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ARTICLE

Newly Diagnosed Atrial Fibrillation and Acute Stroke

The Framingham Study

Huey-Juan Lin, Philip A. Wolf, Emelia J. Benjamin, Albert J. Belanger, and Ralph B. D'Agostino

ABSTRACT: *Background and Purpose* When atrial fibrillation (AF) is first documented at the time of onset of acute stroke, it is difficult to establish a temporal relationship between AF and stroke. Did AF precede and precipitate the stroke, or did the arrhythmia appear as a result of stroke? Following the course of the newly diagnosed AF may help to clarify this relationship.*Methods* The Framingham Study cohort of 5070 members, aged 30 to 62 years and free of cardiovascular disease at entry, has been under surveillance for the development of cardiovascular disease, including stroke. We followed the course of AF, which was documented for the first time on or soon after hospital admission for stroke.*Results* During 38 years of follow-up, 115 of 656 initial stroke events occurred in association with AF: 89 had previously documented AF, 21 had AF discovered for the first time on admission for the stroke, and 5 were admitted with sinus rhythm but developed AF after admission. Of the 21 subjects with AF diagnosed on admission, in 12 (57%) AF persisted thereafter (chronic

AF). Among the other 9 persons presenting with nonpersistent AF, paroxysms recurred in 3 (14%) and became chronic AF in 4 (19%). AF was transient and did not recur in only 2 persons (10%). Of the 5 subjects who developed AF after admission, AF was sustained from the initial diagnosis in 2 and recurred in paroxysms or became established as chronic in 3.*Conclusions* Ninety-two percent (24/26) of subjects presenting with newly discovered AF at the time of acute stroke continued to have this rhythm disturbance in a chronic or paroxysmal form. In only 2 subjects (8%) was the arrhythmia short-lived and nonrecurrent. These follow-up data suggest that in most instances AF was probably the precipitant rather than the consequence of stroke.

Key Words: atrial fibrillation ■ risk factors ■ stroke onset

Epidemiological and clinical studies have generally confirmed that atrial fibrillation (AF) constitutes a major risk factor for stroke.[1] [2] [3] [4] [5] [6] [7] [8] When AF is discovered for the first time on hospital admission for stroke, it is difficult to determine the sequence of events or the duration of this arrhythmia. Previous studies have reported an imminent risk of stroke associated with new-onset AF.[8] [9] [10] [11] It has been suggested that the newly diagnosed AF was responsible for most of the ischemic stroke events.[10] [12] On the other hand, an alternative possibility was raised by Vingerhoets et al[13] that acute stroke may precipitate transient AF. AF is known to occur transiently and to be precipitated by illness or by surgical procedures, for example, acute myocardial infarction, pneumonia, bronchoscopy, and coronary artery bypass grafting. However, the role of acute stroke as a precipitant of transient AF remains elusive. Recognizing

the prognostic and therapeutic implications of this issue and the difficulty of determining the accurate time sequence of onset of AF and stroke, we examined the course of the newly documented AF after stroke in the Framingham Study. We determined how frequently AF would persist after the acute phase of stroke, based on surveillance of this general population sample. Through this approach, we hope to provide a more complete picture of the relationship between acute stroke and newly diagnosed AF.

SUBJECTS AND METHODS

The Framingham cohort of 5070 men and women, aged 30 to 62 years and free of cardiovascular disease and stroke at entry to the study in 1948 to 1950, has been followed prospectively with biennial examinations. Sampling procedures, response rates, and methods of examination and follow-up have been published previously.[14] On each routine biennial examination, physical examinations and 12-lead electrocardiograms (ECGs) were performed, and details surrounding all interim illness were sought and reviewed. Surveillance was maintained for cardiovascular disease and stroke by daily monitoring of all admissions to the only local hospital to which most patients were referred by their physicians. Since 1968, whenever possible, the study neurologists have examined subjects in the hospital at the time of acute stroke. If criteria for stroke were met, stroke subtype was determined after review by a panel of investigators including a neurologist.

AF was identified both at the time of biennial examination and on interim hospitalizations and outside examinations. Onset was considered to be the time of the first documentation on ECG without prior history of AF. For those subjects in whom AF was discovered

for the first time on admission for stroke or during the acute hospital stay, the course of AF was sought by scrutiny of ECGs and all available medical information, including interim hospitalizations, records of drugs used to control AF, data from visits to physicians, and routine biennial examinations. All AF ECGs were reviewed and verified by a cardiologist. *Chronic* AF was defined as AF that persisted from the initial diagnosis. When there was reversion to sinus rhythm, AF was considered *paroxysmal*. According to the pattern, paroxysmal AF could be either *transient* for one single episode only or *recurrent* for more than one episode.

RESULTS

During 38 years of follow-up, 656 initial completed strokes occurred in 292 men and 364 women. There were 115 strokes that occurred in association with AF; 89 of them had prior documentation of AF, 21 had AF discovered for the first time on admission for the stroke, and the other 5 subjects were in sinus rhythm on admission but developed AF during the acute hospitalization for stroke (Figure). Among these three groups, the distribution of sex and stroke subtype was not significantly different from one another, but subjects with the first documentation of AF on admission were older than the other groups (Table 1).

Of the 21 subjects with acute stroke who were discovered for the first time to have AF on admission, 57% (12/21) continued thereafter to be in AF. In the other 9 subjects AF reverted to sinus rhythm; in 7 of them AF recurred in either a chronic (n=4) or paroxysmal (n=3) form. AF was transient and nonrecurrent in only 2 subjects (Table 2 and Figure), 1 of whom presented with a primary cerebellar

hemorrhage and was the only patient with hemorrhagic stroke among subjects with newly diagnosed AF.

Among the 5 subjects with first AF documentation 2 to 14 days after admission, AF was sustained from the initial diagnosis (n=2) or recurred in later course (n=3) (Table 2 and Figure).

DISCUSSION

It is not an uncommon clinical situation that AF is documented for the first time at the time of hospital admission for stroke. In a hospital-based retrospective study, 11 of 46 AF subjects with ischemic events were diagnosed for the first time to have AF at the time of their embolism.[9] In a population-based hospital stroke registry, among 185 initial strokes associated with AF, 24 had the initial documentation of AF at the time of admission for stroke.[13] Similarly, in the present study 21 of 115 stroke subjects with AF had this arrhythmia first discovered on stroke admission. For these patients it was difficult to establish whether AF was the consequence or the cause of stroke.

Investigations on the time course of AF for embolic complications have demonstrated that the risk of stroke in subjects with AF seems highest during the early months after the initial diagnosis of AF.[8 9 10 15] This distinct clustering of strokes can be seen in both chronic AF[9 10] and paroxysmal AF,[8] as well as immediately after transition from paroxysmal AF to chronic AF.[8] It has been suggested that this clustering of thromboembolic complications should be taken into consideration when patients with AF are evaluated for stroke prevention.[8 10 11]

On the other hand, numerous studies have described a variety of cardiac arrhythmias including AF associated with acute stroke.[16 17 18 19 20 21 22 23 24 25] While any attempt to attribute the onset of cardiac

arrhythmia to acute stroke should exclude the alternative possibility of preexisting cardiac diseases, only a few studies have included comparisons with prior history to document that the AF associated with acute stroke actually was new.[16 17 18 21 23 24] In these studies AF was found in 4% to 7% of subjects with subarachnoid hemorrhage[23 24 26] and in 3% to 9% of those with other types of stroke.[16 17 18 21] However, the causal relationship between stroke and AF was seldom discussed in detail. The report of Vingerhoets et al[13] was the first study to specifically address the hypothesis that some patients with acute stroke might develop transient AF as a consequence of the stroke. They compared 41 subjects with newly diagnosed AF during hospitalization for stroke, including 24 with AF at the time of admission and 17 with AF soon after admission, to stroke subjects with prior history of AF (n=144) or with another cardioembolic source (n=332). A higher frequency of primary hematoma (9.8% versus 2.8% and 0.9%) and more involvement of parietoinsular and brain stem areas were seen in the subjects with newly diagnosed AF. The AF described was generally transient and rarely recurred, a finding that was based on observations during acute hospitalization (23 days on average; range, 3 to 77 days) and considered evidence of cerebral arrhythmogenicity. Nevertheless, in view of the fact that many persons with chronic AF experience this arrhythmia intermittently before it becomes established, follow-up data after stroke would be essential in addressing the significance of “transient” AF at the acute stage of stroke. Unfortunately, such information was not generally available in these studies.

In the present study we approached this issue by scrutinizing the course of the newly diagnosed AF after stroke. We have assumed that if AF was persistent or recurrent after the acute phase of stroke,

this arrhythmia was more likely to be a primary cardiac event rather than a consequence of the acute stroke.

Among the 21 subjects in whom AF was documented for the first time on stroke admission, more than half (12/21) were in chronic AF, ie, AF persisted from the first documentation. Even if the AF was paroxysmal initially (9/21), most of these subjects (7/9) had recurrence of paroxysms or transition to chronic AF. If we exclude the five in-hospital fatal subjects whose information regarding the course of AF might be limited by the short observation period (within 3 to 25 days), 15 of 16 subjects who survived the first month after stroke continued to have this rhythm disturbance. In subjects who remained in AF after the acute phase of stroke, it seemed likely that AF led to rather than resulted from the stroke.

It is notable that one of the two persons with transient AF only, who was followed for nearly 3 years, was the only subject presenting with intracerebral hemorrhage among the stroke subjects with newly diagnosed AF. As described above, a predominance of primary cerebral hemorrhage was seen in the series of Vingerhoets et al.[13] Since primary intracranial hemorrhage is not likely to be precipitated by AF, the newly discovered AF may have a different significance for subjects with ischemic stroke and those with hemorrhagic stroke. The question of whether common vascular disorders lead to AF and to intracranial hemorrhage independently or the hemorrhage predisposes to AF remains to be elucidated by further physiological study and clinicopathologic correlation.

In the five subjects in whom sinus rhythm was recorded on admission but AF appeared 2 to 14 days after the onset of stroke, AF might not directly account for the stroke. In contrast to the finding in the study of Vingerhoets et al[13] that AF disappeared after a few days in 16 of 17 persons with AF after admission, the arrhythmia in

our subjects was either persistent from the very onset or recurrent in later course. In subjects who developed AF soon after stroke onset, AF might be a manifestation of coexistent cardiovascular diseases instead of a consequence of stroke.

Strengths and Limitations

All these subjects were derived from a population sample under prospective long-term follow-up and systematic medical surveillance. The population basis and availability of accurate information of the prestroke and poststroke cardiovascular conditions in stroke subjects enabled us to clarify the natural history of AF with less selection bias than most of the hospital-based series. Unfortunately, the number of cases in this study was small. Furthermore, the accuracy of classification of AF is certainly affected by the length and intensity of follow-up. A portion of our subjects (6/26) with newly discovered AF died shortly after stroke onset (within 3 to 25 days), which inherently weakened the ascertainment of the course of AF. For those who survived the acute stage, we followed the course of AF by tracing all medical details surrounding the interim hospitalizations as well as biennial routine examinations. Nevertheless, without continuous ECG monitoring, misclassification of the type of AF could have happened; in particular, some paroxysms of AF might not be detected, and accordingly we might overestimate the frequency of “transient AF.” Despite this potential error of classification, because of the small number of transient AF subjects in our study, the main finding is unlikely to be altered.

In conclusion, our study showed that 92% (24/26) of the newly discovered AF at acute stroke was sustained or recurred after the acute stage. While we cannot state definitively that the AF was present before the onset of stroke and precipitated the stroke, our

follow-up data wherein most of the subjects remained in AF suggest that the newly documented AF seemed more likely to be a primary cardiac event, with or without precipitating the stroke, rather than a transient consequence of acute stroke. In addition to the substantial risk of thromboembolism associated with AF, subjects with AF who have had one or more embolic events are at high risk of further emboli.[27] The previous report of the Framingham Study[10] also indicated that recurrence after initial stroke occurred early and sooner in persons with AF. Most subjects with newly diagnosed AF at the time of nonhemorrhagic stroke should be strongly considered for anticoagulant therapy.

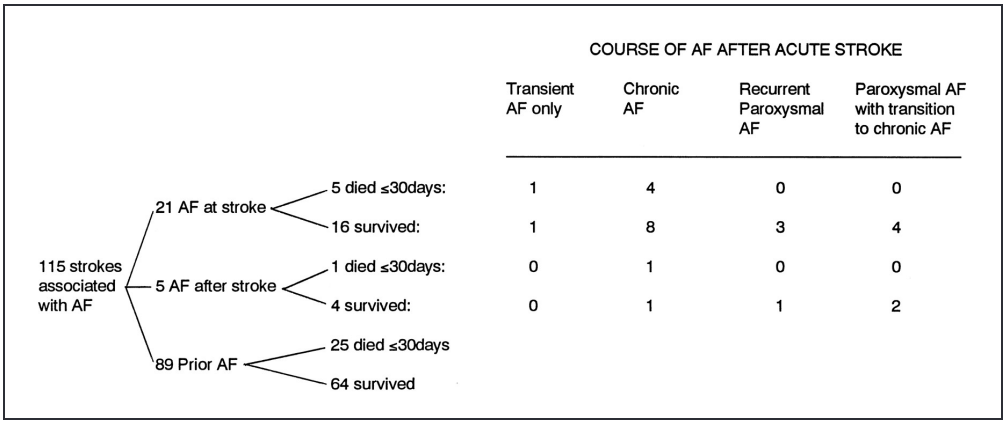

Figure 1. Distribution of stroke subjects associated with atrial fibrillation (AF) according to time of onset of AF. All but 2 of 26 subjects with AF first ascertained at the time of stroke had subsequent recurrent or chronic AF.

Table 1. Distribution of Sex, Age, and Stroke Subtype in 115 Stroke Subjects Associated With AF (Table view)

	Prior AF	AF on Admission	AF After Admission
No.	89	21	5
% men	37	48	60
Age range, y (median)	44-97 (75)	63-94 (82)	66-84 (72)
Stroke subtype, ischemic/hemorrhagic	86/3	20/1	5/0

AF indicates atrial fibrillation.

Table 2. Types of AF in 26 Stroke Subjects With Newly Diagnosed AF (Table view)

Type of AF	21 Subjects With AF on Admission		5 Subjects With AF After Admission		
	No. (%)	Length of Follow-up	No. (%)	Day Poststroke at Diagnosis of AF	Length of Follow-up
Chronic AF	12 (57)	3 d-74 mo	2 (40)	3, 13	19 d, 1 mo
Recurrent paroxysmal AF	3 (14)	26 mo-100 mo	1 (20)	3	22 mo
Paroxysmal AF with transition to chronic AF	4 (19)	4 mo-62 mo	2 (40)	2, 14	62 mo, 112 mo
Transient AF only	2 (10)	3 d, 32 mo	0 (0)	…	…

AF indicates atrial fibrillation. For definitions of types of AF, refer to text.

ARTICLE INFORMATION

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Note

Reprint requests to Philip A. Wolf, MD, Boston University School of Medicine, Department of Neurology, 80 E Concord St, B-608, Boston, MA 02118. E-mail wolf@med-neurog.bu.edu.

Affiliations

From the Department of Neurology, Boston University School of Medicine (H.-J.L., P.A.W.); Cardiology Section, Boston City Hospital, Boston University School of Medicine (E.J.B.); Department of Mathematics, Boston University (A.J.B., R.B.D'A.); and the Framingham Study, National Heart, Lung, and Blood Institute, Framingham, Mass. .

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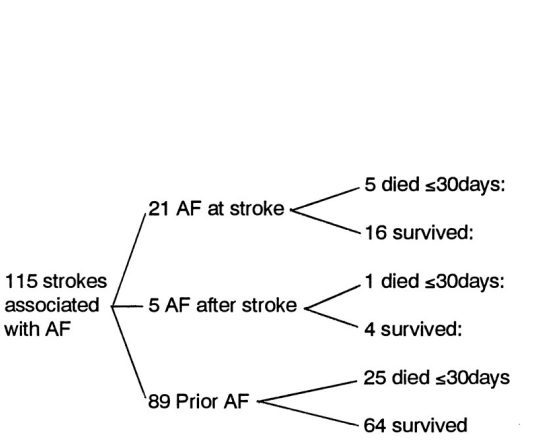
Sections

LIST OF ILLUSTRATIONS



	COURSE OF AF AFTER ACUTE STROKE			
	Transient AF only	Chronic AF	Recurrent Paroxysmal AF	Paroxysmal AF with transition to chronic AF
5 died ≤30days:	1	4	0	0
16 survived:	1	8	3	4
1 died ≤30days:	0	1	0	0
4 survived:	0	1	1	2

Figure 1. Distribution of stroke subjects associated with atrial fibrillation (AF) according to time of onset of AF. All but 2 of 26 subjects with AF first ascertained at the time of stroke had subsequent recurrent or chronic AF.

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