Pilot Randomized Trial of Outpatient Cardiac Monitoring After Cryptogenic Stroke

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Background and Purpose—Observational studies indicate that outpatient cardiac monitoring detects previously undiagnosed atrial fibrillation (AF) in 5% to 20% of patients with recent stroke. However, it remains unknown whether the yield of monitoring exceeds that of routine clinical follow-up.

Methods—In a pilot trial, we randomly assigned 40 patients with cryptogenic ischemic stroke or high-risk transient ischemic attack to wear a Cardionet mobile cardiac outpatient telemetry monitor for 21 days or to receive routine follow-up alone. After thorough investigation, we excluded patients with documented AF or other apparent stroke pathogenesis. We contacted patients and their physicians at 3 months and at 1 year to ascertain any diagnoses of AF or recurrent stroke or transient ischemic attack.

Results—The baseline characteristics of our cohort broadly matched those of previous observational studies of monitoring after stroke. In the monitoring group, patients wore monitors for 64% of the assigned days, and 25% of patients were not compliant at all with monitoring. No patient in either study arm received a diagnosis of AF. Cardiac monitoring revealed AF in zero patients (0%; 95% confidence interval, 0%–17%), brief episodes of atrial tachycardia in 2 patients (10%; 95% confidence interval, 1%–32%), and nonsustained ventricular tachycardia in 2 patients (10%; 95% confidence interval, 1%–32%).

Conclusions—In the first reported randomized trial of cardiac monitoring after cryptogenic stroke, the rate of AF detection was lower than expected, incidental arrhythmias were frequent, and compliance with monitoring was suboptimal. Our findings highlight the challenges of prospectively identifying stroke patients at risk for harboring paroxysmal AF and ensuring adequate compliance with cardiac monitoring.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00715533 (Stroke. 2013;44:528-530.)

Key Words: atrial fibrillation ■ electrocardiography ■ randomized controlled trials ■ stroke ■ transient ischemic attack

Failure to diagnose atrial fibrillation (AF) may result in suboptimal therapy for secondary stroke prevention.1 However, paroxysmal AF is not always apparent on presentation.2 In studies without control groups, cardiac monitoring after stroke has been shown to detect previously undiagnosed AF in at least 5% of patients.3 However, AF eventually may have been diagnosed even without monitoring. Therefore, we performed a pilot randomized trial of outpatient cardiac monitoring in patients with ischemic stroke or transient ischemic attack.

Methods

Patients

We enrolled adult patients with ischemic stroke or high-risk transient ischemic attack (ABCDS score ≥4). Hospitalized patients underwent ≥24 hours of cardiac telemetry, and those with AF before discharge were excluded. We excluded patients with lacunar infarcts, ≥50% stenosis of relevant arteries, likely cardioembolism, or other apparent cause. We excluded patients ineligible to receive anticoagulation or with onset of symptoms >60 days previously. This trial was approved by the University of California, San Francisco, Committee on Human Research. All patients provided written informed consent.

Interventions

Patients were assigned to cardiac monitoring or routine follow-up using random permuted blocks of varying sizes. For practical reasons, blinding was not performed. Patients were discharged with antiplatelet therapy, with a plan to begin anticoagulation if AF had been diagnosed. All patients were scheduled to see their primary care physician within 1 month and our stroke clinic within 3 months, and they were educated to report symptoms of AF at these visits. The monitoring group was additionally assigned 21 days of Cardionet Mobile Cardiac Outpatient Telemetry, which has >99% sensitivity for AF lasting >30 seconds.
seconds. To ensure specificity, all device-labeled AF episodes were manually reviewed by a cardiologist (G.F.).

**Outcomes**

Our primary feasibility outcomes were enrollment of 40 patients in 2 years, completion of assigned monitoring in ≥70% of patients, and full follow-up for ≥90% of patients. Our primary safety outcome was any adverse event resulting directly from use of the cardiac monitoring device. Secondary outcomes included new diagnoses of AF within 3 months and 1 year.

**Statistical Analysis**

We used the t test or rank sum test for comparisons of continuous measures and Fisher exact test for categorical variables. Feasibility and efficacy analyses were performed using the intention-to-treat principle, whereas safety analyses involved the per-protocol population. Post hoc, we examined the relationship between stroke severity and monitoring compliance using multiple regression. Statistical analysis was performed using Stata (version 11; StataCorp). Further details about study design are available in the online-only Data Supplement.

**Results**

We enrolled 40 patients between October 29, 2009 and May 24, 2011. Baseline characteristics were well-balanced between the 2 groups (Table). Patients underwent a mean 49 hours (±32 hours) of inpatient cardiac telemetry before discharge. Outpatient monitoring began 22 days (±12 days) after symptom onset.

All feasibility criteria were met, with full follow-up for 38 patients (95%) and completion of assigned monitoring in 15 of 20 patients (75%). However, 4 of these 15 patients were not fully compliant, resulting in overall compliance of 64%. After controlling for age, we found a nonsignificant trend toward less compliance in patients with higher baseline National Institutes of Health Stroke scale scores (β coefficient, −0.24; P=0.35) and modified Rankin scale scores (β coefficient, −0.26; P=0.32).

No patient received a diagnosis of AF. Cardiac monitoring revealed AF in zero patients (0%; 95% confidence interval, 0%–17%), but did reveal brief episodes (<10 seconds) of atrial tachycardia in 2 patients (10%; 95% confidence interval, 1%–32%). One of these episodes was incorrectly labeled as AF by the automated telemetry software (online-only Data Supplement). Nonsustained ventricular tachycardia was detected by cardiac monitoring in 2 patients (10%; 95% confidence interval, 1%–32%).

No serious adverse event occurred that was attributable to the monitoring intervention. One of the 15 monitored patients (7%; 95% confidence interval, 2%–32%) had development of contact dermatitis, which resolved within a few days of removing the leads.

**Discussion**

In the first reported randomized trial of cardiac monitoring after cryptogenic stroke, we have established the safety and feasibility of randomizing patients to outpatient cardiac monitoring or usual follow-up. However, patients wore monitors for only 64% of the assigned time. This may be because of the inconvenience of devices with multiple leads, particularly for patients with functional limitations. Our results indicate that the tolerability of outpatient monitoring must be carefully considered when devising strategies to rule out AF as a cause of stroke.

**Table. Patient Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All (n=40)</th>
<th>Cardiac Monitoring (n=20)</th>
<th>No Monitoring (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) or mean/median (SD/IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67 (12)</td>
<td>65 (15)</td>
<td>69 (9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Women</td>
<td>17 (43)</td>
<td>8 (40)</td>
<td>9 (45)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>14 (35)</td>
<td>6 (30)</td>
<td>8 (40)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (73)</td>
<td>15 (75)</td>
<td>14 (70)</td>
<td>0.99</td>
</tr>
<tr>
<td>Antihypertensive medication on admission</td>
<td>21 (53)</td>
<td>11 (55)</td>
<td>10 (50)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (25)</td>
<td>4 (20)</td>
<td>6 (30)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (45)</td>
<td>8 (40)</td>
<td>10 (50)</td>
<td>0.75</td>
</tr>
<tr>
<td>Statin medication on admission</td>
<td>14 (35)</td>
<td>5 (25)</td>
<td>9 (45)</td>
<td>0.32</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Current/former tobacco use</td>
<td>10 (25)</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>0.99</td>
</tr>
<tr>
<td>TIA as index event</td>
<td>13 (33)</td>
<td>8 (40)</td>
<td>5 (25)</td>
<td>0.50</td>
</tr>
<tr>
<td>NIH Stroke Scale score on admission</td>
<td>3 (2–4)</td>
<td>3 (3–7)</td>
<td>2 (1–4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Modified Rankin scale score at discharge</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Systolic blood pressure on admission, mm Hg</td>
<td>153 (25)</td>
<td>156 (24)</td>
<td>150 (25)</td>
<td>0.44</td>
</tr>
<tr>
<td>Left atrial volume index</td>
<td>26 (10)</td>
<td>28 (9)</td>
<td>24 (10)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cortical infarcts on MRI*</td>
<td>18 (64)</td>
<td>6 (50)</td>
<td>12 (75)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; MRI, magnetic resonance imaging; NIH, National Institutes of Health; SD, standard deviation; TIA, transient ischemic attack.

*Twenty-eight patients underwent MRI.
The low rate of AF detected in our monitoring group differs from most published studies of similar monitoring techniques after stroke. This may be because of chance, because our pilot study aimed to establish feasibility and lacked power to examine clinical outcomes, which is apparent in the wide confidence interval around our AF detection rate (0%–17%) and was exacerbated by imperfect compliance with monitoring. The low AF rate also may reflect differences in populations, although comparison of our cohort with other published cohorts does not reveal obvious differences (online-only Data Supplement). Last, our results may indicate publication bias discouraging the reporting of negative studies. Regardless, the failure of monitoring to detect any AF in our study reinforces the importance of randomized trials for establishing the role of cardiac monitoring after stroke.

Despite not detecting arrhythmias meeting the standard definition of AF, cardiac monitoring did reveal 2 brief episodes of atrial tachycardia. Nonspecific supraventricular tachyarrhythmias have been reported to occur in >23% of patients with cryptogenic stroke undergoing cardiac monitoring. Recent evidence indicates that atrial tachycardias increase AF risk and may increase stroke risk, even in the absence of clinically apparent AF. The significance and optimal management of these nonspecific arrhythmias await clarification by future studies.

Given the remaining uncertainties in this field and the different monitoring strategies available, further comparative studies such as ours and the ongoing Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) and CRYptogenic STroke And underlying Atrial Fibrillation (CRYSTAL-AF) trials will be needed to identify optimal strategies for diagnosing AF as a cause of cerebral ischemia, thereby reducing the incidence of recurrent stroke.

Sources of Funding
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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

Supplemental Methods

This trial was registered at clinicaltrials.gov (NCT00932425) before the onset of patient enrollment. Our reporting of the trial design and results follows CONSORT guidelines.1 The trial was initially limited to patients with cryptogenic stroke (not TIA) within the prior 2 weeks, but to increase enrollment we expanded our eligibility criteria after 6 months to include patients with high-risk TIA and symptom onset within the prior 2 months.

The Cardionet Mobile Cardionet Outpatient Telemetry system includes a pager-sized device and three cutaneous leads that record a two-channel continuous ECG.2 A validated detection algorithm automatically captures episodes of AF based on RR interval variability and QRS morphology. A daily report as well as any abnormal rhythms were automatically transmitted by the device via an integrated cellular data connection to a remote monitoring station staffed by technicians. In accordance with guidelines from the American Heart Association, AF was electrocardiographically defined as an arrhythmia lasting >30 seconds and characterized by flutter waves or the replacement of consistent P waves with rapid oscillations or fibrillatory waves varying in amplitude, shape, and timing.3

Secondary outcomes were new diagnoses of AF within 3 months (to account for cases of AF that would have become clinically apparent relatively soon even if they were not captured during cardiac monitoring) and 1 year, and recurrent stroke or TIA within 1 year. We contacted patients and their primary physicians or neurologists at 3 months and 1 year after discharge, and used validated questionnaires to inquire about clinical diagnoses of AF and recurrent stroke or TIA.4 All reported secondary outcome events were verified by review of relevant medical records.

Supplemental Results

Six eligible patients declined enrollment in the trial because they were unwilling to wear a monitor at home. In another three cases, the treating neurologists advised that eligible patients not be enrolled because of a high suspicion for cardioembolic stroke from occult AF. In total, we enrolled 40 of 49 eligible patients (82%; 95% CI, 68-91%). Of the 20 patients assigned to usual follow-up, one dropped out within 1 week of enrollment and another was lost to follow-up.

All patients underwent echocardiography, including transesophageal echocardiography in 12 patients (30%). Thirty-five patients (88%) received noninvasive imaging of their intracranial vessels. Patients were discharged on aspirin (55%), clopidogrel (40%), or both (3%).

Both patients with monitoring-detected ventricular tachycardia were referred for cardiology consultation. One of these patients received a new diagnosis of hypertensive heart failure that resulted in optimization of medical therapy and eventually initiation of anticoagulation for secondary stroke prevention after follow-up echocardiography revealed a newly-reduced ejection fraction (<35%).

One patient (2.5%; 95% CI, 0-13%) suffered a lacunar stroke (usual follow-up group), and three patients (7.5%; 95% CI, 2-20%) experienced a TIA after their index event (two in the usual follow-up group and one in the monitoring group).
**Supplemental Table.** Patients’ baseline characteristics alongside those of other reported cohorts undergoing prolonged cardiac monitoring after cryptogenic stroke.

<table>
<thead>
<tr>
<th></th>
<th>Current study</th>
<th>Elijovich et al(^5)</th>
<th>Flint et al(^6)</th>
<th>Tayal et al(^7)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>67 (12)</td>
<td>65 (15)</td>
<td>65 (14)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>Women</td>
<td>43</td>
<td>60</td>
<td>40</td>
<td>49</td>
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<tr>
<td>Hypertension</td>
<td>73</td>
<td>75</td>
<td>66</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>35</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
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<td>50</td>
<td>91</td>
<td>75</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5</td>
<td>15</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
<td>n/a</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>25</td>
<td>5</td>
<td>n/a</td>
<td>36</td>
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<tr>
<td>TIA as index event</td>
<td>33</td>
<td>38</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>43</td>
<td>25</td>
<td>n/a</td>
<td>15</td>
</tr>
<tr>
<td>Cortical infarcts on MRI</td>
<td>64</td>
<td>n/a</td>
<td>n/a</td>
<td>85</td>
</tr>
</tbody>
</table>
Supplemental Figure. Example of a brief episode of atrial tachycardia detected by outpatient cardiac monitoring in a patient with recent stroke.
Supplemental References