

# Silent Atrial Fibrillation and Cryptogenic Strokes



James E. Dalen, MD, MPH, ScD (hon), Joseph S. Alpert, MD

Department of Medicine, University of Arizona, Tucson.

## ABSTRACT

A new suspected cause of cryptic strokes is “silent atrial fibrillation.” Pacemakers and other implanted devices allow continuous recording of cardiac rhythm for months or years. They have discovered that short periods of atrial fibrillation lasting minutes or hours are frequent and usually are asymptomatic. A meta-analysis of 50 studies involving more than 10,000 patients with a recent stroke found that 7.7% had new atrial fibrillation on their admitting electrocardiogram. In 3 weeks during and after hospitalization, another 16.9% were diagnosed. A total of 23.7% of these stroke patients had silent atrial fibrillation; that is, atrial fibrillation diagnosed after hospital admission. Silent atrial fibrillation is also frequent in patients with pacemakers who do not have a recent stroke. In a pooled analysis of 3 studies involving more than 10,000 patients monitored for 24 months, 43% had at least 1 day with atrial fibrillation lasting more than 5 minutes. Ten percent had atrial fibrillation lasting at least 12 hours. Despite the frequency of silent atrial fibrillation in these patients with multiple risk factors for stroke, the annual incidence of stroke was only 0.23%. When silent atrial fibrillation is detected in patients with recent cryptogenic stroke, anticoagulation is indicated. In patients without stroke, silent atrial fibrillation should lead to further monitoring for clinical atrial fibrillation rather than immediate anticoagulation, as some have advocated.

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**KEYWORDS:** Anticoagulation for silent atrial fibrillation; Cryptogenic strokes; ECG monitoring; Silent atrial fibrillation

More than 25% of ischemic strokes per year in the US are classified as cryptogenic: that is, after extensive evaluation, no cause is determined.<sup>1</sup>

Some<sup>2,3</sup> have suggested that cryptogenic strokes may be due to paradoxical embolism of venous thrombi across a patent foramen ovale. This led to surgical closure of patent foramen ovals in some patients, and then patent foramen ovale closure by a transvenous device in thousands of patients.<sup>4</sup> However, 3 randomized clinical trials failed to find a benefit of patent foramen ovale closure.<sup>5</sup> Paradoxical embolism is a rare cause of ischemic strokes.<sup>5</sup>

Cardioembolism is the commonest cause of ischemic stroke,<sup>6</sup> and atrial fibrillation is the commonest cause of cardioembolism.<sup>7</sup> The percentage of ischemic strokes due to cardioembolism increases with age; in one series it

accounted for <5% of strokes in patients younger than 45 years of age and 53% in patients older than 70 years. This parallels the increasing prevalence of atrial fibrillation with increasing age.<sup>8</sup>

The risk of stroke in patients with atrial fibrillation can be determined by a score based on the presence or absence of congestive heart failure, hypertension, diabetes, history of stroke or transient ischemic attack (TIA), vascular disease, age >75 years, sex (CHA<sub>2</sub>DS<sub>2</sub>-VASc).<sup>9</sup>

Multiple randomized clinical trials have shown that anticoagulation with warfarin or one of the newer oral anticoagulants reduces the rate of stroke in patients with atrial fibrillation by at least two-thirds and reduces death by 25%.<sup>10</sup>

Anticoagulation is effective in patients with paroxysmal atrial fibrillation as well as patients with chronic atrial fibrillation. Hohnloser et al<sup>11</sup> randomized 6706 patients with atrial fibrillation to treatment with oral anticoagulants or aspirin plus clopidogrel to prevent strokes. Twelve hundred two of these patients had paroxysmal atrial fibrillation defined as sinus rhythm at randomization, but atrial fibrillation by electrocardiogram (ECG) on 2 separate occasions, at least 2 weeks apart in the 6 months prior to

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Requests for reprints should be addressed to James E. Dalen, MD, MPH, ScD (hon), Department of Medicine, University of Arizona, 13500 N Rancho Vistoso Blvd #45, Tucson, AZ 92118.

E-mail address: [jdalenmd@gmail.com](mailto:jdalenmd@gmail.com)

randomization. The other 5495 patients had chronic atrial fibrillation. The incidence of stroke during follow-up in those with paroxysmal atrial fibrillation (2.0%/y) was not significantly different from those with chronic atrial fibrillation (2.2%/y).

Hart et al<sup>12</sup> compared the rate of stroke in patients treated with aspirin in 1126 patients with permanent atrial fibrillation with 460 patients with intermittent atrial fibrillation on admission, but sinus rhythm documented within the prior 6 months. The rates of stroke during 2-year follow-up was nearly the same: 3.2% vs 3.3%.<sup>12</sup>

## DETECTION OF SILENT ATRIAL FIBRILLATION

The ability of modern dual-chamber pacemakers to function as permanently implanted cardiac monitors has led to the observation that transient atrial fibrillation lasting minutes or hours is frequent in patients with pacemakers. The vast majority of these episodes are asymptomatic and are termed “silent atrial fibrillation.”<sup>13</sup>

These observations lead to many important questions. Are patients with episodes of silent atrial fibrillation at increased risk of stroke? Is silent atrial fibrillation a major cause of cryptic stroke? How long must these episodes last to increase the incidence of left atrial thrombi? Would oral anticoagulants prevent strokes in these patients? Which patients with silent atrial fibrillation should be anticoagulated?

## INCIDENCE OF CLINICAL ATRIAL FIBRILLATION AND SILENT ATRIAL FIBRILLATION IN PATIENTS WITH ISCHEMIC STROKE

Approximately 20% of patients presenting with ischemic stroke are known to have atrial fibrillation prior to the stroke.<sup>14</sup> Atrial fibrillation first detected AT or after admission for stroke is termed silent atrial fibrillation. Silent atrial fibrillation during the admission for stroke can be detected by serial ECGs, Holter monitoring, continuous telemetry, or continuous ECG monitoring. After discharge, external Loop Event monitors<sup>15</sup> and implantable loop recorders<sup>16</sup> and outpatient telemetry can be utilized for long-term monitoring.

Sposato et al<sup>14</sup> performed a meta-analysis of 50 studies comprising 11,658 patients with ischemic stroke from 1980 until 2014 who were assessed for silent atrial fibrillation.

As shown in the **Table**, the ECG on admission detected new atrial fibrillation in 7.7%. During the hospital admission, new atrial fibrillation was documented in another 5.1%. After discharge, serial Holter monitors detected

10.7% with atrial fibrillation. Additional postdischarge testing with mobile telemetry and external or implantable loop recording detected an additional 16.9%. Of note, the percentage detected was essentially the same with mobile telemetry or external or implantable loop recorders. The total percentage of patients with new (or silent) atrial fibrillation was 23.7%<sup>14</sup> (**Table**).

### CLINICAL SIGNIFICANCE

- Silent atrial fibrillation is very frequent in patients with recent cryptogenic stroke. Anticoagulation is indicated in these patients if atrial fibrillation is diagnosed.
- Silent atrial fibrillation is also very frequent in patients without a history of recent stroke.
- Stroke is uncommon in patients with silent atrial fibrillation who do not have a history of recent stroke. If silent atrial fibrillation is detected in these patients, further electrocardiographic monitoring rather than anticoagulation is indicated.

## INCIDENCE OF SILENT ATRIAL FIBRILLATION IN PACEMAKER PATIENTS WITHOUT A RECENT STROKE

Healey et al<sup>17</sup> monitored 2580 patients with pacemakers or other implanted devices for 3 months. None had a recent stroke, but 7% had a past history of stroke. The average age was 77 years; none had a history of atrial fibrillation. They defined silent atrial fibrillation as an atrial rate >190/min lasting >6 minutes. During the first 3 months, 10.1% had silent atrial fibrillation. During an additional 2.5 years of follow-up, an additional 24.5% had one or more episodes of silent atrial fibrillation.<sup>17</sup>

Connolly et al<sup>18</sup> followed 2568 patients for 3 years after placement of a ventricular or a dual-chamber pacemaker. None had a recent stroke. The average age was 70 years; 20% had a history of intermittent atrial fibrillation. Less than 10% had a past history of stroke or TIA. During 3 years of follow-up, the incidence of new atrial fibrillation was 6.6% with a ventricular pacemaker, compared with 5.3% with a dual-chamber pacemaker.<sup>18</sup>

The largest series of pacemaker patients without a recent ischemic stroke who were monitored for silent atrial fibrillation was reported by Boriani et al.<sup>13</sup> They pooled the results of 3 prospective trials totaling 10,016 patients. The median age was 70 years. Five percent had persistent

**Table** Detection of New AF in Patients with Recent Stroke or TIA<sup>14</sup>

Detected	# Tested	% New AF
Admission ECG	2896	7.7%
In-hospital monitoring	4618	5.1%
Postdischarge, serial Holters		10.7%
Postdischarge additional tests	1723	16.9%
Mobile telemetry	417	15.3%
External loop recording	829	16.2%
Implant loop recording	477	16.9%
Overall proportion of patients with new (silent) AF = 23.7%		

AF = atrial fibrillation; ECG = electrocardiogram; TIA = transient ischemic attack.

atrial fibrillation and 19% had a history of paroxysmal atrial fibrillation. Six percent had a past history of stroke; none had a recent ischemic stroke. Atrial fibrillation was defined as an atrial rate of >175/min lasting 5 minutes or longer.

During 3 months of monitoring, 24% had at least 1 day of atrial fibrillation lasting more than 5 minutes, 18% at least 1 hour, and 6% had an episode of atrial fibrillation lasting more than 1 day.<sup>13</sup> During 24 months of monitoring, 43% had an episode of silent atrial fibrillation lasting 5 minutes or longer.<sup>13</sup>

## INCIDENCE OF STROKES IN PATIENTS WITH SILENT ATRIAL FIBRILLATION

In the report by Healey et al,<sup>17</sup> during 2.5 years of follow-up, the incidence of ischemic stroke or systemic embolism was 1.54%/y in those with silent atrial fibrillation during the first 3 months, compared with 0.62% in those without silent atrial fibrillation (hazard ratio 2.52,  $P = .01$ ).

In the study by Connolly et al,<sup>18</sup> the annual incidence of stroke was essentially the same in the 2 types of pacemakers: 1.1% and 1.0%. The incidence of stroke in those with or without silent atrial fibrillation was not reported.

During 24 months of follow-up in a meta-analysis involving more than 10,000 patients by Boriani et al,<sup>13</sup> there were 57 ischemic strokes, an incidence of 0.23%/year. Of those with strokes, 46% had at least 5 minutes of atrial fibrillation prior to the stroke. The incidence of stroke was 0.27%/y for those without atrial fibrillation and 0.30%/y for those with atrial fibrillation of 23 hours or more. This very low incidence of strokes occurred in a population with many risk factors for stroke: median age 70 years, hypertension 59%, diabetes 25%. Nearly 70% had a CHADS<sub>2</sub> score of 2 or more.

## DISCUSSION

The incidence of silent atrial fibrillation in patients with a recent stroke is significant, nearly 25% in the report of more than 11,000 patients by Sposato et al.<sup>14</sup> However, the incidence of silent atrial fibrillation is even higher in patients without a recent stroke who have continuous monitoring by an implanted pacemaker. In the more than 10,000 patients without a recent stroke in the meta-analysis by Boriani et al<sup>13</sup> who were monitored by a pacemaker, 43% had an episode of atrial fibrillation lasting more than 5 minutes during 24 months of monitoring.

The incidence of strokes is much lower than the incidence of silent atrial fibrillation in these reports.<sup>13,17,18</sup>

The annual risk of stroke in those without a recent stroke was 1.0% to 1.1% in the series reported by Connolly et al<sup>18</sup> and 0.71 in the series reported by Healey et al.<sup>17</sup>

In the series by Healey et al,<sup>17</sup> silent atrial fibrillation was detected in 10.1% during 3 months of observation. The incidence of stroke during follow-up was 0.71%/y. The incidence of stroke was greater in those with silent atrial fibrillation: 1.54/y vs 0.62/y without atrial fibrillation

(hazard ratio 2.52,  $P < .01$ ). The total number of strokes in the 2580 patients followed for 2.5 years was 46.<sup>1</sup>

Boriani et al<sup>13</sup> reported an incidence of recurrent stroke of 0.23%/y. In 4287 patients with an episode of silent atrial fibrillation lasting 5 minutes or longer, the incidence was 0.31%/y, compared with 0.24%/y for 5729 patients without silent atrial fibrillation.

The percentage of strokes that were cryptic in these 3 reports was not reported; as a result, the incidence of silent atrial fibrillation in patients with cryptic stroke vs all ischemic strokes could not be determined.

Several studies have reported that the risk of recurrent stroke in patients with cryptogenic stroke is lower than in all patients with other ischemic strokes.<sup>1,19,20</sup> Kent et al<sup>20</sup> reported an annual recurrence of ischemic stroke of 0.98%/y in 2303 patients with cryptic stroke treated with medical therapy or transvenous closure of a patent foramen ovale plus medical therapy.

The indication for anticoagulation in patients with silent atrial fibrillation is not clear, because the shortest duration of atrial fibrillation necessary for a left atrial thrombus to form and result in stroke is unknown.<sup>10</sup> There is some indirect evidence that suggests that it may take more than 48 hours of atrial fibrillation for a left atrial thrombus to form.

Clinical guidelines recommend anticoagulation prior to and after cardioversion for patients with atrial fibrillation present longer than 48 hours, but not for patients with atrial fibrillation known to be <48 hours in duration.<sup>10,21</sup> This recommendation is consistent with reports of embolic stroke after cardioversion. Airaksinen et al<sup>22</sup> reported the results of cardioversion of 3143 patients with atrial fibrillation lasting <48 hours. None received anticoagulation prior to or after cardioversion; there were 38 (0.7%) strokes within 30 days of cardioversion. This suggests it may take more than 48 hours of atrial fibrillation for a thrombus to form in the left atrium.

Hansen et al<sup>23</sup> reported the results of cardioversion with or without anticoagulation in 16,274 patients. The incidence of stroke, TIA, or systemic embolism was 4.0% in those who received anticoagulation and 10.3% in those without anticoagulation. The duration of atrial fibrillation in these patients was not reported. These 2 studies<sup>22,23</sup> make it clear that cardioversion can result in embolic stroke, and the risk is less in those with atrial fibrillation lasting <48 hours and is less in those who are treated with anticoagulation. This suggests that left atrial thrombi are most likely to be formed after 48 hours of atrial fibrillation. It also implies that it is unlikely that silent atrial fibrillation lasting minutes or hours will cause the formation of a left atrial thrombus.

Many recommend that patients with cryptic strokes should be monitored for the presence of silent atrial fibrillation.<sup>24-26</sup>

Given the current knowledge of silent atrial fibrillation, what are the indications for anticoagulation if silent atrial fibrillation is detected? If silent atrial fibrillation is documented in a patient with a recent cryptic stroke, anticoagulation would be indicated in the absence of contraindications.

Is anticoagulation indicated if silent atrial fibrillation is detected in patients without a history of stroke? In a survey of electrophysiologists by the European Heart Rhythm Association in 2013, the overwhelming majority considered that a single episode of silent atrial fibrillation is an indication for anticoagulation without further tests in patients with a CHADS<sub>2</sub> score of 1 or more.<sup>24</sup>

The 2016 European Society of Cardiology guidelines for the management of atrial fibrillation note that the shortest duration of atrial fibrillation conveying a stroke risk is unknown, and it is unknown if patients with silent atrial fibrillation will benefit from anticoagulation.<sup>10</sup> An ongoing clinical trial will address these uncertainties.<sup>10</sup>

Given the very low incidence of stroke in patients with silent atrial fibrillation who do not have a history of recent stroke<sup>13,17,18</sup> and an annual risk of major bleeding of 2% with anticoagulation,<sup>27</sup> many<sup>10,28</sup> (including the authors) would recommend further monitoring to detect clinical atrial fibrillation prior to initiating anticoagulation when silent atrial fibrillation is detected in patients without a history of stroke.

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