Lifetime Risk for Development of Atrial Fibrillation
The Framingham Heart Study

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Background—Atrial fibrillation (AF) is the most common cardiac dysrhythmia and a source of considerable morbidity and mortality, but lifetime risk for AF has not been estimated.

Methods and Results—We included all participants in the Framingham Heart Study who were free of AF at index ages of 40 years and older. We estimated lifetime risks for AF (including atrial flutter) to age 95 years, with death free of AF as a competing event. We followed 3999 men and 4726 women from 1968 to 1999 (176 166 person-years); 936 participants had development of AF and 2621 died without prior AF. At age 40 years, lifetime risks for AF were 26.0% (95% CI, 24.0% to 27.0%) for men and 23.0% (21.0% to 24.0%) for women. Lifetime risks did not change substantially with increasing index age despite decreasing remaining years of life because AF incidence rose rapidly with advancing age. At age 80 years, lifetime risks for AF were 22.7% (20.1% to 24.1%) in men and 21.6% (19.3% to 22.7%) in women. In further analyses, counting only those who had development of AF without prior or concurrent congestive heart failure or myocardial infarction, lifetime risks for AF were approximately 16%.

Conclusions—Lifetime risks for development of AF are 1 in 4 for men and women 40 years of age and older. Lifetime risks for AF are high (1 in 6), even in the absence of antecedent congestive heart failure or myocardial infarction. These substantial lifetime risks underscore the major public health burden posed by AF and the need for further investigation into predisposing conditions, preventive strategies, and more effective therapies. (*Circulation*. **2004;110:1042-1046.**)

Key Words: atrial fibrillation ■ epidemiology ■ risk factors

Atrial fibrillation (AF) is the most common chronic cardiac dysrhythmia, currently affecting nearly 2.3 million people in the United States.[1] AF is a major cause of morbidity and mortality, increasing risks for death,[2,3] congestive heart failure (CHF),[3] and embolic phenomena, including stroke.[3,4] Prior studies have established that key risk factors for the development of AF include increasing age, hypertension, myocardial infarction, CHF, and valvular heart disease.[5–7] Thus, with the aging of the population and improved survival after the occurrence of myocardial infarction and CHF, AF is emerging as a major public health concern.[8] To date, however, there have been no studies of the lifetime risk for development of AF.

Lifetime risk methods estimate the absolute risk for development of a disease before dying by accounting for the risk of development of the disease of interest as well as the risk for competing causes of death. These estimates are useful in assessing the burden of disease in a population, predicting the future burden of disease, and comparing absolute lifetime risks between common diseases. Given that lifetime risk estimates provide an absolute risk estimate, they may be more easily understood by clinicians and patients than relative risk estimates, and they may help to motivate beneficial changes in lifestyle or health behaviors. The best example of lifetime risk data being used effectively to change behavior is the widely publicized data on the lifetime risk for breast cancer (1 in 8 for women at age 40 years).[9] Knowledge of the high lifetime risk for breast cancer appears to have contributed to markedly increased rates of screening for breast cancer in the early 1990s.[10,11]

The Framingham Heart Study, with its well-defined cohort, long-term follow-up, and careful documentation of risk factors and events, provides a unique opportunity to estimate lifetime risk for AF and to examine factors that may modify remaining lifetime risk in men and women at different ages.

TABLE 1.   Characteristics at Earliest Examination During Study Period (1968 to 1999)

	Age, y									
	<40		40–49		50–59		60–69		70–84	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Hypertension, %	17.4	5.9	33.5	20.2	44.2	35.4	58.1	58.4	57.3	74.1
Antihypertensive therapy, %	1.1	0.9	5.8	4.3	9.7	13.2	19.0	22.3	12.7	26.8
Prior myocardial infarction, %	0.1	0	1.7	0.1	4.9	0.5	7.0	1.2	8.1	1.9
Prior CHF, %	0	0	0	0	0.2	0.6	1.7	1.5	2.4	2.7

Methods

Study Participants

Study design and entry criteria for the Framingham Heart Study cohorts have been detailed elsewhere.[12,13] For the present analysis, we included all participants who were free of AF before their earliest examination between 1968 and 1999, provided they were examined at least once between the ages of 40 and 94 years and they had follow-up after their earliest eligible examination. Only 32 participants were lost to follow-up during the study period.

Case Ascertainment

Cardiovascular and AF events during follow-up were ascertained from medical histories, physical examinations, ECGs, and review of interim medical records of those who appeared as well as those who failed to appear for their scheduled examinations. ECGs from the following sources were evaluated: routine Framingham Heart Study clinic examinations, hospital records, and outside physician records.[5,13] Participants were deemed to have had AF if paroxysmal or persistent AF or atrial flutter was verified on review by 1 of 2 Framingham Heart Study cardiologists who reviewed all of the tracings. All suspected cardiovascular events were reviewed by a panel of 3 trained physicians who applied established criteria for such events.[14]

Statistical Analysis

All statistical analyses were performed with the use of SAS statistical software.[15] For calculation of lifetime risk, a modified technique of survival analysis was used, as described previously.[16–18] Each subject was followed up from entry through 1999 until the occurrence of a first AF event, death free of AF, attainment of age 95 years, or last Framingham examination or medical contact at which the subject was known to be free of AF. Lifetime risk estimates were calculated only through age 94 years, because few participants survived past age 94. Age-specific hazards, incidence rates, cumulative incidence, and survival probabilities were calculated as in a Kaplan-Meier analysis.[19] In a simple Kaplan-Meier analysis of disease onset, one assumes that all subjects eventually will get the disease. Subjects who die are treated as censored observations. In lifetime risk estimation, the multiple-decrement life-table approach treats death as a true competing event, and the decedent's risk for subsequent events is set to zero. This is a more appropriate assumption when attempting to determine the public health burden of disease because decedents can no longer be at risk for the disease of interest.[16] Thus, adjustment was made for the competing risk of death to yield a true remaining lifetime risk for AF.[20] These calculations were repeated separately for men and women at index ages of 40, 50, 60, 70, and 80 years.

We performed secondary analyses to examine lifetime risk for AF attributable to causes other than CHF. In this analysis, we excluded participants with a history of CHF before or at the index examination, and only considered as cases those who had development of AF without antecedent or concurrent CHF during follow-up. We also excluded participants with CHF diagnosed concurrently with AF, because often it was not possible to ascertain which condition came first. Similar analyses were performed only counting those who had

development of AF without baseline, antecedent, or concurrent CHF or myocardial infarction.

For each index age, we also grouped participants according to the blood pressure measurement at the examination most closely preceding (up to 6 years before) the index age. Participants were assigned to one of the following 4 groups, according to blood pressure: systolic <130 and diastolic <85 mm Hg; the higher of systolic 130 to 139 or diastolic 85 to 89 mm Hg; the higher of systolic 140 to 159 or diastolic 90 to 99 mm Hg; and systolic ≥160 or diastolic ≥100 mm Hg. In 2 separate analyses, we assigned participants who were receiving antihypertensive therapy to the highest blood pressure stratum; we then repeated the analysis, assigning blood pressure stratum regardless of treatment status.

Results

Study Sample

There were 3999 men and 4726 women in the study sample who were followed up from 1968 through 1999, for a total of 176 166 person-years. Baseline characteristics of the study sample at the initial examination are shown in Table 1. During follow-up, 936 participants had development of AF and 2621 died without prior AF.

Lifetime Risk for AF

Lifetime risks for AF in men and women at selected index ages are shown in Table 2. At age 40 years and older, lifetime risks for AF were approximately 1 in 4 for both men and women. Remaining lifetime risk did not change across index ages because of rapidly increasing age-specific AF incidence rates with advancing age, which is illustrated in Figure 1, in which the slopes of the cumulative risk curves rise more steeply with each decade of index age.

Lifetime Risk for AF Without CHF

To understand the effect of CHF on lifetime risk for AF, we excluded participants with a history of CHF before the index age and only counted those who had development of AF without antecedent or concurrent CHF during follow-up. In

TABLE 2.   Lifetime Risk for AF at Selected Index Ages by Sex

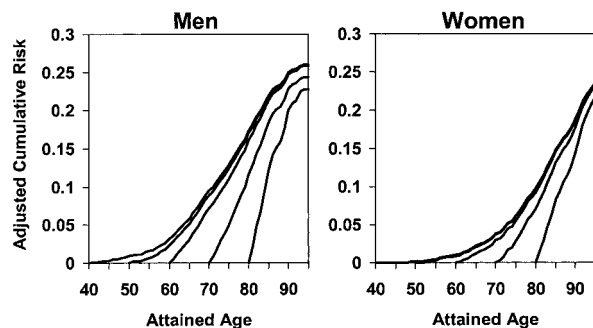| Index Age, y	Men	Women
40	26.0 (24.0–27.0)	23.0 (21.0–24.0)
50	25.9 (23.9–27.0)	23.2 (21.3–24.3)
60	25.8 (23.7–26.9)	23.4 (21.4–24.4)
70	24.3 (22.1–25.5)	23.0 (20.9–24.1)
80	22.7 (20.1–24.1)	21.6 (19.3–22.7)

All values are percentages.

Figure 1. Cumulative risk for AF at selected index ages for men and women, with death free of AF considered a competing event. Lifetime risk for a given index age is cumulative risk through age 94 years.

this setting, estimated lifetime risks were 5% to 6% lower (Table 3, top, and Figure 2A).

Lifetime Risk for AF Without CHF or Myocardial Infarction

In a similar analysis, we excluded participants with history of CHF or myocardial infarction at the index age and only considered those who had AF in the absence of antecedent or concurrent CHF or myocardial infarction. Again, lifetime risk for AF was reduced similarly for men and women, by 7% to 10%. Thus, lifetime risks for AF in the absence of CHF or myocardial infarction were about 16% for men and women (Table 3, bottom, and Figure 2B).

Lifetime Risk for AF by Blood Pressure Strata

Because hypertension is an important independent risk factor for AF, we examined lifetime risk for AF according to blood pressure strata at each index age. Overall, lifetime risks were fairly similar across blood pressure strata (Table 4) in younger participants, with somewhat better discrimination of remaining lifetime risk at older index ages. Assigning blood pressure level by ignoring treatment status did not change the results materially (data not shown).

TABLE 3.   Lifetime Risk for AF in the Absence of Antecedent or Concurrent Diagnosis of CHF or CHF or Myocardial Infarction

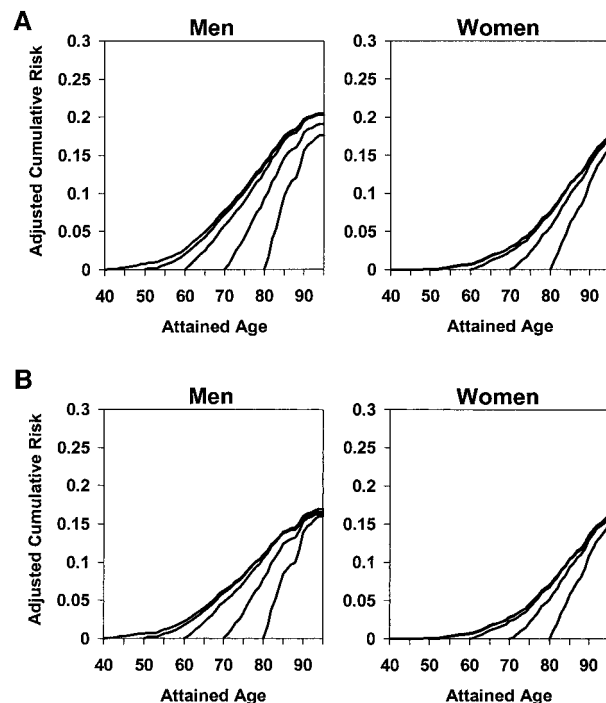| Index Age, y	Men	Women
Lifetime risk for AF without antecedent or concurrent CHF		
40	20.5	17.0
50	20.5	17.3
60	20.3	17.4
70	19.1	17.0
80	17.6	15.9
Lifetime risk for AF without antecedent or concurrent CHF or myocardial infarction		
40	16.3	15.6
50	16.6	15.9
60	16.8	16.1
70	16.5	15.9
80	16.0	14.8

All values are percentages.

Figure 2. Cumulative risk for AF at selected index ages for men and women, with occurrence of CHF or death free of AF considered competing events (A), or occurrence of CHF, myocardial infarction, or death free of AF considered competing events (B). Lifetime risk for a given index age is cumulative risk through age 94 years.

Discussion

Principal Findings

For men and women 40 years of age and older, the remaining lifetime risk for development of AF is approximately 1 in 4. Of note, lifetime risks for AF were similar in men and women at all ages. When we considered only participants who had AF in the absence of antecedent CHF or myocardial infarction, lifetime risks were somewhat lower, at approximately 1 in 6. Knowledge of blood pressure level helped to discriminate remaining lifetime risks for AF somewhat better in older than in younger participants.

Implications

The high lifetime risk for AF that we report underscores the important public health burden posed by AF. With the aging of the population, the concomitant increased prevalence of predisposing factors, increased rates of cardiac surgical procedures,[1] and improved survival after myocardial infarction and onset of CHF,[21] the prevalence of AF is almost certain to increase in the coming decades. Several studies of secular trends have already documented increasing prevalence of AF over the past several decades.[22–25]

After the onset of AF, there is a significantly increased risk of death, and AF appears to diminish substantially the female survival advantage over men.[2] AF also increases the risk for stroke nearly 5-fold.[4] It is estimated that 15% of all strokes are attributable to AF, and the proportion increases markedly with age.[4] AF is also associated with other embolic events and reduced quality of life.[26,27]

TABLE 4. Lifetime Risk for AF by Blood Pressure Levels at Selected Index Ages

| | Lifetime Risk for AF | | | | | | | |
| | Men | | | | Women | | | |
Index Age, y	SBP <130 and DBP <85	SBP 130–139 or DBP 85–89	SBP 140–159 or DBP 90–99	SBP ≥160 or DBP ≥100 or Treated	SBP <130 and DBP <85	SBP 130–139 or DBP 85–89	SBP 140–159 or DBP 90–99	SBP ≥160 or DBP ≥100 or Treated
40*	27.4	22.3	25.1	30.7	18.6	14.8	21.1	20.4
50	27.0	23.2	24.5	34.2	24.3	20.8	21.9	27.8
60	21.8	23.6	23.8	31.1	19.9	20.0	25.7	26.4
70	17.4	26.0	23.0	29.2	16.7	22.6	17.5	27.5
80	18.2	13.7	27.7	26.6	15.8	17.1	22.3	24.0

All values are percentages.

*Lifetime risk through age 90 years only because of limited length of follow-up. SBP indicates systolic blood pressure (in mm Hg); DBP, diastolic blood pressure (in mm Hg).

Even when AF is diagnosed and treated, the antiarrhythmic and antithrombotic medications required to prevent recurrences or for prophylaxis against embolic phenomena carry their own attendant risks.[28–30] Recent large clinical trials (RACE[29] and AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management][30]) suggest that strategies designed to maintain sinus rhythm do not improve survival compared with rate control and anticoagulation. Event rates with either strategy were higher than optimal, given the unpredictability of warfarin anticoagulation and the high rates of recurrent AF. Thus, in light of the high lifetime risk and suboptimal results with treatment, prevention of AF deserves increased attention.

We anticipate that public health and clinical prevention strategies designed to decrease the prevalence of predisposing conditions, such as CHF and myocardial infarction, would reduce the lifetime risk for AF. However, as we observed, AF occurs commonly even in the absence of overt CHF or myocardial infarction. Valvular heart disease may account for some of the residual lifetime risk for AF.[5,7,31] Several investigators have published associations between AF and specific genetic loci or alleles,[32–34] and there is ongoing interest in discovery of genetic determinants of AF. Tachy-brady or "sick sinus" syndrome and degenerative conduction system disease, which are poorly understood and for which there are no specific preventive modalities at present, also may account for a large proportion of incident AF. Our data would suggest, therefore, that further research into predisposing conditions is warranted, as are investigations into the efficacy of preventive strategies in high-risk subgroups.

Hypertension is firmly established as a risk factor for AF.[5–7,31] However, in the context of the present study design, we observed that the lifetime risk for AF did not increase markedly with increasing level of baseline blood pressure, particularly for younger index ages. Several factors may explain this apparent paradox. One reason is the presence of the competing risk for death in lifetime risk analysis. Although hypertension confers increased risk for AF, it is also associated with higher risk for death from other causes.[1,35,36] Thus, individuals with the highest blood pressures have a shorter lifespan over which AF may occur, effectively limiting their lifetime risk for AF. In addition, we assigned blood pressure level only at the index age because current methods of lifetime risk estimation do not allow for updating of covariates during follow-up. The relatively weak gradient of lifetime risk for AF across blood pressure strata in younger participants may be due to the long interval between baseline blood pressure assessment and incidence of AF,[7] during which time a large proportion of participants would have had development of hypertension.[18,37]

The lifetime risks for AF are of a magnitude similar to the lifetime risks for CHF, which we have reported previously to be 1 in 5 for men and women 40 years of age and older.[38] AF is predominantly a disease of the elderly; thus, as with CHF, at older ages the increasing incidence of AF keeps pace with the increased risk of death from other causes, leading to a fairly constant remaining lifetime risk for AF regardless of index age. In contrast, the lifetime risk for CHD decreases with advancing index age[17] because of depletion of susceptible individuals and because the increased risk of death outpaces the age-specific incidence of CHD.

In comparison with noncardiovascular diseases, the lifetime risk for AF of 1 in 4 is strikingly high. At age 40 years, women have a remaining lifetime risk for breast cancer of 1 in 8, and at age 70 years, it is 1 in 14.[9] At age 50 years, the lifetime risk for hip fracture (a major cause of death in older persons) is 1 in 6 for white women and 1 in 20 for white men.[39]

We estimated the lifetime risk for AF, which accounts for the competing risk of death from other causes before the development of AF, rather than calculating the unadjusted Kaplan-Meier cumulative incidence. Kaplan-Meier cumulative incidence tends to overestimate the risk of disease, especially when the competing risk of death is high. For example, we estimate that the remaining lifetime risk for AF is 26% for men at 40 years of age; using the same data, the unadjusted Kaplan-Meier cumulative incidence is 55%.

Potential Limitations
The Framingham Heart Study cohort is composed almost exclusively of white individuals, which may limit the generalizability of our findings to other ethnic groups, in whom the risks of AF—and the contributing roles of CHF, myocardial infarction, and hypertension—may differ. It is possible that

because of their participation in periodic examinations, Framingham participants may have been motivated to modify risk factors, which could have reduced their lifetime risk for AF. We included cases of atrial flutter with AF, given the correlation between the two dysrhythmias. We did not distinguish between participants with paroxysmal and persistent AF; therefore some participants may only have had a single episode of paroxysmal AF. However, individuals with an index AF event have a high rate of recurrence and of conversion to persistent AF.[40] Furthermore, paroxysmal AF appears to be associated with risk for stroke that is similar to persistent AF.[41]

Acknowledgments

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