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Atrial Fibrillation in Patients with Cryptogenic Stroke

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ABSTRACT

BACKGROUND

Atrial fibrillation is a leading preventable cause of recurrent stroke for which early detection and treatment are critical. However, paroxysmal atrial fibrillation is often asymptomatic and likely to go undetected and untreated in the routine care of patients with ischemic stroke or transient ischemic attack (TIA).

METHODS

We randomly assigned 572 patients 55 years of age or older, without known atrial fibrillation, who had had a cryptogenic ischemic stroke or TIA within the previous 6 months (cause undetermined after standard tests, including 24-hour electrocardiography [ECG]), to undergo additional noninvasive ambulatory ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hour monitor (control group). The primary outcome was newly detected atrial fibrillation lasting 30 seconds or longer within 90 days after randomization. Secondary outcomes included episodes of atrial fibrillation lasting 2.5 minutes or longer and anticoagulation status at 90 days.

RESULTS

Atrial fibrillation lasting 30 seconds or longer was detected in 45 of 280 patients (16.1%) in the intervention group, as compared with 9 of 277 (3.2%) in the control group (absolute difference, 12.9 percentage points; 95% confidence interval [CI], 8.0 to 17.6; P<0.001; number needed to screen, 8). Atrial fibrillation lasting 2.5 minutes or longer was present in 28 of 284 patients (9.9%) in the intervention group, as compared with 7 of 277 (2.5%) in the control group (absolute difference, 7.4 percentage points; 95% CI, 3.4 to 11.3; P<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group than in the control group (52 of 280 patients [18.6%] vs. 31 of 279 [11.1%]; absolute difference, 7.5 percentage points; 95% CI, 1.6 to 13.3; P=0.01).

CONCLUSIONS

Among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older, paroxysmal atrial fibrillation was common. Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring. (Funded by the Canadian Stroke Network and others; EMBRACE ClinicalTrials.gov number, NCT00846924.)

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The prevention of stroke related to atrial fibrillation is a global public health priority. Strokes due to atrial fibrillation are common and frequently devastating (70 to 80% of patients die or become disabled[1,2]), yet they are largely preventable with anticoagulant therapy (64% reduction in the risk of stroke and 25% reduction in mortality).[3] However, because atrial fibrillation is often intermittent and asymptomatic, it can be a silent risk factor that easily evades detection.[4,5]

Since patients who have had a stroke or transient ischemic attack (TIA) due to atrial fibrillation face a high annual risk of stroke recurrence,[6] strategies to improve the detection and treatment of atrial fibrillation promise to reduce the burden of recurrent strokes. In the absence of atrial fibrillation, the standard treatment for secondary prevention of stroke is antiplatelet therapy; however, when atrial fibrillation is present, antiplatelet therapy is only modestly effective (22% reduction in risk, as compared with placebo),[3] and anticoagulation is strongly recommended instead (39%[3] to 63%[7] reduction in the risk of stroke as compared with antiplatelet therapy). Currently, 1 in 6 strokes is attributed to atrial fibrillation, but 1 in 4 of the estimated 12 million ischemic strokes annually (and half the TIAs) has no cause identified after a standard diagnostic workup and is labeled "cryptogenic."[8,9] Undiagnosed atrial fibrillation is often suspected as the cause of many cryptogenic strokes, but anticoagulation is not recommended unless atrial fibrillation has been documented.

An unsolved problem is how to detect "covert" atrial fibrillation in patients with stroke. Screening is typically limited to electrocardiographic (ECG) monitoring for a short period (e.g., 24 hours), which is not sufficiently sensitive for the detection of paroxysmal atrial fibrillation[10-12]; as a result, it is likely that atrial fibrillation is being routinely underdiagnosed and undertreated with this approach. Observational studies have shown that there is improved detection of atrial fibrillation with serial or prolonged ECG monitoring,[10-13] yet such studies have had little effect on practice. Without a definitive trial, it is unknown whether intensive monitoring would increase atrial fibrillation detection and treatment rates more than standard monitoring and follow-up.

We conducted a randomized trial of prolonged noninvasive ambulatory ECG monitoring to guide the treatment of patients with unexplained stroke or TIA. We hypothesized that monitoring for 30 days with the use of an automated device for detecting atrial fibrillation, as compared with one additional round of conventional 24-hour ECG monitoring, would enhance the detection and treatment of atrial fibrillation in high-risk patients who would be candidates for anticoagulant therapy.

Methods

Study Population

Patients were eligible for enrollment if they were 55 years of age or older, did not have known atrial fibrillation, and had had an ischemic stroke or TIA of undetermined cause (according to TOAST [Trial of Org 10172 in Acute Stroke Treatment] criteria[14]) within the previous 6 months, diagnosed by a stroke neurologist after a standard workup, including 12-lead ECG, ambulatory ECG monitoring with the use of a Holter monitor for a minimum of 24 hours, brain and neurovascular imaging, and echocardiography (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, lists the eligibility criteria; Table S2 lists the diagnostic investigations). Patients were excluded if the most likely etiologic diagnosis had already been determined (large-vessel or small-vessel disease or other known cause).

Study Design and Oversight

In this investigator-initiated, open-label, multicenter trial, we randomly assigned participants in a 1:1 ratio to undergo ambulatory ECG monitoring with a 30-day event-triggered loop recorder (intervention group) or one additional round of 24-hour Holter monitoring (control group). Randomization was performed with the use of a Web-based system and a variable block size. Patients were enrolled by vascular neurologists at 16 stroke centers within the Canadian Stroke Consortium. The trial was coordinated at the Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, and Sunnybrook Research Institute, University of Toronto.

The protocol (available at NEJM.org) was tested in a pilot study,[15] approved by Health Canada

and the ethics board at each study site, and embedded in routine stroke care, with all the participants providing written informed consent. The steering committee, which was independent of commercial influence, was responsible for the study design and execution, data analysis, and authorship decisions. The first author wrote the first and subsequent drafts of the manuscript. The steering committee made the decision to submit the manuscript for publication. All the authors vouch for the accuracy of the data and confirm that the contents of this article adhere to the specifications in the protocol.

The ECG devices were purchased for the trial. The device manufacturers had no role in the trial design, data accrual, or data analysis and had no access to the study data.

ECG MONITORING

The event recorder (ER910AF Cardiac Event Monitor, Braemar) automatically recorded atrial fibrillation on the basis of irregularity in the R-R interval, an established method for the detection of atrial fibrillation,[16] over a period of 30 beats at any rate. The devices had a 30-minute memory capacity and were programmed to record up to 2.5 minutes per episode. Recorders were attached to a dry-electrode (nonadhesive) belt worn around the chest (Cardiac Bio-Systems)[17] to enable better compliance by the patients with prolonged monitoring than has been typically observed with conventional adhesive skin-contact electrodes. The intervention group was instructed to wear the monitor as much as possible for 30 days. If atrial fibrillation was detected before 30 days, patients could stop wearing the monitor.

Recorded ECG data were transmitted transtelephonically for central interpretation. All the episodes of atrial fibrillation were adjudicated by a cardiologist and an internist who were unaware of the patient's demographic and clinical characteristics, and any disagreements were resolved by discussion with an independent cardiologist. Results were sent to the study sites, and decisions regarding anticoagulant therapy were made at the discretion of the treating physicians.

The patients in the control group were assigned to one additional round of conventional 24-hour ambulatory ECG monitoring with a Holter monitor from the local laboratory at their study site. All the reports were reviewed centrally by one physician.

OUTCOMES

The primary outcome was the detection of one or more episodes of ECG-documented atrial fibrillation or flutter lasting 30 seconds or longer within 90 days after randomization (documented by the study monitors or detected clinically, apart from the study monitors). Secondary outcomes included oral anticoagulant use at 90 days, atrial fibrillation lasting 30 seconds or longer that was detected by the study monitor, atrial fibrillation of any duration that was detected by the study monitor, atrial fibrillation lasting 2.5 minutes or longer (the maximum recording duration per episode) that was detected by the study monitor, adherence to monitoring, and a switch from antiplatelet to anticoagulant therapy in the period from randomization to 90 days.

STATISTICAL ANALYSIS

The primary analysis compared the proportion of patients in each group who had the primary outcome and was performed with the use of Pearson's chi-square test in the intention-to-monitor population, which consisted of all patients who underwent randomization and for whom the atrial-fibrillation status could be assessed (patients who underwent any amount of monitoring or had 90-day follow-up). Secondary analyses assessed the proportions of patients with atrial fibrillation detected by means of the study monitors among patients who underwent any monitoring. We used Pearson's chi-square test to compare the proportions of patients for whom anticoagulant or antiplatelet therapy was prescribed. There were no interim analyses. See the Supplementary Appendix for the sample-size calculation and descriptions of additional analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From June 2009 through March 2012, a total of 572 patients underwent randomization, and 90-day follow-up was complete in 97.7% of the patients (Fig. 1). The mean (±SD) age of the patients was 72.5±8.5 years (range, 52 to 96) (Table 1). Randomization occurred a mean of 75.1±38.6 days after the qualifying event (62.9% of patients had

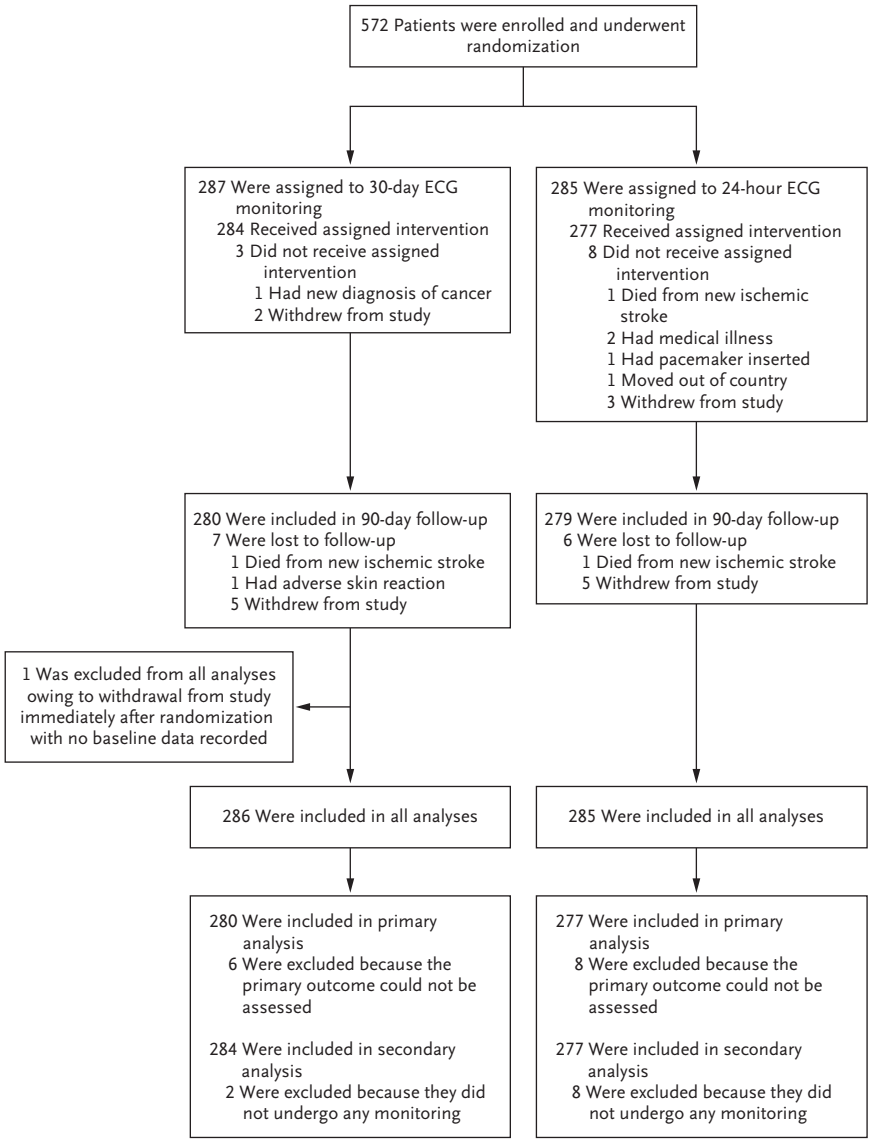

Figure 1. Randomization, Electrocardiographic (ECG) Monitoring, and Follow-up.

Six patients assigned to 30-day ECG monitoring and eight patients assigned to 24-hour ECG monitoring were excluded from the analysis of the primary outcome because they did not undergo any monitoring or because there were no outcome data available at 90-day follow-up.

an ischemic stroke and 36.9% had a TIA). Of the patients, 93.9% were ambulatory and independent (some patients had initially severe embolic strokes reversed by means of thrombolysis), and the median $CHADS_2$ score of the patients was 3 points (range, 2 to 6). Scores on the $CHADS_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or TIA is assigned 2 points. Before enrollment, participants underwent conventional screening for atrial fibrillation with one or more 12-lead ECGs and one or more 24-hour Holter ECG studies, totaling a mean of 32.8±12.9 hours of monitoring; 9.1% of the patients also underwent inpatient telemetry ECG monitoring for a mean duration of 53.6±42.6 hours.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intervention Group (N=286)	Control Group (N=285)
Age		
Mean age — yr	72.5±8.5	73.2±8.8
≥75 yr — no. (%)	104 (36.4)	118 (41.4)
Female sex — no. (%)	132 (46.2)	125 (43.9)
Race — no. (%)†		
White	257 (89.9)	260 (91.2)
Asian	15 (5.2)	14 (4.9)
Black	6 (2.1)	2 (0.7)
Other	8 (2.8)	9 (3.2)
Modified Rankin scale score ≤2 — no. (%)‡	274 (95.8)	263 (92.3)
Medical history — no. (%)		
Hypertension	204 (71.3)	191 (67.0)
Diabetes	55 (19.2)	55 (19.3)
Hyperlipidemia	191 (66.8)	177 (62.1)
Smoking status		
Current smoker	19 (6.6)	24 (8.4)
Previous smoker	141 (49.3)	131 (46.0)
Previous ischemic stroke	45 (15.7)	36 (12.6)
>1 Previous stroke	12 (4.2)	12 (4.2)
Previous transient ischemic attack	42 (14.7)	46 (16.1)
Congestive heart failure	5 (1.7)	7 (2.5)
Myocardial infarction	48 (16.8)	42 (14.7)
Coronary angioplasty or stenting	24 (8.4)	23 (8.1)
Coronary bypass surgery	29 (10.1)	19 (6.7)
Cardiac-valve surgery	6 (2.1)	1 (0.4)
Type of index event — no. (%)		
Ischemic stroke	188 (65.7)	172 (60.4)
Transient ischemic attack	98 (34.3)	113 (39.6)
Oxfordshire classification[18] of the index event — no. (%)§		
Total anterior circulation syndrome	7 (2.4)	5 (1.8)
Partial anterior circulation syndrome	201 (70.3)	216 (75.8)
Posterior circulation syndrome	63 (22.0)	56 (19.6)
Lacunar syndrome	15 (5.2)	7 (2.5)
No. of days from index event to randomization	76.6±37.5	73.7±39.7

* Plus–minus values are means ±SD. There were no significant differences between the two study groups at the 0.05 significance level.
† Race was determined by the investigator.
‡ Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms and 6 indicating death; a score of 2 or less indicates that the patient is ambulatory and functionally independent in activities of daily living.
§ Data were missing for one patient in the control group.

ADHERENCE TO THE PROTOCOL

Among the patients in the intervention group who started to undergo monitoring, 233 of 284 (82.0%) completed 3 or more weeks of monitoring. Among patients in whom atrial fibrillation was not detected before 30 days, 204 of 240 (85.0%) completed 3 or more weeks, and 148 of 240 (61.7%) completed 4 weeks.

DETECTION OF ATRIAL FIBRILLATION IN THE TWO GROUPS

The 30-day ECG monitoring strategy was superior to 24-hour ECG monitoring for the detection of at least one episode of atrial fibrillation lasting 30 seconds or longer (the primary outcome). Atrial fibrillation was detected in 45 of 280 patients (16.1%) in the intervention group, as compared with 9 of 277 (3.2%) in the control group, for an absolute difference of 12.9 percentage points (95% confidence interval [CI], 8.0 to 17.6; P<0.001; number needed to screen, 8) (Table 2). Sensitivity analysis did not alter the conclusions (see the Supplementary Appendix). Atrial fibrillation was detected clinically, rather than by the study monitors, in only 0.5% of patients within 90 days after randomization (see the Supplementary Appendix). Prolonged monitoring was also superior for the detection of continuous atrial fibrillation lasting at least 2.5 minutes: in 28 of 284 patients (9.9%) in the intervention group versus 7 of 277 (2.5%) in the control group, for an absolute difference of 7.4 percentage points (95% CI, 3.4 to 11.3; P<0.001) (Table 2).

ATRIAL FIBRILLATION IN THE INTERVENTION GROUP

The 30-day monitors recorded 218 episodes of atrial fibrillation lasting 30 seconds or longer in 44 patients (range, 1 to 29 episodes per patient). A total of 26 of these patients (59.1%) had 2 or more episodes recorded, and 28 patients (63.6%) had an episode of atrial fibrillation lasting at least 2.5 minutes (the maximum recordable duration per episode).

New instances of atrial fibrillation were detected throughout the 30 days, with half the cases captured within the first week of monitoring and three quarters within 2 weeks (Fig. 2). The detection rate was significantly higher among patients who underwent randomization within 3 months after the index stroke or TIA than among those who underwent randomization after more than 3 months (36 of 195 patients [18.5%] vs. 8 of 89 [9.0%]; P=0.049 for linear association). The patients with atrial fibrillation were older and had more atrial ectopic activity according to baseline Holter monitoring than those without atrial fibrillation (P<0.001 for both comparisons) (Table S3 in the Supplementary Appendix).

EFFECT ON TREATMENT

At randomization, the majority of patients were receiving antiplatelet therapy, as expected. After monitoring, most of the patients with atrial fibrillation received anticoagulant therapy (see the Supplementary Appendix). Use of oral anticoagulant therapy tripled in the intervention group,

Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

Outcome	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		*percentage points*		
Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	12.9 (8.0–17.6)	<0.001	8 (5.7–12.5)
Secondary outcomes‡					
Detection of atrial fibrillation with duration ≥30 sec	44/284 (15.5)	7/277 (2.5)	13.0 (8.4–17.6)	<0.001	8 (5.7–11.9)
Detection of atrial fibrillation with duration ≥2.5 min	28/284 (9.9)	7/277 (2.5)	7.4 (3.4–11.3)	<0.001	14 (8.8–29.4)
Detection of atrial fibrillation of any duration	56/284 (19.7)	13/277 (4.7)	15.0 (9.8–20.3)	<0.001	7 (4.9–10.2)

* The number of patients needed to screen was defined as the number of patients who would need to be screened in order to detect atrial fibrillation in one additional patient (with a 30-day monitoring strategy vs. repeat 24-hour Holter monitoring).
† The primary analysis included all the patients who underwent randomization for whom outcome data were available (i.e., patients who underwent any amount of cardiac monitoring or 90-day follow-up in whom the status of atrial fibrillation could be determined). In the primary analysis, atrial fibrillation was detected either clinically or by means of study monitoring.
‡ The secondary analyses included all the patients who underwent randomization and any amount of cardiac monitoring. The detection of atrial fibrillation in the secondary analyses was by means of the study monitors.

and at 90 days, the proportion of patients treated with anticoagulants was significantly higher in the intervention group than in the control group: 18.6% (52 of 280 patients) versus 11.1% (31 of 279), for an absolute treatment difference of 7.5 percentage points (95% CI, 1.6 to 13.3; P=0.01) (Table 3). In the intervention group, 38 of 280 patients (13.6%) switched from antiplatelet to anticoagulant therapy, as compared with 13 of 279 (4.7%) in the control group, a difference of 8.9 percentage points (95% CI, 4.2 to 13.6; P<0.001).

DISCUSSION

We found that ambulatory ECG monitoring for a target of 30 days was feasible to implement as part of routine stroke care, detected atrial fibrillation in one in six patients (which had not previously been detected by means of standard 24 to 48 hours of monitoring after stroke), was superior to an additional round of 24-hour ECG monitoring and clinical follow-up (the detection rate with 30-day monitoring was increased by a factor of five), and had an incremental yield over a period of 30 days. Moreover, prolonged monitoring nearly doubled the proportion of patients who subsequently received anticoagulant therapy for secondary prevention of stroke — a finding we interpret as a clinically meaningful change in treatment that has the potential to avert recurrent strokes. These findings, taken together with mounting observational data linking subclinical atrial fibrillation to cryptogenic strokes[10-13] and a randomized trial supporting 7-day monitoring in the acute phase after the occurrence of stroke,[19] provide strong evidence supporting adoption of a more intensive approach to the detection of atrial fibrillation in patients with unexplained stroke or TIA.

Evaluating patients for atrial fibrillation after a stroke or TIA is important because of the treatment implications. We targeted patients at risk for stroke recurrence who were potential candidates for anticoagulant therapy, yet in practice such patients typically receive only antiplatelet therapy if atrial fibrillation is not detected. When atrial fibrillation is detected, anticoagulation is strongly advised, whether the atrial fibrillation is paroxysmal or sustained, because the stroke risks are similar[20-22] and patients with either type of atrial fibrillation benefit from anticoagulation.[20,23,24]

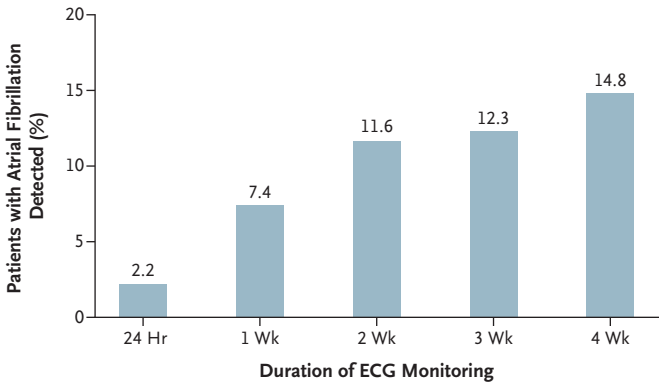

Figure 2. Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA.

The proportion of patients in whom atrial fibrillation was detected increased with increasing duration of ECG monitoring. The data reflect the timing of the first detected episode of atrial fibrillation; data for 2 patients are not shown because the exact date of the detection of atrial fibrillation was unknown. Atrial fibrillation was detected in 6 of 277 patients who underwent monitoring with a 24-hour Holter monitor (the control group). In the group of 284 patients who underwent 30-day monitoring, atrial fibrillation was detected in 21 patients within the first week of monitoring, in 33 within the first 2 weeks of monitoring, in 35 within the first 3 weeks of monitoring, and in 42 within 4 weeks of monitoring (including 1 patient with atrial fibrillation that was first detected on day 34).

The finding of even brief atrial fibrillation in this population is considered important, given increasing evidence that brief subclinical atrial fibrillation predicts subsequent episodes of atrial fibrillation and is an independent risk factor for recurrent stroke.[25] In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), any subclinical atrial tachyarrhythmia lasting longer than 6 minutes predicted clinically evident atrial fibrillation (hazard ratio, 5.6) and stroke or systemic embolism (hazard ratio, 2.5).[4] In the Mode Selection Trial (MOST), any atrial high-rate episode lasting longer than 5 minutes predicted clinical atrial fibrillation (hazard ratio, 5.9) and stroke or death (hazard ratio, 2.8).[26] Our primary outcome of atrial fibrillation lasting 30 seconds or longer is consistent with guidelines[27-30] and, although arbitrary, is a potentially clinically important and actionable finding in this population. Expert opinion differs regarding the minimum duration or frequency of atrial fibrillation captured by ECG that warrants anticoagulation. Until future

Table 3. Anticoagulant Therapy in the Two Monitoring Groups.*

Therapy	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value
	no./total no. (%)		*percentage points*	
Baseline				
Anticoagulant therapy before the index stroke or TIA	3/286 (1.0)	2/285 (0.7)	—	—
Anticoagulant therapy at randomization after the index stroke or TIA	16/286 (5.6)	19/285 (6.7)	—	—
After study monitoring				
Therapy at 90 days after randomization				
Anticoagulant therapy	52/280 (18.6)	31/279 (11.1)	7.5 (1.6 to 13.3)	0.01
Antiplatelet therapy only	223/280 (79.6)	246/279 (88.2)	–8.6 (–14.6 to –2.5)	0.006
Therapy at randomization changed by 90 days				
From antiplatelet therapy to anticoagulant therapy	38/280 (13.6)	13/279 (4.7)	8.9 (4.2 to 13.6)	<0.001
From anticoagulant therapy to antiplatelet therapy	3/280 (1.1)	2/279 (0.7)	0.4 (–1.2 to 1.9)	0.66

* Anticoagulant therapy was defined as the use of any oral anticoagulant (warfarin, dabigatran, rivaroxaban, or apixaban). Antiplatelet therapy was defined as the use of any antiplatelet medication (aspirin, clopidogrel, aspirin–extended-release dipyridamole, dipyridamole, or other antiplatelet agent) and no oral anticoagulant therapy.

studies establish this, we believe prolonged monitoring permits more rational decision making regarding antithrombotic therapy, strengthening recommendations for or against anticoagulation. In this trial, most patients with atrial fibrillation received anticoagulant therapy, even though they would not have met the traditional criteria for duration of atrial fibrillation used in published trials evaluating the treatment of atrial fibrillation.[3] Two thirds of the patients with atrial fibrillation detected in the intervention group had at least 2.5 minutes of continuous atrial fibrillation (episodes could have lasted hours or days, but only the first 2.5 minutes could be captured). The threshold for anticoagulation is generally lower when it is for secondary prevention than it is for primary prevention, and a low threshold appears to be reasonable for our patients who had a high pretest probability of atrial fibrillation,[31] excess atrial ectopy on baseline Holter monitoring,[32] and an elevated stroke risk.[33] With the availability of newer anticoagulants, empirical anticoagulation for suspected but unproven atrial fibrillation is tempting[34] but controversial[35] and has the potential for overuse if sufficient ECG screening is not performed. The absence of atrial fibrillation on prolonged monitoring can help justify antiplatelet therapy and minimize unnecessary long-term anticoagulation in presumably low-risk patients with cryptogenic stroke.

These findings have implications for clinical practice and widespread applicability for secondary prevention of stroke in regions where cardiac monitoring is available. The results of this study support prolonged monitoring after a recent cryptogenic embolic stroke or TIA in selected patients 55 years of age or older who would be considered appropriate candidates for anticoagulant therapy if atrial fibrillation were found. We think that the common practice of relying on 24 to 48 hours of monitoring for atrial fibrillation after a stroke or TIA of undetermined cause is insufficient and consider it an initial screen rather than a final test, especially given our finding that the yield of clinical follow-up alone as a means of detecting atrial fibrillation was negligible. Improving the detection of atrial fibrillation will be increasingly important for an aging population: the rising prevalence of atrial fibrillation, along with declining rates of large-vessel and small-vessel cerebrovascular disease, is likely to result in an increasing number of strokes related to both overt and covert atrial fibrillation.[36]

This study had several limitations. We could not determine the total burden of atrial fibrillation per patient owing to the limited recording capacity of the ECG device, and patients typically stopped the monitoring before 30 days, once any atrial fibrillation was documented. Our results therefore represent the minimum amount of atrial fibrillation that was possible to record, probably underestimating the total duration and frequency of atrial fibrillation. Newer external devices allow unlimited recording of the burden of atrial fibrillation.

In addition, the 16% prevalence of atrial fibrillation that we observed in the intervention group is likely to be a conservative estimate for several reasons. First, patients with large, severe strokes, in which cardioembolism is likely to be most prevalent, were underrepresented; however, they were not the target of this trial, which focused on stroke survivors attending outpatient clinics after hospital discharge, most of whom had had mild, nondisabling strokes and were considered to be ideal candidates for secondary stroke prevention. Second, monitoring started relatively late in many patients (an average of 75 days after the index stroke or TIA), reducing the overall sensitivity for the detection of atrial fibrillation; indeed, the earlier initiation of monitoring identified more patients with atrial fibrillation than later initiation did. Third, we know that the yield of monitoring increases well beyond 30 days, as shown by studies using implanted devices.[4,11,12,27] However, 30 days was a pragmatic choice for this trial, since we thought it was likely to be the upper limit for adherence to monitoring with the external study devices and because subcutaneously implanted recorders are invasive (minimally), costly, and not yet widely accessible for routine first-line screening after stroke. Fourth, because cryptogenic stroke is a heterogeneous entity that has lacked a rigorous uniform definition and not all our patients underwent intracranial vascular imaging or transesophageal echocardiography, the trial probably enrolled patients with other causes of stroke, thus reducing the proportion with atrial fibrillation, as compared with a group of more fully evaluated patients with truly cryptogenic stroke.

Although it is well known that embolism to the brain can be the first manifestation of atrial fibrillation, and the discovery of atrial fibrillation after stroke increases the likelihood that an embolic stroke was due to previously undetected atrial fibrillation, we acknowledge that the detection of atrial fibrillation after stroke cannot prove causation[37] and should not preclude the consideration of many other possible causes.[9] The longer the delay from stroke to the detection of atrial fibrillation, the more difficult it is to infer causation.[38] Also, we did not study age-matched controls without stroke or TIA. However, even if atrial fibrillation is an incidental finding, it influences risk stratification and provides an opportunity to prescribe anticoagulant therapy for maximum risk reduction. Future studies are required to determine the extent of risk reduction associated with prolonged monitoring and its cost-effectiveness.[19,39,40]

In conclusion, the results of our study show that noninvasive outpatient ECG monitoring for 30 days is superior to the standard practice of short-term ECG monitoring for the detection of atrial fibrillation in patients with a stroke or TIA labeled as cryptogenic. This observation suggests that in current practice, a substantial proportion of such patients have paroxysmal atrial fibrillation that goes undiagnosed and untreated. Prolonged ECG monitoring offers greater opportunities for the detection and treatment of one of the most common and important modifiable risk factors for recurrent stroke.

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