Lone Atrial Fibrillation in Elderly Persons
A Marker for Cardiovascular Risk

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**Background:** The risk of stroke in persons aged 60 years and younger with lone atrial fibrillation (LAF) is no greater than in the general population. The effect of older age on the risk of stroke in persons with LAF is less well established.

**Participants and Methods:** The risk of stroke in persons with LAF and without substantial comorbidities was examined in a population-based study at a single institution in Olmsted County, Minnesota, and compared with that in an age- and sex-matched population. The mean age was 74 years (range, 61-97 years). The median duration of follow-up was 9.6 years until death or last follow-up.

**Results:** Of 55 patients, 26 had 31 cardiovascular events during follow-up, occurring a median of 5.1 years after diagnosis (range, 0.7-18 years). Of 11 cerebrovascular events, 6 were transient ischemic attacks and 5 were strokes. The event rates (percentage per person-year) were 0.9% for stroke, 1.1% for transient cerebral ischemia, and 2.6% for myocardial infarction, for a total cardiovascular event rate of 5.0% per person-year. The corresponding rates for the age- and sex-matched control group were 0.2%, 0%, and 1.1%, for a total of 1.3% per person-year. The incidence of total cardiovascular events was significantly greater ($P<.01$) in those with LAF, although there was no difference in survival.

**Conclusion:** Lone atrial fibrillation occurring after age 60 years is a risk marker for a substantial increase in cardiovascular events that warrants consideration for antithrombotic therapy.

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The absence of a consensus about thromboembolic risk in patients with lone atrial fibrillation (LAF) derives in part from its definition and in part from the infrequency with which LAF is diagnosed within a single institution or medical practice. Different patient populations with nonvalvular heart disease and different clinical characteristics have different event rates of thromboembolism. A previous study of patients aged 60 years and younger with LAF (and no hypertension) at our institution documented a low incidence of thromboembolism, leading to the conclusion that long-term anticoagulant therapy probably was not justified in such patients in the absence of documented embolism. These findings seemed to be at variance with a Framingham study report in which the patient population was older and hypertension was not excluded. For these reasons, the present study was designed to test the hypothesis that LAF is associated with a higher risk of thromboembolic cerebrovascular and cardiovascular events in patients older than 60 years than in younger patients.

The study included patients aged 61 years and older who had no evidence of a previous stroke or other cardiovascular disease and no hypertension (even if treated) and who were residents of Olmsted County, Minnesota. The objective was to determine survival and the probability of thromboembolic episodes compared with the probability of such events in an age- and sex-matched sample of the population with no previous stroke or cardiovascular diagnoses.

**RESULTS**

The ages of the patients at the time of diagnosis were as follows: 61 to 70 years, 18 men and 4 women; 71 to 80 years, 7 men and 13 women; and 81 to 97 years, 6 men and 7 women (total, 55 patients). The mean age was 74 years (range, 61-97 years). The median duration of follow-up was 9.6 years until death or last follow-up. No patients were unavailable for follow-up. Follow-up was predominantly in the 1960s and 1970s, which was before the frequent use of warfarin sodium.

At the time of diagnosis, the following ECG abnormalities were noted in ad-
PATIENTS AND METHODS

PATIENT SELECTION

The diagnostic index of the medical records of all patients aged 61 years and older who were residents of Olmsted County and were seen at the Mayo Clinic, Rochester, Minn, between 1950 and 1980 was reviewed. During this period, 2,593 such patients had a diagnosis of atrial fibrillation noted in the diagnostic index. As in the previous study of younger patients with LAF, any patient with 1 of the following features at the time of the initial diagnosis of atrial fibrillation was excluded: previous or concurrent stroke; coronary artery disease according to clinical or laboratory criteria; hyperthyroidism; valvular heart disease; congestive heart failure; cardiomyopathy; chronic obstructive pulmonary disease; cardiomegaly apparent on a chest radiograph; hypertension treated with medications or a mean systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg on 3 separate occasions; lack of electrocardiographic (ECG) documentation of atrial fibrillation; identifiable and potentially life-shortening noncardiac disease (including type 1 diabetes mellitus); and the occurrence of atrial fibrillation only during trauma, surgery, or an acute medical illness. The duration of atrial fibrillation before this diagnosis was unknown.

Only a small percentage of these patients underwent coronary arteriography or exercise stress testing; thus, the diagnosis of the presence or absence of coronary artery disease was made in most cases on the basis of the history or evidence of previous ischemic events on ECG. Fifty-five patients (31 men and 24 women) aged 61 years or older were identified as having LAF. This is a separate group from our original study of patients aged 60 years or younger.1

STATISTICAL METHODS

Survival free of stroke and survival rates were estimated by the Kaplan-Meier product-limit method.3 Data for patients without a stroke were censored at the time of their last follow-up or at the time of their death from a cause other than stroke.

At the time of diagnosis, the isolated form (isolated atrial fibrillation defined as having only 1 documented occurrence) of LAF was present in 7 patients (13%); the recurrent form in 16 (29%), and the chronic form in 32 (58%). By the end of the follow-up period, recurrent LAF had become chronic in 5 patients and continued to be recurrent in 11.

Patients with LAF in this study were otherwise relatively healthy because of the exclusion criteria noted. This produces a bias for the comparison of survival and stroke rates with an age- and sex-matched sample from the general population. Therefore, a control group of patients from Olmsted County with similar baseline characteristics was defined as follows. In 1978, a random 10% sample of the population of Olmsted County was selected. From that sample, we randomly selected patients in different age groups so that we could evaluate about 1% of the population aged 45 to 54 years, 2.5% of the population aged 55 to 64 years, and 3.5% of the population aged 65 years and older. The intent was to have a sample of the population weighted for the older age groups. The patients who were selected were initially contacted by telephone. Those who were unwilling to be examined for any reason, including infirmity, were replaced by a random selection of others in the same age and sex group.

Those who participated had a standardized examination, including a health inventory, with particular attention to cerebrovascular and cardiovascular history. The examination included blood pressure and pulse measurements and auscultation of the heart, neck, and orbits in the sitting and lying positions. The 509 persons who were evaluated were followed up by a standardized follow-up questionnaire every 6 months and through the medical record linkage system at the time of any medical contact.4 The patients with LAF were observed by a review of their medical records at the time of medical contact.

From this sample of 509 patients, those who had hypertension; type 1 diabetes mellitus; any type of stroke, including transient ischemic attack (TIA) or amaurosis fugax; evidence of coronary artery disease; second- or third-degree heart block; congestive heart failure; or atrial fibrillation or atrial flutter were excluded. Among the remaining 147 persons, 55 were matched as controls by age and sex to the 55 patients with LAF. Forty-six were matched exactly for year of age, 3 were within 1 year, 3 were within 2 years, 1 was within 3 years, 1 was within 4 years, and 1 was within 5 years.

The rates of survival and survival free of stroke were compared with those of the age- and sex-matched control group by the log-rank test.5 The event rates in patients with LAF and the matched control group were calculated using person-year analysis. The McNemar χ² and paired 2-tailed t tests were used to compare various event rates between the case-control matched pairs.

DEATHS

Thirty-seven of the 55 patients were dead at last follow-up: 10 of sepsis, 5 of myocardial infarction, 5 of cancer, 4 of sudden cardiac death, 4 of congestive heart failure (including 1 patient in whom valvular disease had developed), and 2 of stroke. One patient each died of the following causes: renal failure, suicide, amyotrophic lateral sclerosis, chronic pancreatitis, gastrointestinal tract hemorrhage, widespread arteriosclerosis, and pulmonary embolism.

The estimated survival (mean ± SE) was 80% ± 5% at 5 years and 57% ± 7% at 10 years for patients with LAF. This was not significantly different from that of the age-and sex-matched controls: 89% ± 4% at 5 years and 68% ± 7% at 10 years (P = .20, log-rank test). Survival among the subgroups with isolated, recurrent, or chronic atrial fibrillation at diagnosis was not significantly different.
OTHER CARDIOVASCULAR EVENTS

Twenty-six of the 55 patients had 31 cardiovascular events (including deaths with cardiovascular events) during follow-up, and they occurred at a median of 5.1 years after diagnosis (range, 0.7-18 years) (Table 1). Of the 11 cerebrovascular events, 6 were TIAs and 5 were ischemic strokes; in 1 patient, the TIA was considered to be due to carotid occlusive disease. The probability of survival free of stroke was 96% at 5 years and 91% at 10 years, not significantly different from that in the controls: 98% at 5 years and 98% at 10 years (P = .15, log-rank test). In patients with chronic atrial fibrillation, the probability of survival free of stroke was 93% at 5 years and 89% at 10 years.

The survival rates free of stroke or TIA, whichever was first, were 90% at 5 years and 80% at 10 years for the patients with atrial fibrillation and 98% at 5 years and 98% at 10 years for the age- and sex-matched controls. The difference was significant (P < .01, log-rank test).

Four patients had pulmonary emboli, all after a prolonged period of bed rest, evidence of deep vein thrombosis, or both. Although listed in Table 1, these were not considered to be the consequence of atrial fibrillation. Fourteen patients had myocardial infarctions (mean age, 78 years; range, 69-91 years), with evidence of underlying coronary artery disease in most. The survival rates free of myocardial infarction in the patients with LAF at baseline were 88% at 5 years and 69% at 10 years, significantly different from the 92% and 89% at 5 and 10 years, respectively, in the controls (P = .02, log-rank test). The event rates of cardiovascular events, determined by the person-years method, are listed in Table 2. The overall cardiovascular event rate of 5.0% per person-year is notably high.

Nine patients had dementia during the follow-up period, and their records were reviewed again by a neurologist (J.P.W.). Six other patients had dementia diagnosed before or within 30 days after the diagnosis of atrial fibrillation and were excluded from this analysis of the occurrence of dementia. The incidence of dementia in this cohort was not significantly different from the expected—5.2 patients—derived from incidence rates from the age- and sex-matched Rochester population.

DEVELOPMENT OF OTHER DISEASES

Cardiac diagnoses other than myocardial infarction made during the period of follow-up were as follows: mitral regurgitation of varying severity (4 patients), mild aortic stenosis (2 patients), aortic nodular sclerosis (3 patients), coronary artery disease (8 patients), permanent pacemaker implantation (1 patient), and other cardiac surgery (1 patient). In the follow-up period, 14 patients underwent echocardiographic examinations, during which increased left atrial size was noted in 8 patients, calcification of the mitral annulus in 9 patients, aortic valve sclerosis in 9 patients, mitral valve in 1 patient, and asymptomatic ruptured chordae in 1 patient.

MEDICATIONS

Fifty-one of the 55 patients had received cardiac medications during follow-up: digoxin (50 patients), quinidine sulfate (9 patients), propranolol hydrochloride (8 patients), aspirin (4 patients), and dipyridamole (1 patient) (some patients were taking multiple drugs). Nine patients were treated with warfarin (mean duration, 3.1 years); of these, 4 had a TIA before the use of warfarin and no further cerebrovascular episodes during a treatment period of 1 to 10 years, 2 had a stroke before the warfarin treatment, and 3 had no cerebrovascular events before treatment.

This study provides strong evidence that the risk of cerebral ischemic events is increased in elderly patients with LAF in comparison with the risk in age- and sex-matched control patients with an equivalent absence of other cardiovascular diseases. These data contrast with the low risk...
of thromboembolism seen in younger patients (≤60 years old) with LAF from the same population base. Cumulative event rates of TIA and myocardial infarction were significantly higher—5.0% per person-year compared with 1.3% per person-year in the controls (Table 2).

Our study resolves some of the apparent discrepancies in previously reported estimates of thromboembolic risk in patients with LAF. Because the risk of thromboembolism apparently is influenced by age in populations that are otherwise clinically identical (both derived from a single stable population with consistent, rigorously documented follow-up), the definition of the study population is critically important. The previous report1 from this institution presented results that differed from those of several reports from the Framingham cohort,2-7 a non–population-based study,7,10 and a large randomized study,11 all of which included older patients.

This and the previous study1 included a unique, rigorously defined study population without hypertension (even under treatment) or any suggestion of cardiovascular or pulmonary disease and thus encompassed only 2% to 3% of all patients with atrial fibrillation. This allowed the evaluation of the effect of atrial fibrillation alone on the incidence of stroke and TIA in the absence of evidence of other cardiovascular disease. The previous study confirmed the absence of an increased risk of stroke when atrial fibrillation is present in otherwise healthy patients without hypertension who are aged 60 years and younger.1 This was also suggested prospectively in the Stroke Prevention in Atrial Fibrillation study,12 in which none of 70 such patients had stroke or TIA. The present study suggests that age plays a major role in the incidence of stroke in these otherwise apparently healthy patients, probably through the associated development of atherosclerotic vascular disease.

The Framingham study13,14 confirms that the risk of stroke increases with age in those with atrial fibrillation, as in our study. Patients in the Framingham study were excluded if they had evidence of rheumatic valvular disease, and all others were included. Moreover, in more than a third of the 68 cases of stroke in the cohort of 303 patients identified during the 30-year study, atrial fibrillation was first diagnosed at the time of the stroke. Both of these factors tend to overestimate the risk of stroke if the data derived from this study are applied to patients with stringently defined LAF before the thromboembolic event. Wolf et al14 estimated that the risk of stroke attributable to atrial fibrillation (after adjustment for other cardiovascular conditions) was 8.5% in patients aged 60 through 69 years, 18.8% at 70 through 79 years, and 30.7% at 80 through 89 years. In a previous study,2 the Framingham group excluded patients whose diagnosis of atrial fibrillation was made at the time of stroke but, nevertheless, found a 4-fold increase in the risk of stroke in the 30 patients studied. The mean age of the patients was approximately 70 years at the start, and the strokes occurred at a mean of 8.5 years into follow-up, thus reflecting an elderly population.

In the Framingham study, many patients had a history of controlled hypertension, but patients with overt hypertensive heart disease were excluded. Nonetheless, the powerful effects of hypertension on the risk of stroke in patients with nonrheumatic atrial fibrillation were recently highlighted in a study12 of patients in the Stroke Prevention in Atrial Fibrillation trial who were treated with placebo. Hypertension was 1 of the 3 major risk factors for stroke, and the risk increased from 2.5% per year in patients with no risk factors to 7.2% per year in patients with 1 of the 3 risk factors (including hypertension). This would explain the high risk of stroke in the Framingham study that included an older population, many of whom had hypertension.

In patients aged 60 years and younger with LAF, the risk of stroke, TIA, or myocardial infarction is small at 1.5 events per 100 patient-years and occurs mainly late in follow-up, whereas in older patients, the risk is appreciably higher at 50 events per 100 patient-years. This may relate in part to the presence of subclinical atherosclerotic cardiovascular disease, increasing blood pressure with age, increasing left ventricular dysfunction, or left atrial enlargement.12,13,15 Also, a higher incidence of coronary artery disease may have been found in the control population because there were more sensitive diagnostic techniques available in 1978.

The therapeutic implications are better defined but not finalized. Based on pathogenesis and risk,16 the risk of stroke is so low among the younger age group that it does not warrant the risk of anticoagulation therapy and the inconvenience of regular monitoring. Because the incidences of stroke, TIA, and myocardial infarction all increase after age 60 years, antithrombotic treatment should be considered if not contraindicated.17-19 Some20-28 (but not all) studies have reported that there is a risk of bleeding in this population. Two studies,29,30 however, have documented a greater response to anticoagulant treatment with increasing age. In 2 recent retrospective studies31,32 of patients receiving long-term anticoagulant therapy, there was no association between age and bleeding complications.

The Stroke Prevention in Atrial Fibrillation II randomized clinical trial33 showed no significant difference in the occurrence of ischemic stroke and systemic embolism between patients receiving treatment with warfarin and those being treated with aspirin. Oral anticoagulant treatment, however, was more beneficial than aspirin therapy in patients with nonrheumatic atrial fibrillation who had a recent TIA or minor ischemic stroke.34 Oral anticoagulant treatment was also more beneficial than low-dose (75-mg) aspirin therapy for the primary prevention of thromboembolic events in patients with atrial fibrillation.35

Although the long-term population-based method of this historical cohort study enhances the reliability, potential weaknesses should be recognized. Treatment was not randomized, although few patients received anticoagulant treatment. The number of patients is relatively small, but this is a consequence of adhering strictly to a clinical definition of LAF in a geographically defined population. Despite careful attention to exclusion criteria, it is possible, or even likely, that occult cardiovascular disease may have been present in some patients and in some controls. This may have led to overestimating the rate of events. Cardiovascular disease risk factors were incomplete in our cohort and, therefore, not reported. This small cohort may not have had an equal incidence of cardiovascular risk factors such as smoking or hyperlipidemia compared with the control group, and this may have affected the mechanism
and incidence of thromboembolic events. Nine patients received anticoagulant therapy at various times for limited durations, at the discretion of the clinician; this may have resulted in an understimation of the actual unmedicated-event rate and decreased the difference from the control group. A relatively high incidence of dementia in these patients was observed during follow-up, but the incidence of dementia was not significantly higher than that in the population in the same age and sex distribution.

The moderately high risk of cardiovascular events suggests that if patients have a thromboembolic stroke, they should be treated with warfarin if there is no contraindication to treatment. In this study, only 4 patients were taking long-term aspirin therapy, which reflects the fact that this sample was drawn from patients starting in 1950. This is a strength of the study because it gives a true natural history of the disease without medical intervention, although it may make it less applicable to today's patient population. Nine patients were treated with warfarin in this study; in 4, treatment was started after the occurrence of a TIA, and these patients had no cerebrovascular episode during the treatment period. The low-risk cohort study in the Stroke Prevention in Atrial Fibrillation III trial found that about 5% of patients per year had high-risk criteria for stroke—hypertension, heart failure, TIA or stroke, or women older than 75 years—and it should be emphasized that patients should be observed annually for the occurrence of these risk factors. If a risk factor appears, then it is reasonable to reassess the patient for long-term anticoagulation therapy. 25

CONCLUSIONS

This study, our previous study, 1 and the Framingham study 13,18 are complementary. Younger patients—aged 60 years and younger—without hypertension are at low risk, older patients without hypertension can be considered at an increased but intermediate risk, and older patients with hypertension are at a much higher risk. The key to the most effective use of aspirin or warfarin in patients with non-rheumatic atrial fibrillation depends on an assessment of their risk of stroke and the risk of bleeding while receiving antithrombotic therapy. The data from these 3 studies of patients with LAF provide information for risk stratification and the choice of therapy in an individual patient. The importance of these observational cohort studies is determined by the paucity of patients with LAF in the randomized trials and their relatively short follow-up.

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REFERENCES