Long-Term Progression and Outcomes With Aging in Patients With Lone Atrial Fibrillation

A 30-Year Follow-Up Study

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Background—The long-term natural history of lone atrial fibrillation is unknown. Our objective was to determine the rate and predictors of progression from paroxysmal to permanent atrial fibrillation over 30 years and the long-term risk of heart failure, thromboembolism, and death compared with a control population.

Methods and Results—A previously characterized Olmsted County, Minnesota, population with first episode of documented atrial fibrillation between 1950 and 1980 and no concomitant heart disease or hypertension was followed up long term. Of this unique cohort, 76 patients with paroxysmal (n=34), persistent (n=37), or permanent (n=5) lone atrial fibrillation at initial diagnosis met inclusion criteria (mean age at diagnosis, 44.2±11.7 years; male, 78%). Mean duration of follow-up was 25.2±9.5 years. Of 71 patients with paroxysmal or persistent atrial fibrillation, 22 had progression to permanent atrial fibrillation. Overall survival of the 76 patients with lone atrial fibrillation was 92% and 68% at 15 and 30 years, respectively, similar to 86% and 57% survival for the age- and sex-matched Minnesota population. Observed survival free of heart failure was slightly worse than expected ($P=0.051$). Risk for stroke or transient ischemic attack was similar to the expected population risk during the initial 25 years of follow-up but increased thereafter ($P=0.004$), although CIs were wide. All patients who had a cerebrovascular event had developed ≥1 risk factor for thromboembolism.

Conclusions—Comorbidities significantly modulate progression and complications of atrial fibrillation. Age or development of hypertension increases thromboembolic risk. **(*Circulation*. 2007;115:3050-3056.)**

Key Words: arrhythmia ■ fibrillation ■ risk factors ■ survival

Atrial fibrillation is a heterogeneous disorder with variable origin, clinical profile, and natural history.[1–3] In young patients without structural heart disease, atrial fibrillation usually occurs in a paroxysmal or persistent form, whereas in the elderly with structural heart disease, it is more commonly permanent.[4] In experimental models, it has been shown that "atrial fibrillation begets atrial fibrillation," and it is widely believed that over the long term, atrial fibrillation progresses in frequency and duration to become permanent.[5,6] However, whether permanent atrial fibrillation is the end stage of progression from paroxysmal forms or whether patients with paroxysmal and permanent arrhythmia represent 2 distinct populations is unknown. In patients in whom atrial fibrillation progresses, predictors of progression are not well defined. In addition, the long-term risk of mortality, heart failure, and stroke with advancing age in patients who initially present at a young age with lone atrial fibrillation is unclear.

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The purpose of the present study was to determine the rate and predictors of progression from paroxysmal to permanent atrial fibrillation over 30 years in young persons initially presenting without structural heart disease.[7] Another objective was to determine the long-term risk of heart failure, thromboembolism, and death in all patients with lone atrial fibrillations compared with the age- and sex-matched Minnesota population. The extended follow-up provides a unique opportunity to examine the relation between the rhythm disturbance and the development of comorbidities over time.

Methods

Study Population

We previously defined a population of Olmsted County, Minnesota, residents who were <60 years of age when atrial fibrillation was

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From the Divisions of Cardiovascular Diseases (A.J., V.L., P.A.F., J.M.T., S.L.K., D.L.P., S.C.H., W.-K.S., B.J.G.) and Biostatistics (D.O.H.), Mayo Clinic, Rochester, Minn.

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initially documented by ECG.[7] Patients included in the study had a first episode between 1950 and 1980 and had no concomitant heart disease or hypertension. Patients with any of the following at initial diagnosis were excluded: coronary artery or valvular heart disease (including mitral valve prolapse); cardiomyopathy; cardiomegaly on chest radiography; preexcitation syndrome; history of congestive heart failure; stroke or transient ischemic attack; treated hypertension, a mean systolic blood pressure >140 mm Hg, or a mean diastolic blood pressure >90 mm Hg on 3 separate occasions; hyperthyroidism; chronic obstructive pulmonary disease; or noncardiac diseases that potentially could shorten the lifespan (including insulin-dependent diabetes mellitus). We required manual review of all the charts of patients in the original cohort and informed consent for chart review. By this process, with our current entry criteria, 21 patients initially reported were not included in the present study. An echocardiogram was not available at diagnosis for most of these patients. Patients with permanent atrial fibrillation at diagnosis or with atrial fibrillation related to surgery, trauma, or acute medical illness (such as pulmonary embolus or sepsis) also were excluded from the analysis of progression. For long-term outcome (mortality, heart failure, and stroke/transient ischemic attack), all patients with lone atrial fibrillation, including those with permanent atrial fibrillation at diagnosis, were analyzed. Of this unique cohort, those who had paroxysmal or persistent atrial fibrillation and were followed up long term were included for progression to permanent atrial fibrillation. The research proposal was approved by the Institutional Review Board of the Mayo Foundation.

Follow-Up Evaluation

The Mayo Clinic serves as a primary care institution for residents of Olmsted County, Minnesota, and follow-up visits for the 76 patients with lone atrial fibrillation were scheduled as needed. Follow-up information was obtained from the Mayo Clinic comprehensive inpatient and outpatient medical record system.[8] Follow-up began after the initial diagnosis of atrial fibrillation and continued until either October 2003 or death (median, 26.8 years; range, 2.5 to 42.2 years). Patients who had moved from the county and were alive were contacted by telephone. Information beyond 7 years after the diagnosis of atrial fibrillation could not be obtained for 3 patients (follow-up information was available for 2.5, 6.4, and 6.8 years). Person-years of follow-up were calculated from the date that atrial fibrillation was identified.

Atrial fibrillation was defined as paroxysmal if it terminated spontaneously without intervention, as persistent if medication or electrical intervention was required to restore sinus rhythm, and as permanent if sinus rhythm could not be restored or maintained despite intervention. All clinical records, including history and physical examination reports, laboratory results, ECGs, and Holter monitoring data for every outpatient encounter and hospital admission, were reviewed. Patients were classified as progressors if permanent atrial fibrillation developed.

Cause of death was determined from review of hospital records, death certificate, or autopsy report and classified as cardiovascular (acute myocardial infarction, heart failure, thromboembolic), sudden arrhythmic (within 1 hour after symptom onset or with documented arrhythmia), noncardiac, or unknown. Congestive heart failure was defined by clinical symptoms (dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea), physical examination (elevated jugular venous pressure, peripheral edema, weight gain), or pulmonary congestion on chest x-ray. Stroke was defined as a neurological deficit lasting >24 hours; transient ischemic attack was defined as a neurological deficit resolving within 24 hours. In the event of stroke or thromboembolic event, all records were reviewed, and the event was classified as definitely, possibly, or definitely not embolic (Clear evidence of cerebral hemorrhage or stenotic or severely atherosclerotic vessel in the clinically defined anatomic distribution).

Statistical Analysis

The study outcomes were long-term progression of lone paroxysmal or persistent atrial fibrillation to permanent atrial fibrillation and overall mortality, mortality from cardiovascular causes, and congestive heart failure or stroke/transient ischemic attack in all study patients. Rates for these end points were estimated with the Kaplan-Meier method. Expected survival was estimated using age- and sex-specific mortality rates obtained from the state of Minnesota. Expected rates of congestive heart failure and stroke/transient ischemic attack were obtained from age- and sex-specific incidence rates in Olmsted County. Observed event rates in lone atrial fibrillation patients were compared with expected rates using a 1-sample log-rank test. Development of risk factors for progression to permanent atrial fibrillation, mortality, congestive heart failure, or stroke/transient ischemic attack was evaluated with Cox proportional hazards models. Multivariable models were constructed from the stepwise selection technique. Only factors with a univariate value of $P<0.10$ were used as potential predictors for the multivariable models. Entry and exit probability values for this selection were 0.05. The proportional hazards assumption was tested for each of the potential predictors for each end point. Potential risk factors that were investigated included age, gender, preexisting arrhythmias, other systemic disease, smoking, alcohol use, caffeine use, stress, spontaneous trigger, abnormal QRS repolarization abnormalities on ECG, use of class I drugs, history of murmur, use of digoxin, body mass index, and heart rate.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Demographic Characteristics

A total of 3623 residents of Olmsted County with the diagnosis of atrial fibrillation were evaluated at the Mayo Clinic between 1950 and 1980.[7] This population has been described previously.[7] Present study entry criteria were met by 76 patients with lone atrial fibrillation: paroxysmal in 34, persistent in 37, and permanent in 5 at diagnosis. Baseline characteristics of these patients are summarized in Table 1. Mean age at the time of diagnosis of lone atrial fibrillation was 44.2±11.7 years; 50% of patients were ≥45 years of age, and 78% were male. Mean duration of follow-up was 25.2±9.5 years (median, 26.8 years; range, 2.5 to 42.2 years). Follow-up was short for 8 patients: Three were lost to follow-up, and 5 died within 10 years (5.4, 5.9, 6.0, 8.7, and 9.7 years) after diagnosis.

Progression to Permanent Atrial Fibrillation

Of the 76 patients, 5 had permanent atrial fibrillation at diagnosis and were excluded from the analysis of progression. Of the remaining 71 patients with paroxysmal or persistent atrial fibrillation who were at risk for progression, 22 had progression to permanent atrial fibrillation with a 30-year cumulative probability of 29% (95% CI, 16 to 42; Figures 1A and 2). In most of these patients, progression to permanent atrial fibrillation occurred within 15 years after diagnosis (Figure 1A). During follow-up, 22 patients received treatment with a class I or III antiarrhythmic agent (quinidine, 15 patients; propafenone, 2 patients; flecainide, 2 patients; sotalol, 2 patients; and amiodarone, 1 patient). At the latest follow-up or time of death, 63 patients were receiving treatment with an atrioventricular node–slowing agent (digoxin, 57 patients; β-blocker, 7 patients; and calcium channel blocker, 1 patient); 37 were receiving an antiplatelet agent (aspirin, 29 patients; dipyridamole, 4 patients; and clopidogrel, 4 patients); and 24 patients were taking warfarin.

TABLE 1. Baseline Characteristics of 76 Patients With Lone Atrial Fibrillation Diagnosed Between 1950 and 1980

Characteristic	Value
Age at documentation of AF, mean±SD (range), y	44.2±11.7 (15 to 60)
Age distribution	
<30 y	11 (14)
31 to 40 y	18 (24)
41 to 50 y	21 (28)
51 to 60 y	26 (34)
AF type at diagnosis	
Paroxysmal	34 (45)
Persistent	37 (49)
Permanent	5 (7)
Men, n (%)	59 (78)
Body mass index, mean±SD, kg/m^2	27.6±6.0
History of smoking	39 (51)
Any alcohol use	42 (55)
Caffeine use	48 (63)
History of supraventricular tachycardia or premature complexes	17 (22)
ECG	
QRS complex abnormalities	8 (11)
Repolarization abnormalities	32 (42)
Conduction disease	2 (3)
Left atrial enlargement	0
Left ventricular hypertrophy	1 (1)
Use of antiarrhythmics within 30 d of initial diagnosis of AF, % of patients	
Class I	9
Class III	0
β-Blocker or calcium channel blocker	8
Digoxin	34

Values are n (%) unless otherwise noted. AF indicates atrial fibrillation.

Predictors of Progression to Permanent Atrial Fibrillation

Older age at diagnosis and presence of QRS abnormalities on ECG were univariate predictors of progression to permanent atrial fibrillation (Figure 1 and Table 2). For every decade of age at the time of the initial diagnosis of atrial fibrillation, the independent risk of progression increased 1.7-fold (95% CI, 1.1 to 2.8; $P=0.023$; Figure 1B). The presence of QRS abnormalities on ECG (prolonged QRS duration of 110 to 120 ms, notching or slurring of the QRS complex, or low anterior forces with small R waves in the precordial leads) was associated with a 3-fold increase in risk of progression (hazard ratio [HR], 3.2; 95% CI, 1.1 to 10.0; $P=0.041$; Figure 1C). The presence of premature supraventricular complexes or supraventricular tachycardia on ECG or Holter recording was protective and associated with decreased risk of progression to permanent atrial fibrillation (HR, 0.1; 95% CI, 0.02 to 1.0; $P=0.048$; Figure 1D). Sex, body mass index, history of smoking, or alcohol or caffeine use was not associated with increased risk of progression. In the multivariable model, age was the sole independent predictor of progression in this group of patients.

Overall Survival

Overall survival of patients with lone atrial fibrillation was 92% and 68% at 15 and 30 years, respectively, similar to the 86% and 57% rates for the age- and sex-matched Minnesota population ($P=0.12$, log-rank test; Figure 3A). Of the 76 patients with lone atrial fibrillation, 27 died during the 30-year follow-up. Mean age of patients who died was 76.0±12.7 years compared with 65.4±14.4 years for those who were alive at the latest follow-up. The mean interval from initial diagnosis of atrial fibrillation to death was 25.2±9.5 years (range, 2.5 to 42.2 years). No sudden cardiac deaths occurred; 12 deaths were related to cardiovascular disease and 15 to noncardiovascular causes. Four patients died of progressive congestive heart failure resulting from severe mitral regurgitation (2 patients), nonischemic dilated cardiomyopathy (1 patient), and restrictive cardiomyopathy (1 patient). Five patients died after acute myocardial infarction, and 3 died of complications after stroke. Noncardiovascular deaths were as follows: respiratory failure in 6 patients with chronic obstructive pulmonary disease or pneumonia; malignancy in 4; and sepsis, pulmonary embolism after deep venous thrombosis, acquired immunodeficiency disease, liver cirrhosis, and Alzheimer's disease in 1 each.

Survival Free of Congestive Heart Failure

During follow-up, congestive heart failure was diagnosed in 14 patients. Mean age at initial diagnosis of congestive heart failure was 74.1±12.4 years (range, 43 to 92 years), and the mean interval from the diagnosis of atrial fibrillation to development of congestive heart failure was 24.9±8.9 years (range, 13 to 41 years). Overall, observed survival free of congestive heart failure in patients with lone atrial fibrillation tended to be slightly worse than expected but was not significant ($P=0.051$; Figure 3B). The probability of survival free of congestive heart failure in patients with lone atrial fibrillation was 97% at 15 years and 81% at 30 years compared with expected rates of 97% and 85%, respectively ($P=0.051$, log-rank test). Congestive heart failure was considered to be due to rapid ventricular rate response in 5 patients: 3 with well-preserved left ventricular function (left ventricular ejection fraction, 0.63, 0.65, and 0.61) and 2 with tachycardia-induced cardiomyopathy with left ventricular ejection fraction of 0.35 and 0.40 at initial presentation with congestive heart failure, which subsequently normalized (left ventricular ejection fraction, 0.65 and 0.60, respectively) after rhythm control. Other causes of congestive heart failure were left ventricular dysfunction after acute myocardial infarction (left ventricular ejection fraction, 0.28±0.10) in 2 patients, nonischemic cardiomyopathy (left ventricular ejection fraction, 0.33±0.05) in 2, valvular heart disease in 3, and restrictive cardiomyopathy (left ventricular ejection fraction, 0.70) in 1; congestive heart failure was considered related to uncontrolled hypertension in 1 patient.

Survival Free of Stroke or Transient Ischemic Episode

The risk for stroke/transient ischemic attack was similar to that of the expected population risk during the initial 25 years of follow-up but increased thereafter (Figure 3C). The prob-

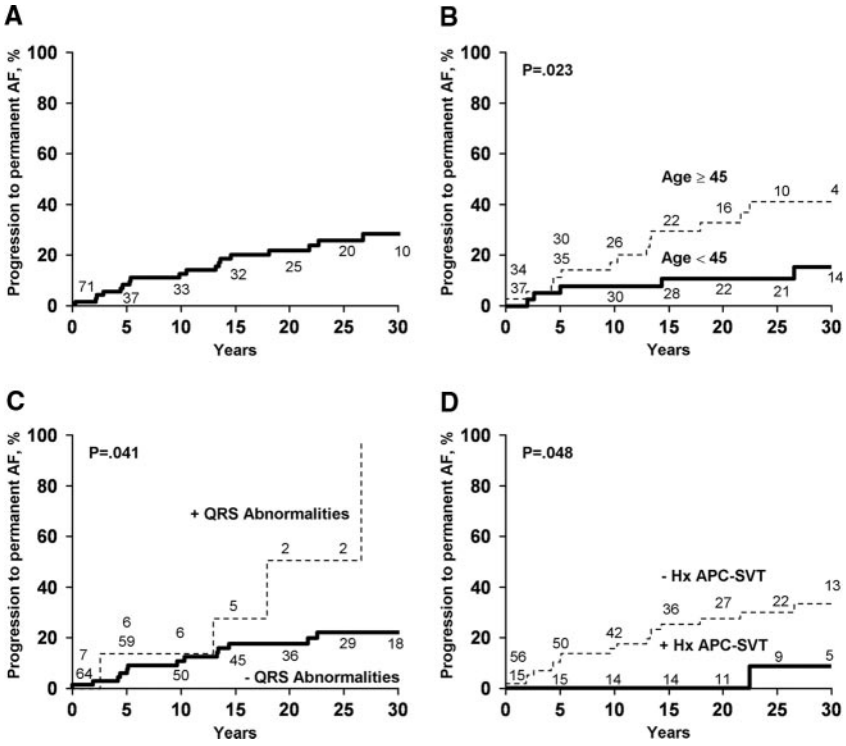

Figure 1. Long-term progression of paroxysmal or persistent lone atrial fibrillation (AF) to permanent AF (A) according to age at diagnosis (B), presence of QRS abnormalities (C), or history (Hx) of premature complexes (APC) or supraventricular tachycardia (SVT; D).

ability of survival free of stroke/transient ischemic attack was 94% at 15 years and 88% at 25 years (similar to expected rates of 96% and 89%, respectively) but was significantly worse at 30 years (72% versus 85% in expected; $P=0.004$, log-rank test). Of the 17 cerebrovascular events (5 strokes, 12 transient ischemic attacks) observed over the 30-year follow-up, 10 occurred in those with permanent atrial fibrillation and 7 in those with paroxysmal or persistent atrial fibrillation. Four of these neurological events were characterized as embolic, 3 as probably embolic in patients who had underlying atherosclerotic vascular disease, and 6 as nonembolic; in 4, the cause of transient ischemic attack could not be ascertained. In patients with nonembolic cerebrovascular event, 3 had severe atherosclerotic cerebrovascular disease and 2 had intracranial hemorrhage (1 with brain tumor, 1 with subdural hematoma). Symptoms and signs of stroke in 1 patient were subsequently found to be due to hemangioblastoma of the cervical spinal cord. The mean age of patients who had stroke/transient ischemic attack was 73.6±10.7 (range, 54.2 to 94.0 years), and the mean interval from diagnosis of atrial fibrillation to the cerebrovascular event was 21.8±10.2 years (range, 0 to 34 years).

All patients who had a cerebrovascular event had developed ≥1 risk factors for thromboembolism (hypertension in 12, heart failure in 4, diabetes mellitus in 3). Of the 17 patients

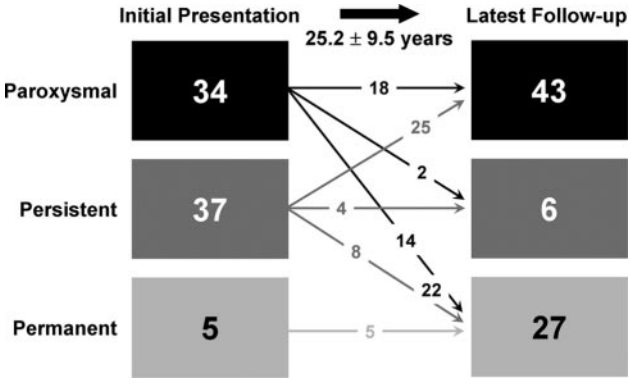

Figure 2. Distribution of paroxysmal, persistent, and permanent forms of atrial fibrillation at initial diagnosis and latest follow-up.

TABLE 2. Univariate Predictors of Progression to Permanent Atrial Fibrillation, Mortality, Congestive Heart Failure, and Stroke or Transient Ischemic Attack

	HR	95% CI	*P*
Progression			
Age at diagnosis (10-y increase)	1.72	1.08 to 2.75	0.023
QRS abnormalities	3.25	1.05 to 10.0	0.041
Class I antiarrhythmic	2.53	0.92 to 6.98	0.072
Preexisting arrhythmia	0.13	0.02 to 0.98	0.048
Death			
Age at diagnosis (10-y increase)	3.45	2.00 to 5.95	<0.001
Cardiovascular death			
Age at diagnosis (10-y increase)	4.57	1.94 to 10.8	0.001
Congestive heart failure			
Age at diagnosis (10-y increase)	2.08	1.11 to 3.89	0.022
Murmur	3.90	1.24 to 12.3	0.020
Caffeine use	0.26	0.07 to 0.92	0.037
Class I antiarrhythmic	2.53	0.85 to 7.55	0.097
Preexisting arrhythmia	0.19	0.03 to 1.47	0.112
Stroke or transient ischemic attack			
Age at diagnosis (10-y increase)	2.43	1.39 to 4.24	0.002
QRS abnormalities	2.59	0.84 to 7.98	0.098

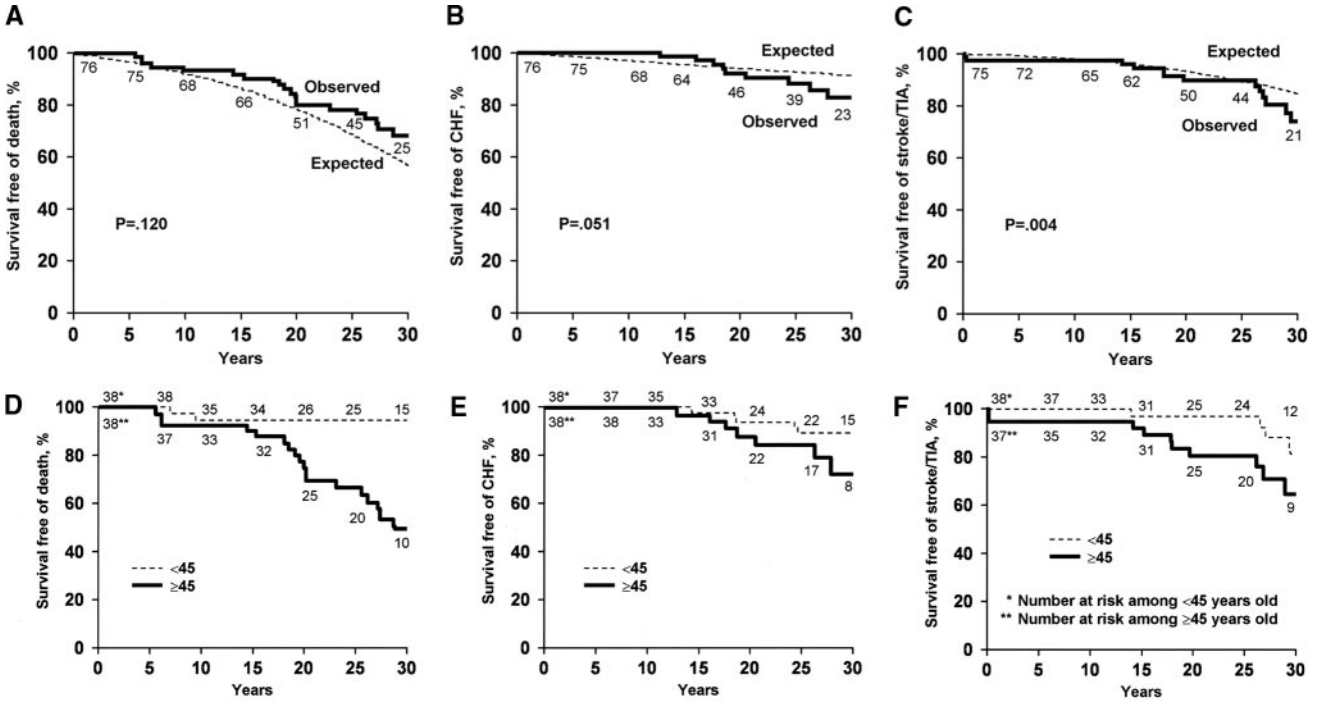

Figure 3. Long-term observed survival free of death (A), congestive heart failure (CHF; B), and stroke or transient ischemic attack (TIA; C) in patients with lone atrial fibrillation (solid line) and an age- and sex-matched Minnesota population (dashed line). Long-term survival free of death (D), CHF (E), and stroke or TIA (F) in patients with lone atrial fibrillation <45 years of age (dashed line) and ≥45 years of age (solid line) at initial diagnosis of atrial fibrillation.

who had neurological events, 11 were not taking antiplatelet agents or anticoagulants at the time of the event. None of the patients who had a cerebrovascular event were receiving warfarin therapy. After initiation of warfarin therapy, no patient had recurrence of stroke/transient ischemic attack.

Predictors of Long-Term Clinical Outcomes

Older age at diagnosis of atrial fibrillation was the sole univariate predictor of increased mortality and cardiac mortality (Table 2). The overall outcome and number at risk for death, congestive heart failure, or stroke/transient ischemic attack over the 30-year follow-up for those <45 and those ≥45 years of age at initial diagnosis of atrial fibrillation are shown in Figure 3D through 3F. In a multivariable analysis, the only risk factor in the final model for the risk of stroke/transient ischemic attack, overall mortality, and cardiac mortality was age at diagnosis.

Discussion

The present study has elucidated the long-term outcome over 30 years of paroxysmal atrial fibrillation in patients without structural heart disease or hypertension and describes the interaction of the arrhythmia with increasing age and the development of risk factors. Key findings are the low risk of progression to permanent atrial fibrillation, mortality, congestive heart failure, and stroke/transient ischemic attack. Equally important is the finding that thromboembolic complications occurred only after the development of risk factors (including advanced age), highlighting their important interaction with atrial fibrillation.

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting ≈2.3 million persons in the United States. With an expanding elderly population,[3] the consequences of this epidemic become increasingly important. Atrial fibrillation may be the consequence of a systemic condition in which atherosclerosis, obesity, hypertension, and "inflammation" contribute to the development of the arrhythmia and its thromboembolic complications.[9–15] There is evidence that in some patients rapidly discharging foci "trigger" the arrhythmia, whereas in others, diseased atrial substrate has a dominant role.[1,6,9] Thus, a previously studied population of younger patients in Olmsted County with atrial fibrillation but without apparent structural heart disease[7] who had long-term follow-up provides a unique opportunity to examine the natural history of atrial fibrillation and its interaction with other cardiovascular risk factors over an extended follow-up.

Overall, the cumulative probability of progression of paroxysmal or persistent to permanent atrial fibrillation over 30 years appeared to be unexpectedly low. In patients without structural heart disease, little information is available about the electrophysiological properties of the atrium predisposing to paroxysmal or progression to permanent atrial fibrillation.[16] Because most patients, particularly those with premature complexes and supraventricular arrhythmias, did not progress to permanent atrial fibrillation, a primary electric disorder may be present.[17,18] This concept is supported by the observation made during catheter ablation in patients with lone atrial fibrillation that rapidly discharging foci not only initiate but also maintain the arrhythmia; isolation of the triggers terminates ongoing fibrillation.[19,20] In animal models,

atrial fibrillation can induce electrophysiological changes that tend to perpetuate arrhythmia,[5] but our findings suggest that in humans without structural heart disease, these proarrhythmic effects are insufficient for progression to the permanent form of the arrhythmia in the absence of comorbidities. These comorbidities may include hypertension, diastolic dysfunction, heart failure, and advancing age, all of which promote cellular hypertrophy, interstitial fibrosis, cellular senescence, and electrophysiological heterogeneity.[21–23] The importance of these risk factors in the progression is further supported by our finding that permanent atrial fibrillation developed in patients with an abnormal QRS complex at diagnosis, suggesting occult structural or substrate abnormalities.

After >30 years of follow-up of our rigorously defined cohort,[7] findings confirm that overall survival is not affected adversely by lone atrial fibrillation. The probability of stroke in young patients with lone atrial fibrillation is similar to the expected age- and sex-matched general population risk and increases only after 25 years, with advancing age or development of hypertension. These findings corroborate previous reports that the risk of cardiovascular events in lone atrial fibrillation is age dependent and increases significantly with the development of hypertension, diabetes, congestive heart failure, or atherosclerotic vascular disease.[7,24–30] The powerful effect of hypertension on stroke risk[9,13,30] that underlies current guidelines for anticoagulation in atrial fibrillation is further supported by our long-term data that suggest that the increased risk of stroke in atrial fibrillation is due to "the company it keeps."[1,31–35]

Osranek et al[36] previously reported on the outcomes of a subset of the present population (46 patients) that also had undergone echocardiography and observed that increased left atrial volume at diagnosis or follow-up predicted adverse events. We extend these observations by including the larger cohort, and we describe the predictors of and progression to permanent atrial fibrillation. Additionally, we report risk factors for and incidence of death, cardiovascular death, congestive heart failure, and stroke as a function of clinical variables, without the need for imaging studies.

Our observations should be interpreted in the context of limitations imposed by a retrospective study design; it was theoretically possible for bias to exist in the adjudication process. The number of patients with lone atrial fibrillation and the events for each end point were relatively small, thus limiting the power to assess predictors of progression and poor prognosis. In addition, confidence intervals for progression and complications were wide. However, the duration of follow-up in a population-based cohort is the longest reported in the literature, allowing us to analyze arrhythmia progression and long-term outcomes. The selection bias present in hospital-based series or a referral population also was avoided by the use of a community-based population. The exact burden and duration of atrial fibrillation could not be determined. Possibly, patients did not have episodes of sufficient length to cause the remodeling reported in animal models.[6,7,21] The study data do not include echocardiographic information because echocardiography was not routinely available at the time of the initial diagnosis; the exclusion of structural heart disease was based on clinical evaluation. This may have resulted in the inclusion of patients with minor structural abnormalities not detected on physical examination, chest radiography, or ECG. Despite this, we observed that the complications of atrial fibrillation were associated primarily with the development of overt comorbidities such as hypertension. Recent data suggest that the use of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists may prevent rhythm progression. At the time of diagnosis, none of our patients received treatment with these agents. However, it is possible that these medications were added as hypertension or heart failure developed during follow-up. Ideally, time-dependent Cox regression analysis would have been performed on variables such as hypertension, congestive heart failure, and diabetes. However, because follow-up was not systematized, it was not possible to use this statistical modeling technique. Consequently, the effects of increasing age per se and increasing blood pressure by age on risk of stroke are not readily disentangled.

Conclusions

The present study provides strong evidence that atrial fibrillation is a heterogeneous disorder and that comorbidities significantly modulate disease progression and complications. Because the risk of progression to permanent atrial fibrillation appears low in young patients, invasive therapies should be reserved for highly symptomatic patients. After a young patient with lone atrial fibrillation ages or develops hypertension, heart failure, or diabetes, thromboembolic risk increases. Therefore, screening for comorbidities is essential in this group. Finally, our data raise questions about the mechanism of atrial fibrillation and comorbidities in association with aging. In young patients, it may represent primarily an electrophysiological phenomenon; in the elderly with comorbidities, it may reflect the final common pathway of a vascular inflammatory process associated with atrial dilatation, stretch, fibrosis, and electric inhomogeneity, increasing the risk of complications. Further understanding of the underlying pathophysiology, integrating genomic, proteomic, and functional analyses, will help to define future strategies for the prevention and treatment of atrial fibrillation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The present study reports the long-term clinical outcomes of a previously described Minnesota population with a first documented episode of atrial fibrillation at <60 years of age in the absence of concomitant heart disease or hypertension. With >30 years of follow-up, a low risk of progression to permanent atrial fibrillation was observed, with older age at diagnosis or presence of subtle ECG abnormalities predictive of progression to permanent atrial fibrillation. Overall survival and survival free from cardiovascular death or heart failure were not significantly affected by the presence of lone atrial fibrillation. Stroke or transient ischemic episode occurred only after the development of risk factors, including advanced age or hypertension. The present long-term follow-up study provides evidence for the heterogeneous nature of atrial fibrillation and the important modulatory effects of comorbidities on its progression and complications. Because of the low risk of progression to permanent arrhythmia in young patients with isolated atrial fibrillation, the role of invasive therapies in lone atrial fibrillation needs to be studied carefully in randomized controlled trials. In addition, screening for comorbidities is essential for this group because of the increased risk of complications on their emergence.

Long-Term Progression and Outcomes With Aging in Patients With Lone Atrial Fibrillation: A 30-Year Follow-Up Study

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