Predictors of Finding Occult Atrial Fibrillation After Cryptogenic Stroke

Christopher G. Favilla, MD*; Erin Ingala, MD*; Jenny Jara, BA; Emily Fessler, BA; Brett Cucchiara, MD; Steven R. Messé, MD; Michael T. Mullen, MD; Allyson Prasad, CRNP; James Siegler, MD; Mathew D. Hutchinson, MD; Scott E. Kasner, MD

Background and Purpose—Occult paroxysmal atrial fibrillation (AF) is found in a substantial minority of patients with cryptogenic stroke. Identifying reliable predictors of paroxysmal AF after cryptogenic stroke would allow clinicians to more effectively use outpatient cardiac monitoring and ultimately reduce secondary stroke burden.

Methods—We analyzed a retrospective cohort of consecutive patients who underwent 28-day mobile cardiac outpatient telemetry after cryptogenic stroke or transient ischemic stroke. Univariate and multivariable analyses were performed to identify clinical, echocardiographic, and radiographic features associated with the detection of paroxysmal AF.

Results—Of 227 patients with cryptogenic stroke (179) or transient ischemic stroke (48), 14% (95% confidence interval, 9%–18%) had AF detected on mobile cardiac outpatient telemetry, 58% of which was ≥30 seconds in duration. Age >60 years (odds ratio, 3.7; 95% confidence interval, 1.3–11) and prior cortical or cerebellar infarction seen on neuroimaging (odds ratio, 3.0; 95% confidence interval, 1.2–7.6) were independent predictors of AF. AF was detected in 33% of patients with both factors, but only 4% of patients with neither. No other clinical features (including demographics, CHA2DS2-VASc [combined stroke risk score: congestive heart failure, hypertension, age, diabetes, prior stroke/transient ischemic attack, vascular disease, sex] score, or stroke symptoms), echocardiographic findings (including left atrial size or ejection fraction), or radiographic characteristics of the acute infarction (including location, topology, or number) were associated with AF detection.

Conclusions—Mobile cardiac outpatient telemetry detects AF in a substantial proportion of cryptogenic stroke patients. Age >60 years and radiographic evidence of prior cortical or cerebellar infarction are robust indicators of occult AF. Patients with neither had a low prevalence of AF.

Key Words: atrial fibrillation ■ stroke

Identifying the cause of stroke is essential for the implementation of appropriate secondary stroke prevention, but more than one-third of strokes are considered cryptogenic. Newly diagnosed atrial fibrillation (AF) is only identified in ≤5% of patients with stroke in the inpatient setting, but paroxysmal AF (PAF) may not be present at the time of the stroke or may escape detection during inpatient cardiac monitoring. Thus, outpatient cardiac monitoring is often used to improve the identification of PAF. Identification of occult PAF has important therapeutic implications, as anticoagulation is superior to antiplatelet therapy for secondary stroke prevention in AF.

Although 1 week of outpatient cardiac monitoring may detect PAF in 6% to 8% of cases, increasing the duration of outpatient telemetry monitoring further increases the yield of PAF detection to 9% to 29%. A variety of long-term monitoring techniques may be used, including cardiac event monitor, recordings from pacemaker/implantable cardiac defibrillator, patient-triggered daily ECG, and mobile cardiac outpatient telemetry (MCOT). More recently, the use of an implantable cardiac monitor for detection of AF was evaluated, with detection of PAF in 9% and 12% of patients after 6 and 12 months of monitoring, respectively.

Older age, premature atrial complexes, premature ventricular complexes, and particular patterns of ischemia, such as multiple acute infarcts, infarcts in multiple vascular territories, or multiple chronic infarcts, have all been associated with detection of occult PAF, but these factors have only been examined in small cohorts, and results have been inconsistent. Identifying reliable predictors of occult PAF after cryptogenic stroke would allow clinicians to more efficiently use outpatient cardiac monitoring and ultimately reduce secondary stroke burden.

We hypothesized that the detection of AF after cryptogenic stroke with 28-day MCOT monitoring could be predicted using baseline characteristics, including age, CHA2DS2-VASc...
(combined stroke risk score: congestive heart failure, hypertension, age, diabetes, prior stroke/transient ischemic attack, vascular disease, sex) score, classic cardioembolic clinical syndromes, left atrial size on echocardiography, and neuroimaging patterns typical of acute embolic stroke.

Methods

Patients

We analyzed a retrospective cohort of 250 patients with consecutive stroke and transient ischemic stroke (TIA) referred for 28-day MCOT between April 2010 and November 2012. Eligibility required a confirmed diagnosis of cryptogenic stroke or TIA by TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. If patients underwent MCOT monitoring more than once, only the first MCOT was included in the analysis. The retrospective study protocol was approved by the Institutional Review Board at the Hospital of the University of Pennsylvania.

Data Collection

Medical records, echocardiographic reports, and images from computed tomography or magnetic resonance imaging were reviewed by investigators who were blinded to MCOT results. Clinical data extracted from the medical records included demographic characteristics, CHA2DS2-VASc score, smoking and illicit drug history, details of the clinical stroke presentation (specifically TIA versus stroke, history of palpitations, headache at onset, and classic cardioembolic syndromes of isolated aphasia, top-of-the-basilar syndrome, and spectacular shrinking deficit), concurrent use of medications (aspirin, anticoagulation, or statin), prior TIA, prior stroke, low-density lipoprotein, and hemoglobin A1c. Echocardiographic data included left atrial size, ejection fraction, and presence of patent foramen ovale. Neuroimaging included computed tomography or magnetic resonance imaging of the brain, which was independently reviewed to classify acute and chronic infarctions by size (≤1.5 versus >1.5 cm), location, and further characterized as cortical, subcortical, wedge-shaped, lacunar, borderzone, and multiple territories. All reviewers were blinded to the MCOT results.

AF Detection

All patients had MCOT monitoring ordered for 28 days with the CardioNet MCOT device (Biotelemetry Inc, Malvern, PA). Patients were directed to wear the device (consisting of 3 leads and a sensor) for 24 hours a day. Patients were also instructed to manually activate the device if they experienced any cardiovascular symptoms. All telemetry data were wirelessly transmitted to the monitoring center for initial automated analysis followed by technician review and subsequently cardiologist review. AF episodes were defined as AF of any duration. Total time in AF was calculated as the sum of each individual episode of AF for patients with multiple episodes during the monitoring period.

Statistical Analyses

In univariate analysis, patients with and without AF of any duration were compared using Student t test for continuous variables, χ² test for categorical variables, and Wilcoxon ranked-sum test for ordinal or interval variables. In the multivariable analysis, logistic regression was used while adjusting for age, prior cortical or cerebellar stroke, sex, and race. Age was dichotomized as <60 versus ≥ 60 years a priori based on presumed increased prevalence of AF with increasing age. In a sensitivity analysis, the multivariable analysis was repeated using only AF ≥30 seconds. All analyses were performed with Stata/SE 12.1 (StataCorp, College Station, TX).

We aimed for a population of 250 subjects assuming that ≥50 would have the outcome of AF based on prior studies. This would provide the ability to evaluate multivariable models with 5 to 10 independent variables. Ultimately, the inclusion of 31 patients with AF more conservatively provided the ability to evaluate 3 to 6 independent variables in multivariable analysis.

Results

Of the 250 patients with stroke referred for MCOT evaluation during this period, 3 were excluded as they were undergoing repeat MCOT monitoring, 9 for non–cryptogenic stroke, 10 for uncertainty in the diagnosis of stroke, and 3 for silent chronic infarction without symptoms. Some exclusions were overlapping. All patients had an ECG which demonstrated sinus rhythm before study enrollment. The final cohort (Table 1) comprised 227 patients with cryptogenic stroke (179) or TIA (48).

AF was detected in 14% of patients (31 of 227) evaluated with 28-day MCOT. The duration of AF was ≥30 seconds in 58% and <30 seconds in 42%. The median total duration of AF was 4.5 minutes (interquartile range, 0.3–349 minutes). The distribution of AF duration is depicted in Figure 1. Of the 31 patients with AF, only 3 (10%) reported symptoms of palpitations that correlated with arrhythmia detection. Two patients had brief episodes of AF (<30 seconds), whereas 1 patient was in AF for >17 hours during the monitoring period.

Cohort characteristics, comparing patients with and without AF, are reported in Table 1. Although those with AF were older (69.1 versus 61.9; P=0.005), there were no further differences with respect to other demographic factors, clinical stroke features, or echocardiographic findings including left atrial size. Acute imaging findings such as multi-territory infarction or wedge-shaped cortical infarction did not correlate with detection of AF, but prior cortical or cerebellar infarction seen on neuroimaging (separate from the index event) was strongly associated with a higher likelihood of AF (44% versus 22%; P=0.021). Of these radiographically identified prior infarctions, 54% were clinical in nature and 46% were subclinical. Brain region affected by infarction, including insular cortex, did not correlate with AF detection. MCOT was initiated 64 days (median) after stroke, and logistic regression confirmed that time between index event and monitoring did not influence likelihood of capturing AF, with an odds ratio of 0.99 (P=0.61).

In multivariable analysis (Table 2), both age >60 years (odds ratio, 3.7; 95% confidence interval, 1.3–11) and prior cortical or cerebellar infarction (odds ratio, 3.1; 95% confidence interval, 1.2–7.6) seen on neuroimaging were found to be independent predictors of AF of any duration, while adjusting for sex and race. Using these 2 predictors, the likelihood of detecting AF with 28 days of MCOT was depicted in Figure 2. AF was detected among 33% of patients with both risk factors, but only 4% of patients with neither risk factor. Patients with only 1 risk factor (either >60-year old or prior cortical/cerebellar infarction) had an intermediate risk of AF.

Sensitivity analyses, with an outcome of AF ≥30 seconds in duration, yielded the same 2 clinical predictors. Similar results were obtained in both univariate (data not shown) and multivariable (Table 2) analyses.

The selection of antithrombotic agent for secondary stroke prevention in patients who were found to have AF after cryptogenic stroke or TIA was at the discretion of their treating physician. Of the 31 patients with a new diagnosis of AF,
26 (84%) were treated with an oral anticoagulant: 13 (42%) dabigatran, 9 (29%) warfarin, 3 (10%) apixaban, and 1 (3%) rivaroxaban. The remaining 5 patients (16%) were not anticoagulated because 1 patient had multiple prior gastrointestinal bleeds, 3 patients were not willing to accept the risk of bleeding, and 1 patient failed to follow-up.

**Discussion**

AF was detected in 14% of patients with cryptogenic stroke or TIA using MCOT, and about half of AF episodes lasted <30 seconds. Only age >60 years and prior cortical or cerebellar infarction were predictive of finding AF. Patients with both of these risk factors were twice as likely to harbor AF compared with patients with only 1 risk factor, whereas those with neither represented a low-risk subgroup (4% prevalence) in the cohort.

We hypothesized that acute wedge-shaped cortical infarctions or multiple acute infarctions in multiple vascular territories would correlate with AF detection, but that was not the case. Infarction of the insular cortex, particularly on the right, has previously been associated with an increased prevalence of arrhythmia including AF,21 but in this cohort no such relationship was found. With respect to clinical features, we expected older patients to have a higher likelihood of AF detection and this was validated. We also hypothesized that a higher CHA\(_2\)DS\(_2\)-VASc score would correlate with a higher likelihood of AF, as it has been previously suggested that the CHA\(_2\)DS\(_2\)-VASc score may identify patients with stroke that warrant extensive cardiac monitoring for AF.22 One prior study did in fact find that both the CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores correlated with AF detection, but only among...

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**Table 1. Clinical, Echocardiographic, and Radiographic Characteristics: Univariate Analysis**

<table>
<thead>
<tr>
<th></th>
<th>AF (n=31)</th>
<th>No AF (n=196)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>69.1±9.6</td>
<td>61.9±13.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>51%</td>
<td>59%</td>
<td>0.34</td>
</tr>
<tr>
<td>Ethnicity (white)</td>
<td>61%</td>
<td>52%</td>
<td>0.20</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc score, median (IQR)</td>
<td>5 (4–6)</td>
<td>5 (3–6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Days from stroke to MCOT, median (IQR)</td>
<td>52 (42–90)</td>
<td>65 (7–136)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

**Clinical features**

- History of palpitations: 27% vs 22%, 0.59
- Transient ischemic attack (index event): 19% vs 21%, 0.79
- History of prior ischemic stroke: 17% vs 16%, 0.98
- Headache at onset: 24% vs 27%, 0.77
- Isolated Wernicke’s aphasia: 3% vs 2%, 0.69
- Top of the basilar: 0% vs 2%, 0.49
- Spectacular shrinking deficit: 0% vs 0%, ...

**Echocardiographic features**

- Left atrial size, cm, median (IQR): 3.6 (3.3–4.2) vs 3.5 (3.2–4.1), 0.39
- Ejection fraction, median (IQR): 65% (60%–65%) vs 63% (60%–65%), 0.85
- Patent foramen ovale: 30% vs 23%, 0.45

**Imaging features**

- Acute wedge-shaped cortical infarction: 9% vs 15%, 0.40
- Acute multiple territorial infarction: 20% vs 13%, 0.36
- Acute small deep infarction: 14% vs 8%, 0.38
- Acute watershed/borderzone infarction: 20% vs 18%, 0.83
- Prior cortical/cerebellar infarction: 44% vs 22%, 0.021

**Acute infarct location**

- Left hemispheric infarction only: 54% vs 46%, 0.44
- Right hemispheric infarction only: 33% vs 43%, 0.43
- Frontal cortical infarction: 41% vs 31%, 0.36
- Temporal cortical infarction: 14% vs 22%, 0.35
- Parietal cortical infarction: 43% vs 31%, 0.22
- Occipital cortical infarction: 18% vs 19%, 0.92
- Insular cortical infarction: 9% vs 11%, 0.71
- Left insular infarction: 9% vs 7%, 0.81
- Right insular infarction: 0% vs 4%, 0.33

AF indicates atrial fibrillation; CHA\(_2\)DS\(_2\)-VASc, combined stroke risk score: congestive heart failure, hypertension, age, diabetes, prior stroke/transient ischemic attack, vascular disease, sex; IQR, interquartile range; and MCOT, mobile cardiac outpatient telemetry.

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**Figure 1. Distribution of atrial fibrillation (AF) duration: burden of AF among the 31 patients with AF in the cohort.**

26 (84%) were treated with an oral anticoagulant: 13 (42%) dabigatran, 9 (29%) warfarin, 3 (10%) apixaban, and 1 (3%) rivaroxaban. The remaining 5 patients (16%) were not anticoagulated because 1 patient had multiple prior gastrointestinal bleeds, 3 patients were not willing to accept the risk of bleeding, and 1 patient failed to follow-up.

**Table 2. Multivariable Analysis of AF Predictors**

<table>
<thead>
<tr>
<th>Predictor of AF of any duration</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 y</td>
<td>3.7</td>
<td>1.3–11</td>
<td>0.014</td>
</tr>
<tr>
<td>Prior cortical or cerebellar infarction</td>
<td>3.0</td>
<td>1.2–7.6</td>
<td>0.021</td>
</tr>
</tbody>
</table>

**Predictor of AF ≥30 s duration**

| Age >60 y                       | 8.9        | 1.07–74 | 0.043   |
| Prior cortical or cerebellar infarction | 5.6      | 1.4–22  | 0.013   |

C-statistic for AF any duration=0.72, for AF ≥30 s=0.82. AF indicates atrial fibrillation; and CI, confidence interval.
Figure 2. Probability of identifying atrial fibrillation (AF), high-risk and low-risk patients: comparing pretest probability of detecting AF based on age and presence or absence of prior cortical or cerebellar infarction. Error bars represent 95% confidence intervals. *P<0.05 as compared with the entire cohort.

non–stroke patients undergoing cardiac evaluation for palpitations. Another small cohort of 51 patients with cryptogenic stroke came to a similar conclusion, but no correlation was identified either in a third cohort of 163 patients with cryptogenic stroke or in our larger cohort. We also hypothesized that specific clinical syndromes such as an isolated Wernicke’s aphasia or a top-of-the-basilar syndrome would correlate with AF detection, but these syndromes were recorded in small numbers, and no association was identified.

We also hypothesized left atrial size, measured by echocardiography, would correlate with AF detection, but this feature was similar in the AF and non-AF groups. Reliable echocardiographic predictors would be useful, but whether such features exist is of some controversy. Larger left atrial size has been associated with an increased prevalence of AF in older adults independent of stroke. In the setting of cryptogenic stroke, small cohorts found that patients with larger left atria had a higher prevalence of newly diagnosed AF. However, this correlation was not seen in the present study nor in other small cohorts of cryptogenic stroke.

The current American College of Cardiology/American Heart Association definition of PAF requires ≥30 seconds of AF, and in the current cohort only about half of patients with AF met this criterion. Prior studies have used a variety of thresholds, ranging from 0 seconds to 5 minutes. AF of any duration was considered clinically relevant as the primary outcome measure in the current study because these patients already had stroke or TIA, and all were therefore considered anticoagulation candidates. Furthermore, many patients with brief episodes of AF may in fact have a larger burden of AF if monitored for a longer period of time. The clinical relevance of brief episodes of AF is not well understood, but Holter monitor and long-term implantable device cohorts have found that a larger burden of AF may convey a higher thromboembolic risk.

The 14% prevalence of newly diagnosed AF in this study falls within the range of prior long-term outpatient monitoring studies using a variety of modalities (9%–29%). but previous cohorts that specifically evaluated ≥4 weeks of MCOT have yielded a 17% to 24% prevalence of AF. A recent randomized trial of MCOT captured AF in 17% of patients after cryptogenic stroke, consistent with the prevalence of prior studies. The current cohort identified a slightly smaller prevalence of AF, and this may be because of a fundamental difference in study population. One obvious explanation is age, as the current cohort is younger than some other reported studies. The inclusion of cryptogenic TIA in the current study should also be considered, although TIA was also included in many prior studies. TIA may represent a lower risk group but was represented equally among patients with and without AF (19% and 21%) and should therefore not affect our conclusions. The inconsistent prevalence of AF in different studies may represent a selection bias that is introduced by variable use of MCOT. As single center studies, these cohorts are subject to physician and institutional decision-making patterns related to referral for MCOT. This selection bias may limit the generalizability of the results. Furthermore, it is likely that any time-limited study will underestimate the true prevalence of AF, as monitoring for longer periods leads to the identification of more cases of AF. In practice, some clinicians repeat MCOT evaluation after a negative study, but the yield of this approach has not been evaluated.

Time between clinical event and MCOT monitoring should be considered in the discussion of AF prevalence. In prior studies, initiation of MCOT 21, 33, and 77 days after the index event yielded a 23%, 17%, and 16% prevalence of AF, respectively. In the current study, monitoring 64 days after stroke or TIA identified a 14% prevalence. One randomized study of MCOT demonstrated a higher yield with earlier monitoring, but in the current cohort, time to monitoring did not affect the likelihood of AF detection.

Although outpatient cardiac monitoring for AF is cost effective, the optimal duration of monitoring remains unclear and is an area for future research. In the current cohort, patients aged ≤60 years and without imaging evidence of prior cortical or cerebellar infarction represent a low-risk subgroup, with only 4% of subjects having AF of any duration. This 4% risk may be underestimated because of the finite monitoring period, and longer monitoring may yield a higher prevalence. It is not clear that even 4% is sufficiently low risk to forgo extended cardiac monitoring. A prior analysis suggested that cardiac telemetry monitoring may be cost effective with an AF detection rate as low as 1%, although this analysis was dependent on a range of assumptions, including a relatively low cost of monitoring in the base case.

Referral bias may have been introduced into the imaging analysis, as classic lacunar infarctions may be labeled as small vessel occlusive disease without referral for outpatient MCOT, and patients with prior cortical infarction may be preferentially referred for MCOT. Although this bias may influence the prevalence of different patterns of ischemia within the cohort and even the prevalence of AF within the cohort, this should not invalidate the robust relationship identified between AF and prior cortical/cerebellar infarction. The lack of true control group is inherent to the retrospective nature of this cohort study and limits generalizability. Our sample size,
which is considerably larger than prior published cohorts of patients who underwent MCOT after stroke,5,15,16 may still be insufficient to detect more modest, but clinically meaningful associations. The inclusion of only 31 patients with AF, rather than the anticipated 50, limited the capacity for exploring additional independent variables in the multivariable model. Future larger scale studies may help to confirm and elucidate predictors of detecting AF.

Conclusions

AF was detected in a substantial proportion of patients with cryptogenic stroke via MCOT evaluation, supporting the concept that a thorough evaluation for PAF with outpatient arrhythmia monitoring is warranted. Clinicians should have a particularly high level of suspicion among patients aged >60 years in whom there is evidence of prior cortical or cerebellar infarction on neuroimaging. Conversely, the low prevalence of newly diagnosed AF among patients aged ≤60 years without prior cortical or cerebellar infarction may guide clinicians in identifying patients who are less likely to benefit from such monitoring. Future research is warranted to clarify the optimal duration and methods of cardiac monitoring.

Disclosures

Dr Kasner has a consulting agreement with Medtronic for serving on a Data Safety Monitoring Board. The other authors report no conflicts.

References

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Stroke. published online April 7, 2015;

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Stroke 2015; 46: 1210-1215. DOI: 10.1161/STROKEAHA.114.007763.

表2 AF予測因子の多変量解析

<table>
<thead>
<tr>
<th>予測因子</th>
<th>オッズ比</th>
<th>95％CI</th>
<th>P値</th>
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<tr>
<td>年齢 &gt; 60歳</td>
<td>3.7</td>
<td>1.3～11</td>
<td>0.014</td>
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<td>皮質もしくは小脳の陳旧性梗塞</td>
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<td>1.2～7.6</td>
<td>0.021</td>
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<td>30秒以上のAFの予測因子</td>
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<td></td>
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<tr>
<td>年齢 &gt; 60歳</td>
<td>8.9</td>
<td>1.07～74</td>
<td>0.043</td>
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<tr>
<td>皮質もしくは小脳の陳旧性梗塞</td>
<td>5.6</td>
<td>1.4～22</td>
<td>0.013</td>
</tr>
</tbody>
</table>

AF（持続時間を問わず）の予測因子

高リスク患者および低リスク患者の心房細動（AF）を特定する指標・年齢および皮質もしくは小脳の梗塞の既往の有無に基づいたAF検出の確率の比較。エラーコーパは95% CIを示す。**コホート全体と比較した時のP < 0.05。