Holter ECG ■ implantable cardiac monitor ■ intermittent atrial fibrillation ■ stroke

About 25% of all ischemic strokes are considered cryptogenic despite intensive diagnostic work-up. It is likely that many of these patients suffer from intermittent atrial fibrillation (iAF) not detected during routine diagnostic procedures. Especially, the low yield of a 1-time 24-hour Holter ECG (7-d ECG) increased the detection rate of iAF to a maximum of 10% to 15%,3,4 and 30-day external event recorders (ECG monitors) 24-h Holter ECG (7-d ECG) increased the detection rate of iAF to a maximum of 10% to 15%,3,4 and 30-day external event recorders (ECG monitors) have shown yields of up to 23%.5

Insertable cardiac monitors (ICM) were developed to detect cardiac arrhythmias during the diagnostic work-up of syncope.

Recently, ICMs have been further refined and now incorporate algorithms to detect iAF, such as the Reveal XT (Medtronic Inc, Minneapolis). In a validation trial, the predefined algorithm had a sensitivity of 96.1% and a specificity of 85.4% when compared with human expert evaluation of conventional Holter-ECGs acquired in parallel. The negative predictive value was 97.4%.7 In the present observational study, we investigated whether the use of ICMs is feasible in patients with cryptogenic stroke and if the detection rate of iAF of the ICM is comparable with the use of a 7-d ECG.

Diagnostic Work-Up

Patients with acute stroke classified as cryptogenic stroke according to the TOAST criteria, who were admitted to our stroke unit between November 2010 and May 2012, were included.8 An intensive diagnostic work-up was performed to determine stroke pathogenesis: All patients had to have embolic stroke patterns on cerebral imaging (MRI, n=52 or computed tomography, n=8; ie, single or multiple cortical lesions or territorial infarctions). Patients with lacunar strokes were excluded. Potential sources of brain embolism were excluded in all patients by investigations of the brain-supplying arteries (Duplex ultrasound, and computed tomography angiography or magnetic resonance angiography), routine ECG, 72-hour continuous rhythm monitoring on the stroke unit and manual reevaluation of the signal, and additional 24-h Holter ECG. All patients received transesophageal echocardiography, including patent foramen ovale testing. Only patients...
with nonsignificant findings in all these investigations were considered for the study. The study was approved by the local ethics committee. For detailed methodology see the online-only data supplement.

**ICM Implantation**

All patients signed informed consent for the procedure and for further follow-up, including ECG transmissions. As this was a pilot trial, no maximum time after the event for the implantation of the device was defined. Patients had to be able to understand and follow the regular ECG transmission procedures independently. The ICM was implanted under local anesthesia.

**7-Day ECG**

Patients were also investigated by 7-d ECG after implantation of the ICM to compare the efficacy of this method with the ICM. The 7-d ECG was evaluated by human experts, for the diagnosis of iAF minimum duration of the episode was 30 seconds.

**Follow-Up**

All patients received platelet aggregation inhibitors at study start. All patients were seen in our hospital every 3 months for clinical events. Patients were immediately contacted by telephone in case iAF was detected, and anticoagulation therapy was recommended in all cases iAF was diagnosed.

Patients were instructed to report daily ECGs of 7-minutes duration via a telephone-based Care-Link interface provided by the manufacturer (Medtronic Inc, Minneapolis). The episodes stored automatically on the device were also transmitted. Transmissions were reviewed independently by 2 experienced cardiologists (S.K. and F.R.) for the presence of iAF. Only episodes that were also considered to be iAF by the human experts were used for diagnosis.

The minimum prospective monitoring period was 12 months, but patients were offered to stay under supervision if desired. Patients with atrial fibrillation (AF) detected were offered to have the device removed before this time point.

The ICM was also left in place in patients with detected iAF to evaluate the total time in AF during the study period. The device was explanted in 18 patients. In these patients, follow-up was 394 days (interquartile range, 372–420). All other patients still contribute data.

The implantation procedure of the ICM itself was well tolerated with no adverse events. Women patients sometimes reported discomfort of the device when wearing a bra. Compliance with the ECG transmission procedure was excellent.

**Statistics**

Patients with and without iAF were compared. Fisher exact test was used to compare dichotomous items, and Mann-Whitney test was used to compare continuous and categorical data. Mc-Namara test for repeated measures was used to compare the diagnostic yield of the ICM and the 7d-ECG.

**Results**

During the study period, 1476 patients were admitted to the Stroke Unit of which 1110 patients had ischemic stroke. Five hundred and two patients (34%) were classified as having cardioembolic stroke. Of these, 467 patients were diagnosed with stroke because of AF. Ninety-eight patients (21% of all patients with AF) were first diagnosed with AF on the admission ECG; in 15 patients (3%), AF was detected during the 72-hour stroke unit monitoring. Six additional patients (1.3%) had iAF only during 24-hour Holter ECG.

Two hundred and thirty-three (21%) patients were classified as having cryptogenic stroke. Of these, 95 patients were considered candidates for ICM implantation, 34 patients did not consent. Therefore, 61 patients with their first-ever clinically manifest stroke were finally included, but 1 patient withdrew consent to participate in regular telephonic ECG transmissions and was excluded from analysis.

Median age of the patients was 63 years (interquartile range, 48.5–72). Implantation of the ICM took place after a median of 13 days (interquartile range, 10–67) after the qualifying event. Median follow-up was 382 days (interquartile range, 89–670). The device was explanted in 18 patients. In these patients, follow-up was 394 days (interquartile range, 372–420). All other patients still contribute data.

The implantation procedure of the ICM itself was well tolerated with no adverse events. Women patients sometimes reported discomfort of the device when wearing a bra. Compliance with the ECG transmission procedure was excellent.

There were no recurrent strokes.

Patient’s details are given in Table 1.

There were no differences between patients with and without iAF in any of the risk factors, the risk scores, in involvement of the insular cortex, or in the time delay from event to implantation.

**Table 1. Demography**

<table>
<thead>
<tr>
<th></th>
<th>No AF (n=50)</th>
<th>IAF (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median; IQR)</td>
<td>61; 30–81</td>
<td>66; 30–85</td>
<td>n.s.</td>
</tr>
<tr>
<td>aHT, % (n)</td>
<td>70 (35)</td>
<td>70 (7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>14 (7)</td>
<td>0</td>
<td>P&lt;0.1</td>
</tr>
<tr>
<td>CHF, % (n)</td>
<td>0</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Vascular disease, % (n)</td>
<td>8 (4)</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Women, % (n)</td>
<td>40 (20)</td>
<td>60 (6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CHADS₂ score (median; IQR)</td>
<td>3; 2–3</td>
<td>3; 2.25–3</td>
<td>n.s.</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score (median; IQR)</td>
<td>4; 3–5</td>
<td>4; 3–5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insular cortex involvement</td>
<td>14 (7)</td>
<td>10 (1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total monitoring time (days, median; IQR)</td>
<td>397; 337–504</td>
<td>312; 242–397</td>
<td>n.s.</td>
</tr>
<tr>
<td>Implantation after event (days, median; IQR)</td>
<td>13; 10–65</td>
<td>30; 10–80</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; aHT, hypertension; CHF, heart failure; iAF, intermittent atrial fibrillation; IQR, interquartile range; and n.s., not significant.
The iAF was detected in 10 patients (17%; 95% CI, 7% to 26%) by the ICM. Episodes of iAF were detected on average 64 days (range, 1–556 days) after implantation. In 7 of these patients, iAF episodes were detected within the first 3 months after implantation (Figure). Only in 3 patients iAF was detected within the first week after the implantation.

The total duration of iAF detected (AF-burden) varied between 2 minutes and >1500 hours between patients (Table 2).

During the 7-day ECG, iAF was found in 1 patient only (1.7%; 95% CI, 0% to 5%). The yield of the ICM to detect iAF was thus significantly higher than during 7-d ECG (P=0.0077). One patient with iAF on the ICM removed the 7-day ECG after 3 days, whereas the ICM detected iAF on day 4.

**Discussion**

In the present pilot study, we have demonstrated the feasibility of ICM implantation to detect occult iAF in patients with cryptogenic stroke. The procedure was well tolerated with no significant side effects. There were no technical or local problems with ICM implantation or with the daily home-based ECG transmission. Once the device was implanted, the patients’ compliance was superior in comparison with an external 7-d ECG. Dislocation of the electrodes is the main problem of 7-d ECG. The same problem was encountered by Stahrenberg et al who were able to receive >5 days of ECG reporting by others 3,4 could not be reproduced in our cohort.1

The low number of patients with iAF on 7-d ECG was unexpected, and possibly indicates that our patients had meticulously been selected during the initial diagnostic work-up. Extensive 72-hour stroke unit monitoring has recently shown to be very sensitive for detecting iAF.9 This may be why the much higher detection rate of iAF of up to 15% during 7-d ECG reported by others3,4 could not be reproduced in our cohort.

Despite the preselection of patients, we still identified an additional 17% of cryptogenic stroke patients during ICM monitoring with iAF. This finding had a strong impact on clinical management, because anticoagulation could be started in all patients detected with iAF immediately after the diagnosis.

**Our Findings Raise New Important Questions**

First, are patients with 1 or 2 brief episodes of iAF at as much risk for recurrent stroke as patients with several hours duration of iAF? In our study, the range of this AF-burden was between 2 minutes and >1500 hours. Boriani et al published a retrospective study on patients with a known history of AF and implanted pacemakers, and found that patients with iAF episodes <5 minutes duration per day had a much lower risk of thromboembolic events than patients with episodes of >24 hours duration.10 Likewise, Glotzer et al found in patients with rhythm-sensitive pacemakers that the risk of future embolic events was highest in the group of patients with a high AF-burden in the 30 days before the event.11 However, it has to be kept in mind that these studies reported on patients with known rhythm disorders and no embolic end points, whereas we looked at patients with end points but no known rhythm disorder. The data may thus not be completely comparable. Second, we found 1 patient with a first iAF episode 556 days after the event. Thus, the question arises, which time interval of monitoring after an event seems reasonable? Most positive findings in our study were within the first 3 to 6 months after implantation; therefore, 1 year seems a reasonable time. However, the time required for monitoring will also depend on the importance of the detection of rare, brief episodes of iAF.

Until data on these issues is more convincing, we stick to the current guidelines and offered anticoagulation to every stroke patient who has iAF or permanent AF detected in the time thereafter.

We were unable to identify clinical factors such as CHADS2- or CHA2DS2-VASc score to be predictive for iAF (Table 1). In a recently published large primary prevention trial, ICMs were implanted in patients with stroke risk factors but no thromboembolic event.12 The authors were also unable to detect specific clinical factors predictive of the occurrence of iAF. However, patients with iAF then had an increased risk, according to established risk scores, to suffer future embolic events.

To conclude, the case number of patients with iAF detected by ICMs is still low, and thus the questions raised...
above are still largely unanswered. We will address some of these in a prospective study starting in our hospital soon, the TRACK-AF study (Thorough evaluation by online Rhythm evaluation, extended Holter monitoring And implantable Cardiac monitor of patients with Kryptogenic stroke to detect Atrial Fibrillation).

Disclosures
None.

References
Occult atrial fibrillation in cryptogenic stroke: A pilot study for detecting atrial fibrillation by 7-day ECG monitoring vs. implantable cardiac monitor

Significant findings that excluded patients from the study:

- Ipsilateral carotid stenosis >30% according to NASCET¹ criteria
- Ipsilateral intracranial stenosis >50% on CTA, MRA or Doppler Ultrasound (focal flow velocity >150 cm/s) supplying the infarction territory
- Significant aortic plaques as assessed by transesophageal echocardiography
- History of AF, AF on admission ECG or during Stroke Unit monitoring or on 24h-Holter ECG
- Absence of high or medium risk cardiac sources of embolism (TOAST-criteria²)
  - Prosthetic heart valves
  - Atrial fibrillation / Atrial flutter
  - Left atrial/atrial appendage thrombus
  - Sick sinus syndrome
  - Recent myocardial infarction (<6 months)
  - Left ventricular thrombus
  - Dilated cardiomyopathy
  - Akinetic left ventricular segment
  - Atrial myxoma
  - Endocarditis
  - Mitral annulus calcification
  - Mitral stenosis without atrial fibrillation
  - Left atrial turbulence (smoke)
  - Patent foramen ovale plus atrial septal aneurysm
  - Congestive heart failure
  - Hypokinetic left ventricular segment
- Implanted pace maker or defibrillator
- Cerebral vasculitis
- dissections of the brain supplying arteries
- Cerebral microangiopathy on imaging and deep small (<1,5 cm) infraction

Literature: