

ORIGINAL ARTICLE

Subclinical Atrial Fibrillation and the Risk of Stroke

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ABSTRACT

BACKGROUND

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One quarter of strokes are of unknown cause, and subclinical atrial fibrillation may be a common etiologic factor. Pacemakers can detect subclinical episodes of rapid atrial rate, which correlate with electrocardiographically documented atrial fibrillation. We evaluated whether subclinical episodes of rapid atrial rate detected by implanted devices were associated with an increased risk of ischemic stroke in patients who did not have other evidence of atrial fibrillation.

METHODS

We enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. We monitored the patients for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) and followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Patients with pacemakers were randomly assigned to receive or not to receive continuous atrial overdrive pacing.

RESULTS

By 3 months, subclinical atrial tachyarrhythmias detected by implanted devices had occurred in 261 patients (10.1%). Subclinical atrial tachyarrhythmias were associated with an increased risk of clinical atrial fibrillation (hazard ratio, 5.56; 95% confidence interval [CI], 3.78 to 8.17; $P < 0.001$) and of ischemic stroke or systemic embolism (hazard ratio, 2.49; 95% CI, 1.28 to 4.85; $P = 0.007$). Of 51 patients who had a primary outcome event, 11 had had subclinical atrial tachyarrhythmias detected by 3 months, and none had had clinical atrial fibrillation by 3 months. The population attributable risk of stroke or systemic embolism associated with subclinical atrial tachyarrhythmias was 13%. Subclinical atrial tachyarrhythmias remained predictive of the primary outcome after adjustment for predictors of stroke (hazard ratio, 2.50; 95% CI, 1.28 to 4.89; $P = 0.008$). Continuous atrial overdrive pacing did not prevent atrial fibrillation.

CONCLUSIONS

Subclinical atrial tachyarrhythmias, without clinical atrial fibrillation, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischemic stroke or systemic embolism. (Funded by St. Jude Medical; ASSERT ClinicalTrials.gov number, NCT00256152.)

*The investigators in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) are listed in the Supplementary Appendix, available at nejm.org.

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ATRIAL FIBRILLATION MAY BE ASYMPTOMATIC and consequently subclinical.^{1,2} Epidemiologic studies indicate that many patients with atrial fibrillation on screening electrocardiograms had not previously received a diagnosis of atrial fibrillation.³ About 15% of strokes are attributable to documented atrial fibrillation, and 50 to 60% to documented cerebrovascular disease,⁴⁻⁷ but in about 25% of patients who have ischemic strokes, no etiologic factor is identified.^{4,8,9} Subclinical atrial fibrillation is often suspected to be the cause of stroke in these patients.¹⁰ However, the prevalence and prognostic value of subclinical atrial fibrillation has been difficult to assess.^{8,9,11,12}

An implanted atrial lead that is in position over the long term, with the analytic software of the modern pacemaker, allows the continuous detection and characterization of individual episodes of rapid atrial rate over long periods.¹² Studies have indicated that, depending on the programming of the pacemaker, the detection of such episodes of rapid atrial rate correlates well with electrocardiographic documentation of atrial fibrillation.¹² There are more than 400,000 pacemakers and implantable cardioverter-defibrillators (ICDs) implanted each year in North America.¹³⁻¹⁵ Subclinical episodes of rapid atrial rate are detected in many of these patients,^{16,17} often in the absence of clinical evidence of atrial fibrillation. The rate of stroke is also high among patients who have received a pacemaker, with stroke occurring in 5.8% of the patients within 4 years after implantation.¹⁸ However, the relationship between device-detected atrial tachyarrhythmias and stroke is not understood.

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) was designed to address two objectives. The first was to prospectively evaluate whether subclinical episodes of rapid atrial rate detected by implanted devices are associated with an increased risk of ischemic stroke in patients who do not have other evidence of atrial fibrillation.¹⁹ The second was to study in a randomized trial the efficacy of continuous atrial overdrive pacing in preventing clinical atrial fibrillation.

METHODS

STUDY OVERSIGHT

The details of the design of ASSERT have been published previously.¹⁹ The steering committee (see the

Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study, and the data were collected and analyzed by the Population Health Research Institute (McMaster University, Hamilton, ON, Canada). The sponsor (St. Jude Medical) had nonvoting membership on the steering committee and assisted in the design of the study and in on-site data collection but had no role in the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. The first two authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the report to the study protocol, which is available at NEJM.org.

PATIENT POPULATION

Patients were eligible for inclusion in the study if they were 65 years of age or older, had a history of hypertension requiring medical therapy, and had undergone their first implantation of a St. Jude Medical dual-chamber pacemaker (for sinus-node or atrioventricular-node disease) or ICD (for any indication) in the preceding 8 weeks. Patients were excluded if they had any history of atrial fibrillation or atrial flutter lasting more than 5 minutes or if they required treatment with a vitamin K antagonist for any reason.

STUDY PROCEDURES

After providing written informed consent, patients had their pacemaker or ICD programmed according to protocol-specific settings.²⁰ The device was programmed so that atrial tachycardia was detected when the heart rate reached 190 beats per minute, electrogram storage was activated, and the atrial fibrillation suppression algorithm was turned off.

At a clinic visit 3 months later, the devices were interrogated in order to classify patients according to whether a subclinical atrial tachyarrhythmia had occurred or had not occurred since the time of enrollment. A subclinical atrial tachyarrhythmia was defined as an episode of rapid atrial rate (190 beats or more per minute), lasting more than 6 minutes, that was detected by the pacemaker or defibrillator.

Also at the 3-month visit, patients with pacemakers (but not patients with ICDs) were randomly assigned to have continuous atrial overdrive pacing programmed as either “on” or “off.” When this feature is turned on, atrial pacing is initiated, with continuous electronic adjustment

to pace the atrium at a rate slightly higher than the patient's intrinsic sinus rhythm, as a means of potentially preventing the initiation of atrial fibrillation. Patients were then followed every 6 months to the end of the study.

STUDY OUTCOMES

For the portion of the study in which the prognostic value of subclinical atrial fibrillation was evaluated, the primary outcome was ischemic stroke or systemic embolism. Secondary outcomes were vascular death, myocardial infarction, stroke from any cause, and atrial tachyarrhythmias documented by surface electrocardiography. The definitions of the individual outcome events are provided in the Supplementary Appendix. All the available device electrograms that showed subclinical atrial tachyarrhythmias, as well as all clinical events, were subject to blinded adjudication by expert committees.

The primary outcome of the randomized trial of continuous atrial overdrive pacing was symptomatic or asymptomatic atrial tachyarrhythmia lasting more than 6 minutes, documented by surface electrocardiographic recording.¹⁹ The results of this randomized comparison are presented only briefly in this report, since this report is intended to focus primarily on the findings of the observational study of the prognostic value of subclinical atrial fibrillation.

STATISTICAL ANALYSIS

On the basis of previously reported data, we estimated that the annual rate of stroke or systemic embolism in patients 65 years of age or older who have hypertension and who have received a pacemaker would be approximately 1%.^{20,21} We then estimated that with enrollment of 2500 patients, the study would have 90% power to detect an increase in the annual risk of ischemic stroke or systemic embolism from 1% to 2% among patients who have had an episode of rapid atrial rate. For the randomized portion of the study, we also estimated that with 2500 patients enrolled, the study would have 90% power to detect a 25% reduction with continuous atrial overdrive pacing in the rate of development of clinical atrial tachyarrhythmias, from a control rate of 8% per year.

The baseline characteristics of patients with and of patients without a subclinical atrial tachyarrhythmia before the 3-month visit were compared with the use of independent t-tests or Fisher's exact test. The primary outcome analysis was a

comparison between these two groups of the cumulative risk of ischemic stroke or systemic embolism occurring after the 3-month visit. Cumulative hazard curves were modeled with the use of the Kaplan–Meier method and were compared with the use of a log-rank test. Cox proportional-hazards modeling was used to adjust for baseline imbalances with respect to prior or no prior stroke or transient ischemic attacks, presence or absence of diabetes mellitus, presence or absence of heart failure, age, sex, and history or no history of coronary artery disease or peripheral arterial disease.

A prespecified analysis was performed according to the baseline CHADS₂ score of the patients. Scores on the CHADS₂, an index of the risk of stroke in patients with atrial fibrillation, range from 0 to 6, with higher scores indicating a greater risk of stroke. An analysis was also performed in which data from patients were censored once clinical atrial fibrillation developed. A time-dependent covariate analysis was performed with the use of data on all atrial tachyarrhythmias that occurred during the study; in this analysis, the detection of a subclinical atrial tachyarrhythmia (of >6 minutes' duration, >6 hours' duration, or >24 hours' duration) triggered a time-dependent variable that remained positive for the remainder of the follow-up period. Data from the randomized evaluation of continuous atrial overdrive pacing were analyzed according to the intention-to-treat principle, with the use of Cox proportional-hazards modeling and log-rank testing.

RESULTS

STUDY PATIENTS

During the period from December 2004 through September 2009, a total of 2451 patients with a newly implanted pacemaker and 129 patients with a newly implanted ICD were enrolled in 23 countries. Between the time of enrollment and the 3-month visit, at least one atrial tachyarrhythmia was detected by an implanted device in 261 patients (10.1%). During this same period, clinical atrial tachyarrhythmias occurred in 7 patients.

Among patients who had subclinical atrial tachyarrhythmias within 3 months after implantation of a device, the median number of episodes of atrial arrhythmia was 2 (interquartile range, 1 to 3). The median atrial rate was 480 beats per minute (interquartile range, 366 to 549), and the median time to detection of the first episode was 35 days (interquartile range, 11 to 66).

The age of the patients and the percentage of patients who had had a prior stroke were similar in the group with subclinical atrial tachyarrhythmias before the 3-month visit and in the group without a subclinical tachyarrhythmia before that visit (Table 1). The prevalence of sinus nodal disease was higher, and the resting heart rate was lower, among patients with subclinical atrial tachyarrhythmias than among those without a subclinical tachyarrhythmia. Aspirin was used by 61.3% and 61.7% of the patients in the two groups, respectively, and none of the patients were receiving a vitamin K antagonist at baseline.

ATRIAL TACHYARRHYTHMIAS DURING THE FOLLOW-UP PERIOD

Patients were subsequently followed for a mean of 2.5 years, during which time 14 patients (0.5%) were lost to follow-up. Over the course of the follow-up period, 194 patients received a vitamin K antagonist, including 47 of the patients who had had a subclinical atrial tachyarrhythmia by 3 months (18.0%).

During the follow-up period, subclinical atrial tachyarrhythmias occurred in an additional 633 patients (24.5%). Clinical atrial tachyarrhythmias on surface electrocardiograms occurred in 41 of the 261 patients who had had subclinical atrial tachyarrhythmias before the 3-month visit (15.7%) and in 71 of the 2319 patients who had not had subclinical atrial tachyarrhythmias before the 3-month visit (3.1%) (hazard ratio, 5.56; 95% confidence interval [CI], 3.78 to 8.17; $P < 0.001$) (Table 2 and Fig. 1A).

STROKE OR SYSTEMIC EMBOLISM

During the follow-up period, 11 of the 261 patients (4.2%) in whom subclinical atrial tachyarrhythmias had been detected before 3 months had an ischemic stroke or systemic embolism (a rate of 1.69% per year), as compared with 40 of the 2319 in whom subclinical atrial tachyarrhythmias had not been detected (1.7%, a rate of 0.69% per year) (hazard ratio, 2.49; 95% CI, 1.28 to 4.85; $P = 0.007$) (Table 2 and Fig. 1B). The risk was virtually unchanged after adjustment for baseline risk factors for stroke (hazard ratio, 2.50; 95% CI, 1.28 to 4.89; $P = 0.008$) and was similar in an analysis in which data from patients were censored once clinical atrial fibrillation developed (hazard ratio, 2.41; 95% CI, 1.21 to 4.83; $P = 0.01$). Of the 51 patients with a stroke or systemic embolism, 11 had had subclinical atrial tachyarrhythmias

detected by 3 months, and none had had clinical atrial fibrillation by 3 months. The population attributable risk of ischemic stroke or systemic embolism associated with subclinical atrial tachyarrhythmia was 13%. There was no association between subclinical atrial tachyarrhythmias and any of the other clinical outcomes (Table 2).

In the time-dependent analysis that included all episodes of atrial tachyarrhythmia detected by devices during the follow-up period, episodes lasting longer than 6 minutes, as compared with no episodes, were associated with an increased risk of ischemic stroke or systemic embolism (hazard ratio, 1.77; 95% CI, 1.01 to 3.10; $P = 0.047$). The increase in risk was similar when the occurrence of episodes longer than 6 hours was compared with the occurrence of no episodes (hazard ratio, 2.99; 95% CI, 1.55 to 5.77; $P = 0.001$) and when the occurrence of episodes longer than 24 hours was compared with the occurrence of no episodes (hazard ratio, 4.96; 95% CI, 2.39 to 10.3; $P < 0.001$). When the patients with episodes of device-detected atrial tachyarrhythmia were stratified according to the duration, in quartiles, of the longest episode (≤ 0.86 hours, 0.87 to 3.63 hours, 3.64 to 17.72 hours, and > 17.72 hours), the annual rates of stroke or systemic embolism were 1.23 (95% CI, 0.15 to 4.46), 0 (95% CI, 0 to 2.08), 1.18 (95% CI, 0.14 to 4.28), and 4.89 (95% CI, 1.96 to 10.07), respectively. A similar analysis of the number of episodes of subclinical atrial tachyarrhythmia, in quartiles (1, 2, 3 or 4, and > 4) yielded annual rates of stroke or systemic embolism of 1.20 (95% CI, 0.25 to 3.50), 2.15 (95% CI, 0.44 to 6.29), 1.89 (95% CI, 0.23 to 6.81), and 1.93 (95% CI, 0.40 to 5.63), respectively.

The relative risk of ischemic stroke or systemic embolism associated with subclinical atrial tachyarrhythmia was consistent across increasing levels of baseline risk of stroke, as assessed by the CHADS₂ score (Table 3). The absolute rate of stroke increased with increasing CHADS₂ score, reaching a rate of 3.78% per year in patients with subclinical atrial tachyarrhythmias and a CHADS₂ score of greater than 2.

RANDOMIZED EVALUATION OF CONTINUOUS ATRIAL OVERDRIVE PACING

We also randomly assigned all patients with pacemakers to receive continuous atrial overdrive pacing or not to receive it; the baseline characteristics of these two groups were well balanced (Table 1). The rate of the development of a clinical atrial

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Device-Detected Subclinical Atrial Tachyarrhythmia			Continuous Atrial Overdrive Pacing†	
	Yes (N=261)	No (N=2319)	P Value	On (N=1164)	Off (N=1179)
Age — yr	77±7	76±7	0.13	76±7	76±7
Male sex — no. (%)	147 (56.3)	1359 (58.6)	0.48	687 (59.0)	658 (55.8)
Systolic blood pressure while sitting — mm Hg	137±20	138±19	0.38	139±20	138±19
Heart rate — beats/min	68±12	70±12	0.001	70±11	69±12
Body-mass index‡	28±5	27±5	0.43	27±5	27±5
Risk factors for stroke — no. (%)					
Prior stroke	18 (6.9)	168 (7.2)	0.84	80 (6.9)	88 (7.5)
Prior transient ischemic attack	13 (5.0)	113 (4.9)	0.94	52 (4.5)	60 (5.1)
History of heart failure	39 (14.9)	335 (14.4)	0.83	142 (12.2)	162 (13.7)
Diabetes mellitus	59 (22.6)	674 (29.1)	0.03	329 (28.3)	325 (27.6)
Prior myocardial infarction	32 (12.3)	427 (18.4)	0.01	175 (15.0)	200 (17.0)
CHADS ₂ score§	2.2±1.1	2.3±1.0	0.47	2.2±1.0	2.3±1.1
Sinus-node disease, with or without atrioventricular-node disease — no. (%)	130 (49.8)	964 (41.6)	0.01	519 (44.6)	498 (42.2)
Atrioventricular-node disease, without sinus-node disease — no. (%)	132 (50.6)	1279 (55.2)	0.16	648 (55.7)	686 (58.2)
Atrial lead in septal position — no. (%)	101 (38.7)	972 (41.9)	0.32	492 (42.3)	498 (42.2)
Duration of hypertension >10 yr — no. (%)	115 (44.1)	965 (41.6)	0.45	486 (41.8)	505 (42.8)
Left ventricular hypertrophy on ECG — no. (%)	6 (2.3)	105 (4.5)	0.09	46 (4.0)	50 (4.2)
Time from implantation of pacemaker or ICD to enrollment — days	25±22	29±40	0.04	28±39	29±39
Medications — no. (%)					
Aspirin	160 (61.3)	1430 (61.7)	0.91	721 (61.9)	705 (59.8)
Beta-blocker	94 (36.0)	849 (36.6)	0.85	398 (34.2)	400 (33.9)
Statin	113 (43.3)	1112 (48.0)	0.15	544 (46.7)	537 (45.5)

* Plus–minus values are means ±SD. The baseline characteristics of the patients are shown according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and 3 months and according to whether patients were randomly assigned after the 3-month visit to have continuous atrial overdrive pacing turned on or off. All patients had a history of hypertension requiring treatment, and no patients were receiving vitamin K antagonist therapy. ECG denotes electrocardiogram, and ICD implantable cardioverter–defibrillator.

† Only patients receiving a pacemaker were enrolled in the portion of the trial in which patients were randomly assigned after the 3-month visit to have continuous atrial overdrive pacing turned on or turned off. There were no significant differences between the two randomized treatment groups in any of the baseline characteristics shown ($P>0.05$ for all comparisons).

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The CHADS₂ score is used to predict the risk of stroke in patients with atrial fibrillation. Scores range from 0 to 6, with higher scores indicating a greater risk of stroke; the categories of congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and the category of prior stroke or transient ischemic attack is assigned 2 points.

tachyarrhythmia was low in both groups, and the intervention did not have a significant effect on this or any other outcome (Table 4). In an analysis of the prognostic value of subclinical atrial tachyarrhythmias with patients stratified according to randomized study group (continuous atrial overdrive pacing vs. no continuous atrial overdrive pacing), a test of interaction was not significant ($P=0.995$).

Table 2. Clinical Outcomes Occurring after the 3-Month Visit, According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

Clinical Outcome	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months				Hazard Ratio with Subclinical Atrial Tachyarrhythmias (95% CI)	P Value
	Present (N=261)		Absent (N=2319)			
	no. of events	%/yr	no. of events	%/yr		
Ischemic stroke or systemic embolism*	11	1.69	40	0.69	2.49 (1.28–4.85)	0.007
Ischemic stroke	10	1.54	36	0.62	2.52 (1.25–5.08)	0.01
Systemic embolism	1	0.15	4	0.07	2.24 (0.25–20.10)	0.47
Myocardial infarction	7	1.07	39	0.67	1.52 (0.68–3.42)	0.31
Death from vascular causes	19	2.92	153	2.62	1.11 (0.69–1.79)	0.67
Stroke, myocardial infarction, or death from vascular causes	29	4.45	206	3.53	1.25 (0.85–1.84)	0.27
Hospitalization for heart failure	20	3.07	131	2.24	1.36 (0.85–2.19)	0.20
Clinical atrial fibrillation or flutter on surface electrocardiogram	41	6.29	71	1.22	5.56 (3.78–8.17)	<0.001

* Five cases of confirmed stroke for which the cause (ischemic or hemorrhagic) was undetermined are included. All five cases occurred in the group of patients who did not have an episode of subclinical atrial tachyarrhythmia between enrollment and 6 months.

A table showing the adverse events that occurred during the randomized portion of the trial is provided in the Supplementary Appendix.

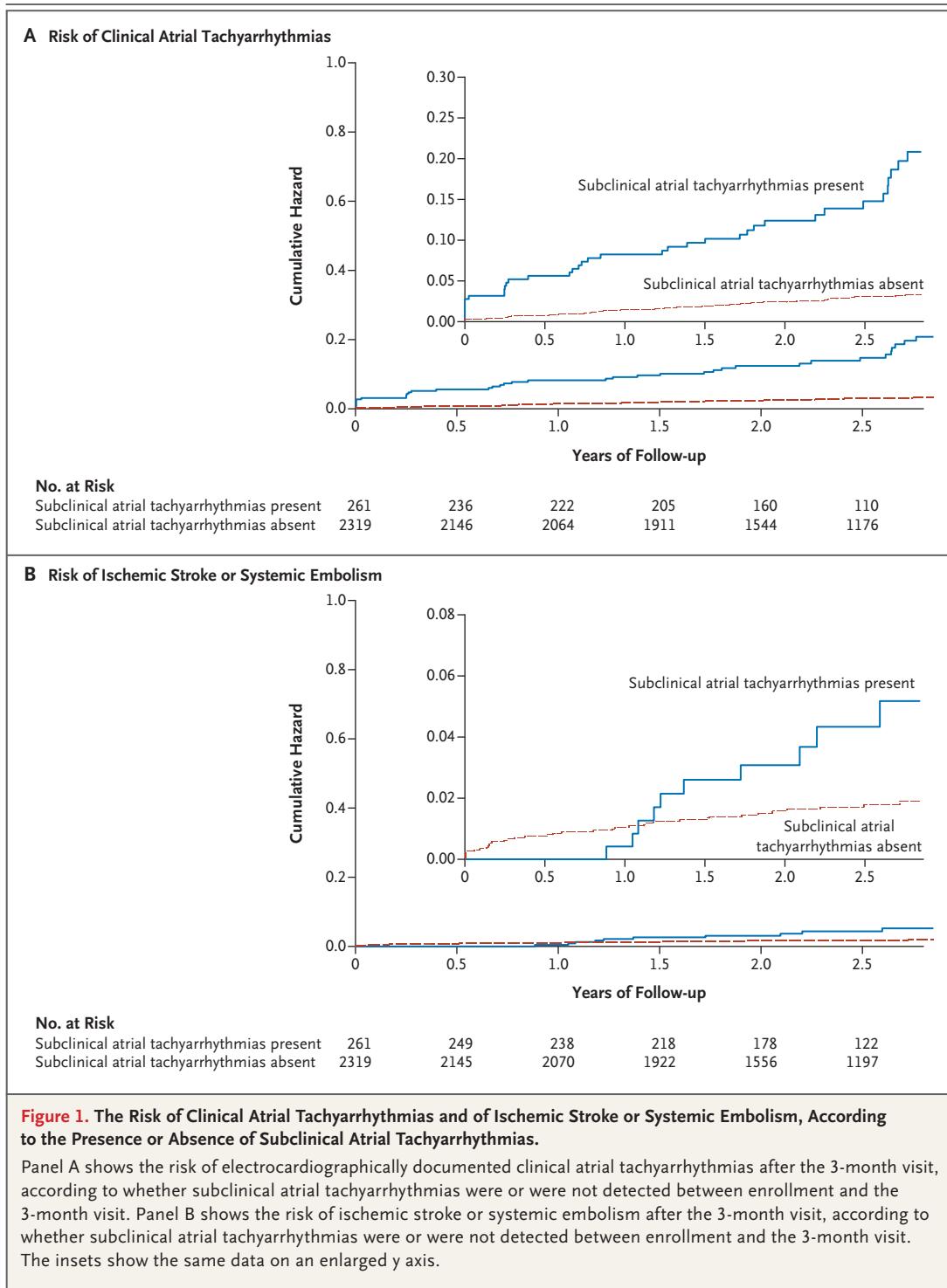
DISCUSSION

A major finding of this study is that among patients 65 years of age or older with a history of hypertension who had undergone implantation of a pacemaker or ICD and were free from clinical atrial fibrillation, there was a substantial incidence of subclinical atrial tachyarrhythmias. Subclinical atrial tachyarrhythmias were detected in one tenth of the patients within 3 months after implantation and were detected at least once during a mean follow-up period of 2.5 years in 34.7% of the patients. Episodes of subclinical atrial tachyarrhythmias were almost eight times as common as episodes of clinical atrial fibrillation. During the course of the study, clinical atrial fibrillation developed in only 15.7% of the patients with subclinical atrial tachyarrhythmias, suggesting that there can be a lag between subclinical events and clinical detection. The median time to the detection, by means of continuous device monitoring, of the occurrence of subclinical atrial tachyarrhythmias within the first 3 months was 36 days,

indicating that Holter monitoring even for several days may fail to detect subclinical atrial fibrillation.

The second major finding of the study is that subclinical atrial tachyarrhythmias were independently associated with an increase by a factor of 2.5 in the risk of ischemic stroke or systemic embolism and that this risk was independent of other risk factors for stroke and of the presence of clinical atrial fibrillation. The population attributable risk of ischemic stroke or systemic embolism associated with subclinical atrial tachyarrhythmias before 3 months was 13%, which is similar to the attributable risk of stroke associated with clinical atrial fibrillation reported by the Framingham investigators.⁶ The results of our study suggested that the risk of stroke was higher when episodes of subclinical atrial tachyarrhythmias were of longer duration, but the study was underpowered for this analysis. Our study also did not analyze device-detected events of 6 minutes or less, which occurred frequently and which might be clinically important.

The risk of stroke with a device-detected atrial tachyarrhythmia was modulated by the patient's risk profile for stroke. When a patient had a CHADS₂ score of higher than 2, the risk of is-



chemic stroke or systemic embolism associated with a subclinical atrial tachyarrhythmia was nearly 4% per year. More than half of the patients were receiving aspirin at baseline, and 18% of patients with subclinical atrial tachyarrhythmias received a vitamin K antagonist during the follow-up period. Both of these treatments could have reduced the risk of stroke and might have

Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline CHADS₂ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

CHADS ₂ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		no. of patients	no. of events	%/yr	no. of patients	no. of events	%/yr	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23–18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62–5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55–9.95)

* The P value for trend is 0.35.

lessened the observed increase in the risk of stroke associated with subclinical atrial tachyarrhythmias. The net benefit of antithrombotic treatment is well established in patients with clinical atrial fibrillation, but there may not be a similar benefit in patients with subclinical atrial tachyarrhythmias; therefore, a randomized trial of anticoagulant therapy in patients with subclinical atrial tachyarrhythmias is desirable.

Two previous studies have reported an increased risk of clinical events with device-detected atrial tachyarrhythmias, but neither study excluded patients with previously diagnosed atrial fibrillation, nor did they adjudicate episodes of device-detected atrial tachyarrhythmias. A retrospective analysis of a subgroup of 312 patients from the Mode Selection Trial (MOST; ClinicalTrials.gov number, NCT00000561)¹⁶ showed that the risk of death or stroke was increased by a factor of 2.5 in patients who had at least one episode of high atrial rate. Glotzer et al. also reported a relationship between device-detected atrial tachycardia and embolic events.¹⁷ However, that study also included patients with previously documented atrial fibrillation and did not show a significant association in the predefined primary analysis.

The prevalence of subclinical atrial tachyarrhythmias may be higher in patients with pacemakers than in other high-risk patient groups. Sinus-node dysfunction is associated with an increased risk of atrial fibrillation.^{20,21} Furthermore, patients with atrioventricular-node disease may be more likely to be asymptomatic when atrial tachyarrhythmias occur, owing to reduced atrio-

ventricular conduction. Nonetheless, the prevalence of subclinical atrial fibrillation in other elderly populations may be high.³ In the Cardiovascular Health Study involving randomly selected persons 65 years of age or older,³ atrial fibrillation was diagnosed by electrocardiography in 2% of the patients; 14% of those patients had no previous diagnosis of atrial fibrillation.

A link between stroke of unknown cause, often called cryptogenic stroke, and subclinical atrial fibrillation has long been suspected. Short-term monitoring studies have shown that subclinical atrial fibrillation is present in some patients who have had a cryptogenic stroke,^{8,9} but long-term continuous monitoring, like that available with a pacemaker, is currently not practical. The data from the present study support the concept that there is a link between subclinical atrial fibrillation and cryptogenic stroke.

The results of this study did not show a benefit of continuous atrial overdrive pacing. However, because the rate of development of clinical atrial fibrillation was low, the study was underpowered for this outcome. Algorithms for continuous atrial overdrive pacing have been evaluated in previous trials,²²⁻²⁷ but most of the trials have had small sample sizes, and there have been differences among the trials in the characteristics of the patient populations, the pacing algorithms used, and the atrial lead positions. These trials have not provided convincing evidence of a benefit.²²⁻²⁷ The present data provide modest evidence that this intervention does not prevent clinical atrial fibrillation.

Table 4. Effect of Continuous Atrial Overdrive Pacing on Clinical Outcomes.

Outcome	Continuous Atrial Overdrive Pacing Turned On (N=1164)		Continuous Atrial Overdrive Pacing Turned Off (N=1179)		Hazard Ratio with Continuous Atrial Overdrive Pacing Turned On (95% CI)	P Value
	No. of Patients	Annual Rate*	No. of Patients	Annual Rate*		
Atrial tachyarrhythmia†	60	1.96	45	1.44	1.38 (0.94–2.03)	0.10
Symptomatic	29	0.95	22	0.71	1.35 (0.78–2.35)	0.29
Asymptomatic	36	1.17	28	0.90	1.31 (0.80–2.16)	0.29
Device-detected atrial tachyarrhythmia with duration >24 hr	134	4.37	125	4.01	1.11 (0.87–1.41)	0.42
Stroke, systemic embolism, myocardial infarction, death from vascular causes, or hospitalization for heart failure	160	5.22	146	4.69	1.13 (0.90–1.41)	0.29
Stroke	21	0.68	25	0.80	0.85 (0.48–1.52)	0.59
Systemic embolism	3	0.10	2	0.06	1.52 (0.25–9.12)	0.64
Myocardial infarction	22	0.72	20	0.64	1.13 (0.62–2.08)	0.69
Death from vascular causes	82	2.67	80	2.57	1.05 (0.77–1.42)	0.78
Hospitalization for heart failure	77	2.51	59	1.89	1.34 (0.95–1.88)	0.09

* The annual rate is the rate per 100 patient-years of follow up.

† Symptomatic or asymptomatic atrial tachyarrhythmia (atrial rate of >190 beats per minute) lasting more than 6 minutes, documented by surface electrocardiographic recording, was the primary outcome of the randomized trial of continuous atrial overdrive pacing.

In summary, subclinical atrial tachyarrhythmias occurred frequently in patients with pacemakers who had a history of hypertension but no prior diagnosis of clinical atrial fibrillation. The subclinical atrial tachyarrhythmias often preceded the development of clinical atrial fibrillation. In patients with pacemakers who did not have clinical atrial fibrillation, the occurrence of subclinical atrial tachyarrhythmias was associated with a significantly increased risk of a subsequent stroke.

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REFERENCES

1. Flaker GC, Belew K, Beckman K, et al. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;149:657-63.
2. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser H. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;43:47-52.
3. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. The

- prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;74:236-41.
4. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology* 1978; 28:973-7.
 5. Wolf PA, Abbot RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. *Arch Intern Med* 1987;147: 1561-4.
 6. *Idem*. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
 7. Petersen P, Godtfredson J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;17:622-6.
 8. Tayal AH, Tian KM, Kelly M, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology* 2008;71:1696-701.
 9. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke* 2004;35:1647-51.
 10. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M. Noninvasive cardiac monitoring for detection of paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke* 2007; 38:2935-40.
 11. Sinha AM, Diener HC, Morillo CA, et al. Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF): design and rationale. *Am Heart J* 2010;160(1): 36e.1-41.e1.
 12. Pollak WM, Simmons JD, Interian A Jr, et al. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. *Pacing Clin Electrophysiol* 2001;24:424-9.
 13. Birnie D, Williams K, Guo A, et al. Reasons for escalating pacemaker implants. *Am J Cardiol* 2006;98:93-7.
 14. Curtis JP, Leubbert JJ, Wang Y, et al. Association of physician certification and outcomes among patients receiving an implantable cardioverter-defibrillator. *JAMA* 2009;301:1661-70.
 15. Wilkoff BL, Auricchio A, Brugada JP, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Europace* 2008;10:707-25.
 16. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MODe Selection Trial (MOST). *Circulation* 2003; 107:1614-9.
 17. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;2:474-80.
 18. Healey JS, Toff WD, Lamas GA, et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. *Circulation* 2006;114:11-7.
 19. Hohnloser SH, Capucci A, Fain E, et al. ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT). *Am Heart J* 2006; 152:442-7.
 20. Kerr CR, Connolly SJ, Abdollah H, et al. Canadian Trial of Physiological Pacing: effects of physiological pacing during long-term follow-up. *Circulation* 2004;109: 357-62.
 21. Skanes AC, Krahn AD, Yee R, et al. Progression to chronic atrial fibrillation after pacing: the Canadian Trial of Physiologic Pacing. *J Am Coll Cardiol* 2001; 38:167-72.
 22. Padeletti L, Pürefellner H, Adler SW, et al. Combined efficacy of atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial tachyarrhythmia. *J Cardiovasc Electrophysiol* 2003;14:1189-95.
 23. Carlson MD, Ip J, Messenger J, et al. A new pacemaker algorithm for the treatment of atrial fibrillation: results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). *J Am Coll Cardiol* 2003;42:627-33.
 24. Ogawa H, Ishikawa T, Matsushita K, et al. Effects of right atrial pacing preference in prevention of paroxysmal atrial fibrillation: Atrial Pacing Preference study (APP study). *Circ J* 2008;72:700-4.
 25. Gold MMR, Adler S, Fauchier L, et al. Impact of atrial prevention pacing on atrial fibrillation burden: primary results of the Study of Atrial Fibrillation Reduction (SAFARI) trial. *Heart Rhythm* 2009; 6:295-301.
 26. Hemels MEW, Ruiters JH, Molhoek P, et al. Right atrial preventive and anti-tachycardia pacing for the prevention of paroxysmal atrial fibrillation in patients without bradycardia: a randomized study. *Europace* 2008;10:306-13.
 27. Lee MA, Weachter R, Pollak S, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency. *J Am Coll Cardiol* 2003;41:1926-32.

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