

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

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ABSTRACT

BACKGROUND

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Current guidelines recommend at least 24 hours of electrocardiographic (ECG) monitoring after an ischemic stroke to rule out atrial fibrillation. However, the most effective duration and type of monitoring have not been established, and the cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation in 20 to 40% of cases (cryptogenic stroke). Detection of atrial fibrillation after cryptogenic stroke has therapeutic implications.

METHODS

We conducted a randomized, controlled study of 441 patients to assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients with cryptogenic stroke. Patients 40 years of age or older with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring underwent randomization within 90 days after the index event. The primary end point was the time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months. Among the secondary end points was the time to first detection of atrial fibrillation within 12 months. Data were analyzed according to the intention-to-treat principle.

RESULTS

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; $P < 0.001$). By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; $P < 0.001$).

CONCLUSIONS

ECG monitoring with an ICM was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke. (Funded by Medtronic; CRYSTAL AF ClinicalTrials.gov number, NCT00924638.)

*A complete list of the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial investigators is provided in the Supplementary Appendix, available at nejm.org.

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ISCHEMIC STROKE IS AMONG THE LEADING causes of death and disability.¹ The cause remains unexplained after routine evaluation in 20 to 40% of cases, resulting in the classification, by exclusion, of cryptogenic stroke.²⁻⁶ Atrial fibrillation is a well-recognized cause of ischemic stroke,⁷ though the risk is markedly reduced by anticoagulation.^{7,8} Documentation of atrial fibrillation is required to initiate anticoagulant therapy after ischemic stroke.⁸ In the absence of documented atrial fibrillation, antiplatelet agents are recommended.⁷ Given the often paroxysmal and asymptomatic nature of atrial fibrillation, it may not be detected with the use of traditional monitoring techniques.⁹⁻¹² Strategies for detection of atrial fibrillation have included in-hospital monitoring,¹³ serial electrocardiography (ECG),^{14,15} Holter monitoring,¹⁶ monitoring with the use of external event or loop recorders,¹⁷⁻²² long-term outpatient monitoring,²³⁻²⁸ and monitoring by means of insertable cardiac monitors (ICMs),²⁹⁻³¹ yielding detection rates ranging from 0 to 25%. However, differences among studies with respect to eligibility criteria, end points, and duration of monitoring make it difficult to translate these findings into changes in clinical practice.³² Current guidelines suggest performing 24 or more hours of ECG monitoring to rule out atrial fibrillation in patients with an ischemic stroke but acknowledge that the most effective duration of monitoring has not been determined.⁷ The use of additional ECG monitoring beyond 24 hours after cryptogenic stroke is currently left to physician discretion. We conducted a randomized, controlled study to assess whether a long-term ECG monitoring strategy with an ICM is superior to conventional follow-up for the detection of atrial fibrillation in patients with cryptogenic stroke.

METHODS

STUDY DESIGN

The Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial was a parallel-group trial comparing the time to detection of atrial fibrillation with an ICM versus conventional follow-up (as described below) in patients with cryptogenic stroke or transient ischemic attack (TIA). Patients were randomly assigned in a 1:1 ratio to one of the two monitoring strategies. The study proto-

col was approved by all relevant institutional review boards or ethics committees, and all patients provided written informed consent before randomization. Patients were enrolled at 55 centers in Europe, Canada, and the United States between June 2009 and April 2012. Details of the study design have been published previously.³³ Protocol modifications included an extension of the enrollment window from 60 to 90 days after the index event and ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels instead of magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) of the head and neck for patients older than 55 years of age.

The primary end point was the time to first detection of atrial fibrillation at 6 months of follow-up. Secondary end points included the time to first detection of atrial fibrillation at 12 months of follow-up, recurrent stroke or TIA, and the change in use of oral anticoagulant drugs. Atrial fibrillation was defined as an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 seconds. Episodes of atrial fibrillation that qualified for analysis were adjudicated by an independent committee. Patients were stratified within the study groups according to the type of index event (stroke or TIA) and the presence or absence of a patent foramen ovale. Randomization lists were created with the use of permuted blocks of random size, with assignments made sequentially. Patients and physicians were aware of the study-group assignments, because patients in the ICM group underwent insertion of the device.

The steering committee designed the study and made the decision to submit the manuscript for publication. The sponsor (Medtronic) had non-voting membership on the steering committee, assisted in the design of the study, data collection, and data analysis, proposed technical content for the manuscript, and contributed to manuscript review, but had no role in the decision to submit the manuscript for publication. An independent data and safety monitoring committee reviewed interim results and monitored safety. All the authors vouch for the completeness and accuracy of the data and analyses and the fidelity of the report to the study protocol, which is available with the full text of this article at NEJM.org.

ELIGIBILITY CRITERIA

Eligible patients were 40 years of age or older and had received a diagnosis of stroke or TIA, occurring within the previous 90 days, that was supported by consistency between symptoms and findings on brain magnetic resonance imaging or computed tomography. Stroke was classified as cryptogenic after extensive testing — including 12-lead ECG, 24 hours or more of ECG monitoring, transesophageal echocardiography, screening for thrombophilic states (in patients <55 years of age), and MRA, CTA, or catheter angiography of the head and neck — did not reveal a clear cause. Ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels, in place of MRA or CTA of the head and neck, were allowed for patients older than 55 years of age. Patients with TIA were enrolled only if symptoms at presentation were speech problems, limb weakness, or hemianopsia. Exclusion criteria have been published previously.³³ The main exclusion criteria were a history of atrial fibrillation or atrial flutter, an indication or contraindication for permanent oral anticoagulant therapy at enrollment, and an indication for a pacemaker or implantable cardioverter-defibrillator.

BASELINE ASSESSMENT

The patient's medical history, physical-examination findings, and use of medications were recorded. Information regarding the index stroke or TIA was collected, including the results of brain imaging and the required testing to establish a consistent diagnosis of cryptogenic stroke.

MONITORING STRATEGIES

Patients assigned to the control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. Monitoring type, duration, and all results were recorded. Patients assigned to the ICM group were scheduled to have the device inserted within 10 days after randomization. ICM settings were programmed in a standardized fashion.³³ The ICM that was used (REVEAL XT, Medtronic) automatically detects and records atrial fibrillation, irrespective of heart rate or symptoms.³⁴ The Medtronic CareLink Network was used to remotely transmit the device data. For patients in both groups, follow-up visits were scheduled at 1, 6, and 12 months and every

6 months thereafter until study closure, with unscheduled visits in the event of symptom occurrence or after the transmission of ICM data, if advised by the investigator. If patients reported an episode of atrial fibrillation since the previous visit, information was collected and source documentation was acquired for adjudication.

STATISTICAL ANALYSIS

Statistical methods have been described previously.³³ Briefly, we estimated that a sample of 450 patients would be required for the study to have 90% power, with the use of a log-rank test for the primary end point. Sample-size calculation was performed with the use of East software, version 5.0 (Cytel), with the assumption of cumulative rates of detection of atrial fibrillation of 5% in the control group and 15% in the ICM group, and accounted for one interim analysis with the use of O'Brien-Fleming stopping boundaries to maintain an overall alpha level of 0.05. The rate of detection of atrial fibrillation was estimated with the use of the Kaplan-Meier method and was compared between groups on an intention-to-treat basis with the use of a log-rank test. Data were censored at the time of death, study exit, or completion of 6 months of follow-up. Cox proportional-hazards regression was used to estimate hazard ratios in the primary analysis and subgroup analyses; for each prespecified subgroup, we used a Wald test for interaction between the subgroup and randomly assigned group without adjusting for multiple comparisons. The time-to-event analytic methods used to analyze the primary end point were also used to analyze other time-to-event end points. The between-group difference in the proportion of participants taking oral anticoagulants at follow-up visits was compared with the use of Fisher's exact test. Analyses were conducted with the use of SAS software, version 9.2 (SAS Institute).

RESULTS**STUDY POPULATION**

During the study period, 447 patients were enrolled and 441 were randomly assigned to either the ICM group (221 patients) or the control group (220 patients). The mean (\pm SD) time between the index event and randomization was 38.1 \pm 27.6 days. Of 208 patients in the ICM group who underwent

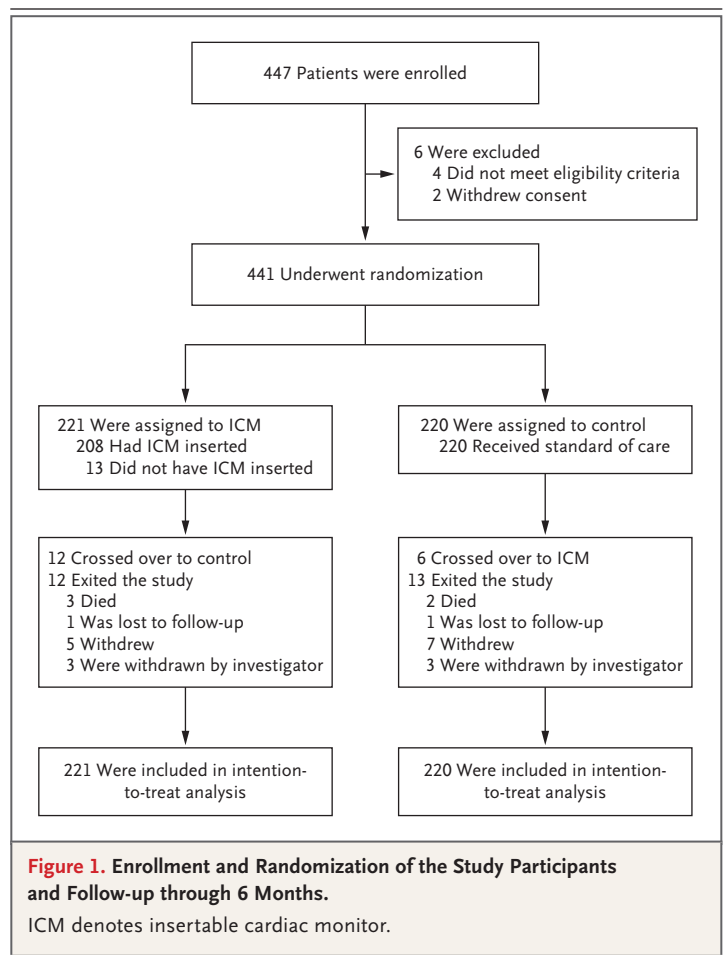
insertion of the device, 184 (88.5%) received the device within 10 days after randomization, with scheduling delays (22 patients) or medical justification (2 patients) accounting for delayed insertions (median delay, 6 days; interquartile range, 1 to 32). Of the 441 randomly assigned patients, 416 (94.3%) completed 6 months of follow-up, 2 were lost to follow-up, 5 died, and 18 exited the study before 6 months. Crossover occurred in the case of 18 patients: 12 in the ICM group and 6 in the control group (Fig. 1).

Baseline characteristics of the randomly assigned patients are shown in Table 1. The mean age was 61.5 ± 11.3 years, 36.5% of patients were women, and 90.9% of index events were classified as nonlacunar stroke. Pre-enrollment screening for atrial fibrillation consisted of Holter monitoring with a median duration of 23 hours (interquartile range, 21 to 24) in 71.2% of patients and telemetry with a median duration of 68 hours (interquartile range, 40 to 96) in 29.7% of patients.

PRIMARY END POINT

The rate of detection of atrial fibrillation at 6 months was 8.9% among patients assigned to the ICM group (19 patients), as compared with 1.4% among patients assigned to the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; $P < 0.001$) (Fig. 2A). The median time from randomization to detection of atrial fibrillation was 41 days (interquartile range, 14 to 84) in the ICM group and 32 days (interquartile range, 2 to 73) in the control group. Atrial fibrillation was asymptomatic in 14 of 19 first episodes in the ICM group (74%) and in 1 of 3 first episodes in the control group (33%). The yield of 3 detected episodes in the control group was from a total of 88 conventional ECG studies in 65 patients, 20 occurrences of 24-hour Holter monitoring in 17 patients, and monitoring with an event recorder in 1 patient.

Sensitivity analyses taking into account the slightly higher rates of patent foramen ovale, hypertension, and coronary artery disease in the ICM group than in the control group at baseline (adjusted hazard ratio, 5.9; 95% CI, 1.7 to 19.8; $P = 0.004$) and the censoring of data at the time of crossover (hazard ratio, 6.1; 95% CI, 1.8 to 20.8; $P = 0.009$) did not significantly alter the results.



SECONDARY END POINTS

The rate of detection of atrial fibrillation at 12 months was 12.4% (29 patients) in the ICM group, as compared with 2.0% (4 patients) in the control group (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; $P < 0.001$) (Fig. 2B). The median time from randomization to detection of atrial fibrillation was 84 days (interquartile range, 18 to 265) in the ICM group and 53 days (interquartile range, 17 to 212) in the control group. Atrial fibrillation was asymptomatic in 23 of 29 first episodes in the ICM group (79%) and in 2 of 4 first episodes in the control group (50%). With monitoring continued from 6 through 12 months, an additional 10 first episodes of atrial fibrillation were detected in the ICM group versus 1 in the control group, despite 34 conventional ECG studies in 33 patients and 12 occurrences of Holter monitoring in 10 patients.

Ischemic stroke or TIA occurred in 11 patients (5.2%) in the ICM group, as compared

with 18 patients (8.6%) in the control group, during the first 6 months after randomization and in 15 patients (7.1%) versus 19 patients (9.1%) during the first 12 months. The rate of use of oral anticoagulants was 10.1% in the ICM group versus 4.6% in the control group at 6 months ($P=0.04$) and 14.7% versus 6.0% at 12 months ($P=0.007$). By 12 months, 97.0% of patients in whom atrial fibrillation had been detected were receiving oral anticoagulants.

SUBGROUP ANALYSIS

The higher rate of detection of atrial fibrillation with ICM than with conventional follow-up was

consistent across all the prespecified subgroups, defined by age, sex, race or ethnic group, type of index event, presence or absence of patent foramen ovale, and CHADS₂ score at 6 months, with no significant interactions (Fig. 3). The results of subgroup analyses at 12 months were consistent with those at 6 months (Fig. 1S in the Supplementary Appendix, available at NEJM.org).

DURATION OF ATRIAL FIBRILLATION

By 12 months of follow-up, among patients in the ICM group with atrial fibrillation detected, the median value for the maximum time in atrial fibrillation in a single day was 11.2 hours (inter-

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Insertable Cardiac Monitor (N=221)	Control (N=220)	P Value
Age — yr	61.6±11.4	61.4±11.3	0.84
Sex — no. (%)			0.77
Male	142 (64.3)	138 (62.7)	
Female	79 (35.7)	82 (37.3)	
Race or ethnic group — no. (%)†			0.60
Asian	3 (1.4)	2 (0.9)	
Black	7 (3.2)	10 (4.5)	
Hispanic or Latino	2 (0.9)	2 (0.9)	
White	194 (87.8)	191 (86.8)	
Other	0	3 (1.4)	
Not available	15 (6.8)	12 (5.5)	
Geographic region — no. (%)			0.32
North America	83 (37.6)	72 (32.7)	
Europe	138 (62.4)	148 (67.3)	
Patent foramen ovale — no. (%)	52 (23.5)	46 (20.9)	0.57
Index event — no. (%)			0.87
Stroke	200 (90.5)	201 (91.4)	
TIA	21 (9.5)	19 (8.6)	
Prior stroke or TIA — no. (%)			
Stroke	37 (16.7)	28 (12.7)	0.28
TIA	22 (10.0)	27 (12.3)	0.45
Score on modified Rankin scale — no. (%)‡			0.85
0–2	184 (83.3)	186 (84.5)	
>2	36 (16.3)	34 (15.5)	
Score on NIH Stroke Scale§	1.6±2.7	1.9±3.8	0.37
Hypertension — no. (%)	144 (65.2)	127 (57.7)	0.12
Diabetes — no. (%)	34 (15.4)	38 (17.3)	0.61

Table 1. (Continued.)

Characteristic	Insertable Cardiac Monitor (N=221)	Control (N=220)	P Value
CHADS ₂ score — no. (%)¶			0.17
2	69 (31.2)	81 (36.8)	
3	92 (41.6)	91 (41.4)	
4	50 (22.6)	34 (15.5)	
5	9 (4.1)	14 (6.4)	
6	1 (0.5)	0	
Hypercholesterolemia — no. (%)	125 (56.6)	128 (58.2)	0.77
Current smoker — no. (%)	43 (19.5)	44 (20.0)	0.91
Coronary artery disease — no. (%)	16 (7.2)	9 (4.1)	0.22
Use of antiplatelet agent — no. (%)	212 (95.9)	212 (96.4)	1.00

* Plus–minus values are means \pm SD. P values were calculated with the use of Student's t-test or Fisher's exact test, as appropriate. TIA denotes transient ischemic attack.

† Race or ethnic group was determined by self-report.

‡ 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 independent. The score was not reported for one patient assigned to an insertable cardiac monitor.

§ Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, with higher scores indicating more severe neurologic deficits. The score was not reported for one patient in the control group.

¶ Scores on the CHADS₂ risk assessment range from 0 to 6, with higher scores indicating a greater risk of stroke.

quartile range, 0.7 to 19.6), and the median value for the mean time in atrial fibrillation per day was 4.3 minutes (interquartile range, 0.7 to 34.5). Among 26 patients for whom data were available, the maximum 1-day duration of atrial fibrillation was more than 12 hours in 46% of patients, more than 6 to 12 hours in 15% of patients, more than 1 to 6 hours in 12% of patients, more than 6 to 60 minutes in 19% of patients, and 6 minutes or less in 8% of patients (Fig. 2S in the Supplementary Appendix).

LONG-TERM FOLLOW-UP

At study closure, 277 patients had completed the scheduled 18-month follow-up visit, 177 had completed the 24-month visit, 94 had completed the 30-month visit, and 48 had completed the 36-month visit (total follow-up, 815.5 patient-years). A relatively small number of patients were followed for more than 24 months, but at 36 months of follow-up, the rate of detection of atrial fibrillation was 30.0% in the ICM group (42 patients) versus 3.0% in the control group (5 patients) (hazard ratio, 8.8; 95% CI, 3.5 to 22.2; $P < 0.001$) (Fig. 2C).

SAFETY

Of 208 ICMs that were inserted, 5 (2.4%) were removed owing to infection at the insertion site or pocket erosion. The most common adverse events associated with the ICM were infection (3 patients [1.4%]), pain (3 patients [1.4%]), and irritation or inflammation (4 patients [1.9%]) at the insertion site. The ICM remained inserted in 98.1% of patients at 6 months and in 96.6% of patients at 12 months.

DISCUSSION

In this randomized trial comparing long-term monitoring by means of an ICM with conventional follow-up in patients with a recent cryptogenic stroke, monitoring resulted in a significantly higher rate of detection of atrial fibrillation, with greater use of oral anticoagulants. Even though treatment modifications were not mandated by the protocol, nearly all patients in whom atrial fibrillation was detected during the study received oral anticoagulants. Prescription of oral anticoagulants was more than doubled in the ICM group, as compared with the control group, at both 6 and

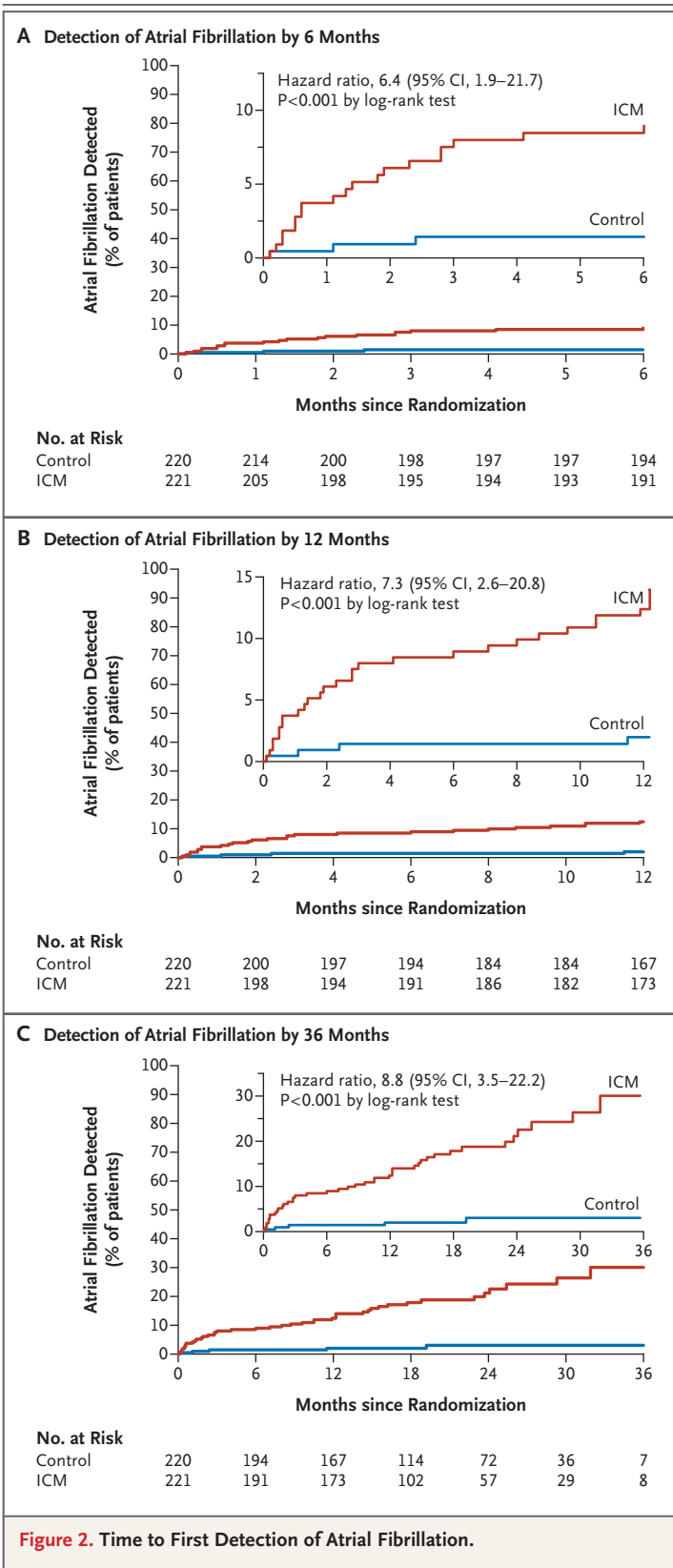


Figure 2. Time to First Detection of Atrial Fibrillation.

12 months, probably as a result of the higher rates of detection of atrial fibrillation. Fewer patients had a recurrent stroke or TIA in the ICM group than in the control group; however, our study was not powered for this end point.

Systematic reviews assessing the detection of atrial fibrillation with external ECG monitoring in patients after cryptogenic stroke have shown a detection rate of newly diagnosed atrial fibrillation of 5 to 20%.^{10,32} Observational studies using an ICM in similar populations have suggested a detection rate of approximately 25%.²⁹ The lower rates of detection in the current study may be related to the comprehensive assessment required before the diagnosis of cryptogenic stroke, the duration of atrial fibrillation used to define the primary end point, independent adjudication of episodes of atrial fibrillation, and differences in baseline characteristics associated with atrial fibrillation, including younger age and a lower prevalence of hypertension. The rate of detection in the control group was low. At 6 months, atrial fibrillation was detected in only 1.4% of patients in the control group (three patients), and only one patient received a diagnosis of atrial fibrillation during the next 6 months. Most of the episodes of atrial fibrillation that were detected in our study were asymptomatic (74% at 6 months and 79% at 12 months in the ICM group). This finding, in combination with the paroxysmal nature of atrial fibrillation after cryptogenic stroke, may account for the low yield of diagnostic strategies based on symptom occurrence or the use of intermittent short-term recordings, which were found in our study to represent conventional follow-up at more than 50 centers across Europe, the United States, and Canada.

The benefit of an ICM strategy for the detection of atrial fibrillation in patients with cryptogenic stroke was clear; the number of ICMs that would need to be implanted to detect a first episode of atrial fibrillation is 14 for 6 months of monitoring, 10 for 12 months, and 4 for 36 months. Further studies are needed to determine which risk factors identify the patients who would derive the most clinical benefit from detection of atrial fibrillation by prolonged monitoring with an ICM, as well as the cost-effectiveness of this approach.

A strength of the study was the use of a comprehensive, systematic baseline diagnostic evalu-

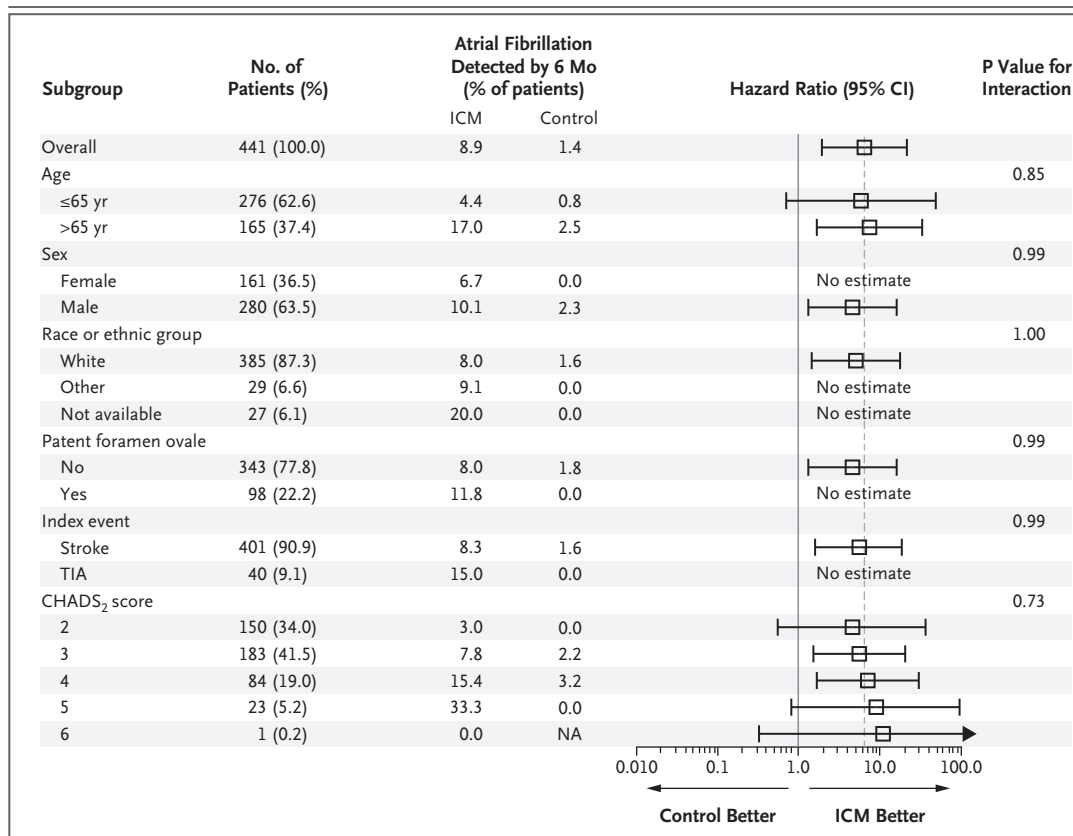


Figure 3. Subgroup Analysis of Time to First Detection of Atrial Fibrillation by 6 Months.

The P values are for the interaction between the randomized group and the subgroup variable. Scores on the CHADS₂ risk assessment range from 0 to 6, with higher scores indicating a greater risk of stroke. The log_e hazard ratio for the CHADS₂ score was modeled as the linear per-unit increase. CI denotes confidence interval, and NA not available.

ation to rule out other causes of stroke. However, our trial has several limitations. First, it is unclear whether newly discovered atrial fibrillation was causally related to the index stroke, because not all strokes, even in patients with documented atrial fibrillation, are due to the arrhythmia. Second, the clinical significance of brief episodes of atrial fibrillation detected with the use of an ICM is unknown. Third, not all episodes of atrial fibrillation can be accounted for, because the device has a limited memory, and once the storage capacity is met, data on the oldest episodes are discarded in order to record new episodes. In addition, the algorithm for detection of atrial fibrillation is not infallible, though

the accuracy for the duration of atrial fibrillation is reported to be 98.5%.³⁴

In conclusion, our study showed that atrial fibrillation was more frequently detected with an ICM than with conventional follow-up in patients with a recent cryptogenic stroke. Atrial fibrillation after cryptogenic stroke was most often asymptomatic and paroxysmal and thus unlikely to be detected by strategies based on symptom-driven monitoring or intermittent short-term recordings.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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