Impact of Atrial Fibrillation on the Risk of Death
The Framingham Heart Study

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Background—Atrial fibrillation (AF) causes substantial morbidity. It is uncertain whether AF is associated with excess mortality independent of associated cardiac conditions and risk factors.

Methods and Results—We examined the mortality of subjects 55 to 94 years of age who developed AF during 40 years of follow-up of the original Framingham Heart Study cohort. Of the original 5209 subjects, 296 men and 325 women (mean ages, 74 and 76 years, respectively) developed AF and met eligibility criteria. By pooled logistic regression, after adjustment for age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack, AF was associated with an OR for death of 1.5 (95% CI, 1.2 to 1.8) in men and 1.9 (95% CI, 1.5 to 2.2) in women. The risk of mortality conferred by AF did not significantly vary by age. However, there was a significant AF-sex interaction: AF diminished the female advantage in survival. In secondary multivariate analyses, in subjects free of valvular heart disease and preexisting cardiovascular disease, AF remained significantly associated with excess mortality, with about a doubling of mortality in both sexes.

Conclusions—In subjects from the original cohort of the Framingham Heart Study, AF was associated with a 1.5- to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions with which AF was related. The decreased survival seen with AF was present in men and women and across a wide range of ages. **(*Circulation*. 1998;98:946-952.)**

Key Words: fibrillation, atrial ■ mortality ■ prognosis ■ stroke ■ cerebrovascular disorders ■ risk factors ■ aging

Atrial fibrillation (AF) is the most common chronic arrhythmia associated with an adverse prognosis. It is estimated that 2.2 million Americans have intermittent or sustained AF.[1] The incidence of AF increases with advancing age, with an annual incidence per 1000 person-years of about 3.1 cases in men and 1.9 cases in women 55 to 64 years of age, rising to 38.0 and 31.4 cases in men and women 85 to 94 years of age.[2] The clinical risk factors for AF include advancing age, diabetes, hypertension, congestive heart failure, rheumatic and nonrheumatic valve disease, and myocardial infarction.[2] The echocardiographic risk factors for nonrheumatic AF include left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular fractional shortening.[3] AF is an independent risk factor for stroke, resulting in an approximate 3- to 5-fold excess risk.[4] Furthermore, whereas the attributable risks for most stroke risk factors decline with advancing age, the attributable risks for stroke associated with AF dramatically increase with age, from 1.5% for those 50 to 59 years of age to 23.5% for those 80 to 89 years of age.[4]

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Although the morbidity of AF is well documented, it has not been clearly established whether AF per se results in excess mortality. The worsened survival seen with AF could reflect the increased mortality of the cardiovascular conditions with which it is associated. Using data from the Framingham Heart Study, we sought to ascertain the mortality associated with AF after adjusting for coexistent cardiac conditions and risk factors in a population-based sample.

Methods

Subjects

The Framingham Heart Study was begun in 1948 to explore risk factors for and consequences of cardiovascular disease in a longitudinal population-based cohort. At entry, 5209 residents of Framingham, Mass, who were 28 to 62 years of age were enrolled. The subjects have received biennial examinations with routine assessment of medical history, physical examination, blood tests, and 12-lead ECGs. The examination procedures were approved by the Investigational Review Board of Boston Medical Center, and all subjects gave informed consent. Previous reports have outlined the

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TABLE 1. Baseline Characteristics of Subjects With and Matched Subjects Without AF

	Men			Women		
	AF (n=296)	No AF (n=592)	*P*	AF (n=325)	No AF (n=650)	*P*
Mean age, y	73.7	73.8	0.95	76.4	76.4	0.98
Hypertension, %	58.4	54.9	0.33	55.0	53.9	0.76
Smoking, %	27.2	21.1	0.048	21.1	14.1	0.01
Diabetes, %	11.3	14.3	0.22	12.4	7.3	0.01
ECG LVH, %	9.9	6.1	0.052	13.9	6.7	0.0006
Myocardial infarction, %	28.0	14.9	0.0001	14.0	5.6	0.0001
Congestive heart failure, %	21.8	3.2	0.0001	28.9	3.7	0.0001
Valvular heart disease, %	19.4	9.1	0.0001	33.5	12.7	0.0001
Stroke or TIA, %	14.0	9.1	0.04	19.9	8.2	0.0001

LVH indicates left ventricular hypertrophy; TIA, transient ischemic attack. Non-AF subjects were matched to AF subjects by age, sex, and calendar year.

study design, response rates, and completeness of follow-up.[5] For the present study, we analyzed 40 years of follow-up. Subjects were excluded from analysis if they had AF at the first examination (n=19). Analyses were restricted to subjects 55 to 94 years of age at each biennial examination. AF was diagnosed if chronic or paroxysmal AF or atrial flutter was present on ECG. ECGs were obtained from the routine biennial Framingham Heart Study clinic examination or from outside hospitals and physicians.[2]

Definition of Clinical Covariables

Hypertension was considered present if the systolic blood pressure was at least 140 mm Hg or the diastolic blood pressure was ≥90 mm Hg on each of 2 successive readings obtained by the clinic physician or if the subject was receiving antihypertensive medication.[6] Diabetes was defined as a nonfasting blood glucose level ≥11.11 mmol/L (200 mg/dL) or the use of insulin or an oral hypoglycemic agent. ECG left ventricular hypertrophy was diagnosed if a subject had voltage criteria for left ventricular hypertrophy accompanied by lateral repolarization changes.[7] Prevalent congestive heart failure and myocardial infarction were determined by a panel of 3 physicians using previously published criteria.[8] Because echocardiography was unavailable for the first 3 decades of the study, valvular heart disease was defined by auscultation criteria as any diastolic murmur or a >2 over 6 systolic murmur on Framingham Heart Study examination. The diagnosis of a stroke or transient ischemic attack was made by a panel of 3 investigators, including a neurologist, after they reviewed all records from relevant hospitalizations and clinic-reported events. Subjects suspected of having a cerebrovascular event were seen by a study neurologist in the hospital and in periodic follow-up.[9]

Statistical Analyses

The primary analysis examined the impact of AF on mortality in men and women using pooled logistic regression analysis.[10] The pooled logistic regression analysis is equivalent to a Cox time-dependent regression analysis.[10] The pooled logistic regression analyses allowed the covariates in the multivariate models to change over time, with the clinical variables redefined at every biennial examination. Missing data were imputed by substituting the most recent values as long as they were obtained within the 2 preceding examination cycles. Cardiovascular disease was defined as congestive heart failure, myocardial infarction (recognized or unrecognized), and stroke or transient ischemic attack; these events were redefined between biennial examinations as long as they occurred at or before the onset of AF. To assess the net effect of AF, we used multivariate models that adjusted for age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack unless otherwise specified.

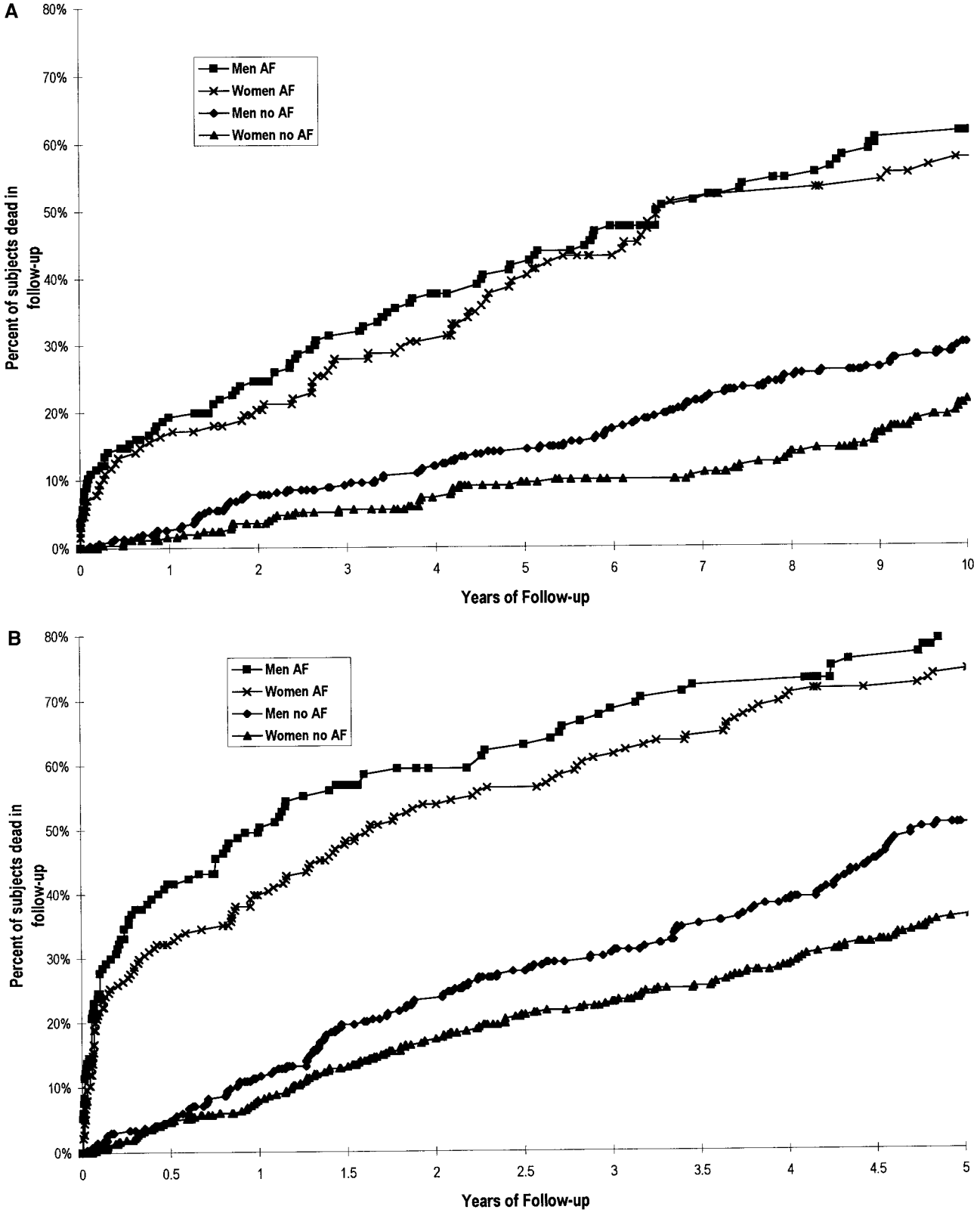
To examine the influence of age and sex on AF mortality, interaction terms were introduced. To remove the impact of conditions with a high case-fatality rate, in 1 analysis, subjects were excluded if they died within 30 days of AF onset. Finally, to investigate whether the poor prognosis with AF was limited to subjects with valvular heart disease or preexisting cardiovascular disease, a multivariate analysis (adjusting for age, hypertension, smoking, diabetes, and left ventricular hypertrophy) was limited to subjects who were free of clinically apparent valvular heart disease, myocardial infarction, congestive heart failure, or stroke or transient ischemic attack.

For descriptive purposes, we used a matched-cohort analysis. Approximately 2 subjects without AF were matched to each AF subject by age, sex, and date of diagnosis of AF (index examination cycle). The characteristics of the AF subjects and matched subjects without AF were defined at the baseline index examination. To describe the mortality after AF, a Kaplan-Meier analysis[11] of the matched-cohort subjects was used to estimate survival and produce mortality curves. A log rank test was used to test the differences in survival between AF and matched non-AF participants.[12] All analyses were sex specific and were performed with the Statistical Analysis System program[13] on a Sun Sparc workstation.

Results

During up to 40 years of follow-up, 296 men (mean age, 73.7 years) and 325 women (mean age, 76.4 years) developed AF. Table 1 displays the baseline characteristics of the AF and the age-, sex-, and calendar year–matched subjects without AF. Subjects with AF were significantly more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease at baseline, including hypertension, smoking, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack. In addition, women with AF were more likely to be diabetic.

The Kaplan-Meier mortality curves are displayed in the Figure (top, subjects 55 to 74 years of age at baseline; bottom, subjects 75 to 94 years of age). For both the younger and older age groups, the mortality of men and women with AF was substantially greater than for the non-AF subjects (log rank test, all $P<0.0001$). At 10 years of follow-up, in the subjects 55 to 74 years of age, 61.5% of men with AF had died compared with 30.0% of men without AF; in women, 57.6% of those with AF had died compared with 20.9% of women without AF. Table 2 details the mortality of AF and



A, Kaplan-Meier mortality curves for subjects 55 to 74 years of age. Vertical axis shows percent of subjects dead at follow-up (0% to 80%); horizontal axis, up to 10 years of follow-up. Subjects included men with AF (n=159), men without AF (n=318), women with AF (n=133), and women without AF (n=266). Both men and women with AF had significantly higher mortality than age-, sex-, and calendar year–matched non-AF subjects. Log rank test for men gave $\chi^2=42.90$ ($P<0.0001$); for women, $\chi^2=70.93$ ($P<0.0001$). B, Kaplan-Meier mortality curves for subjects 75 to 94 years of age. Vertical axis shows percent of subjects dead at follow-up (0% to 80%); horizontal axis, up to 5 years of follow-up. Results are shown for men with AF (n=137), men without AF (n=274), women with AF (n=192), and women without AF (n=384). Both men and women with AF had significantly higher mortality than age-, sex-, and calendar year–matched non-AF subjects. Log rank test for men gave $\chi^2=51.44$ ($P<0.0001$); for women, $\chi^2=101.51$ ($P<0.0001$).

TABLE 2. Kaplan-Meier Death Rates in Subjects With and Matched Subjects Without AF

Age, y and AF Status	n	30 d, %	1 y, %	5 y, %	10 y, %	Median Survival, y	95% CI
Men							
55–64							
AF	45	8.9	15.6	26.9	43.3	12.6	7.8–16.1
No AF	90	0	2.2	5.6	20.1	18.1	15.6–19.7
65–74							
AF	114	9.9	20.8	48.2	70.3	5.1	3.5–7.1
No AF	228	0	2.7	17.7	34.4	12.3	11.0–13.2
75–84							
AF	106	21.7	44.8	74.8	91.2	1.2	0.8–2.5
No AF	212	0.5	10.2	44.4	73.4	6.2	4.6–7.6
85–94							
AF	31	27.4	65.4	94.7	...*	0.4	0.1–1.1
No AF	62	1.6	13.1	72.6	88.9	2.6	2.0–4.5
Women							
55–64							
AF	35	2.9	11.4	40.0	48.6	12.1	4.4–13.3
No AF	70	0	2.9	7.1	16.1	21.3	17.7–30.2
65–74							
AF	98	8.6	18.2	38.9	62.5	6.4	5.0–9.9
No AF	196	0	1.1	10.5	23.2	16.5	14.1–18.1
75–84							
AF	134	17.2	37.3	66.1	93.9	2.2	1.4–3.3
No AF	268	0.4	6.3	27.9	57.2	8.6	7.2–9.9
85–94							
AF	58	26.4	45.3	96.3	...*	1.3	0.4–1.8
No AF	116	0	11.7	56.3	...*	4.3	3.5–5.4

*Cells with too few observations for stable estimates.

matched non-AF subjects by decade of age and sex. The median survival of men 55 to 64 years of age with AF was 12.6 years compared with 18.1 years in men without AF. Median survival was 12.1 years in women with AF and 21.3 years in women without AF. The excess mortality of the AF subjects was apparent within the first 30 days and persisted throughout follow-up. Furthermore, the excess mortality with AF was observed across all 4 decades of age studied.

To estimate the excess mortality attributable to AF, pooled logistic regression analyses were undertaken (Table 3). For

TABLE 3. Impact of AF on Mortality: Pooled Logistic Regression Analyses

		Men				Women			
Covariates	Subjects at Risk	Deaths/Person-Years	OR	*P*	95% CI	Deaths/Person-Years	OR	*P*	95% CI
Age	All eligible	1465	2.4	0.0001	2.1–2.9	1442	3.5	0.0001	3.0–4.1
		19 616				28 439			
Clinical RF	All eligible	1449	1.5	0.0001	1.2–1.8	1438	1.9	0.0001	1.6–2.3
		19 397				28 216			
Clinical RF	30-day survivors	1404	1.1	0.30	0.9–1.4	1391	1.5	0.0001	1.2–1.8
		19 352				28 169			
Clinical RF*	No heart disease or CVD events	599	2.4	0.001	1.8–3.3	660	2.2	0.0001	1.6–3.1
		14 473				22 725			

RF indicates risk factors; CVD, cardiovascular diseases. See text for details. Clinical risk factors include age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack. Analysis of 30-day survivors eliminated all subjects who died in the first 30 days of follow-up. Analysis of subjects without heart disease or CVD events excludes subjects with valvular heart disease, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack at baseline.

*Clinical risk factors adjusted for were age, hypertension, smoking, diabetes, and ECG left ventricular hypertrophy.

TABLE 4. Cause-Specific 1 Year Mortality in Subjects by AF Status

	AF Status, Men				AF Status, Women			
	Yes, n (%)		No, n (%)		Yes, n (%)		No, n (%)	
n	296		592		325		650	
Follow-up interval	30 d	30 d–1 y	30 d	30 d–1 y	30 d	30 d–1 y	30 d	30 d–1 y
CHD	10 (3.4)	19 (6.4)	0	10 (1.7)	12 (3.7)	10 (3.1)	0	5 (0.8)
Stroke	6 (2.0)	2 (0.7)	0	2 (0.3)	8 (2.5)	5 (1.5)	0	3 (0.5)
Other CVD	4 (1.4)	5 (1.7)	1 (0.2)	2 (0.3)	7 (2.2)	10 (3.1)	1 (0.2)	4 (0.6)
Other	23 (7.8)	24 (8.1)	1 (0.2)	21 (3.5)	18 (5.5)	17 (5.2)	1 (0.2)	13 (2.0)
Unknown	2 (0.7)	3 (1.0)	0	0	2 (0.6)	6 (1.8)	1 (0.2)	8 (1.2)
Total dead	45 (15.2)	53 (17.9)	2 (0.3)	35 (5.9)	47 (14.5)	48 (14.8)	3 (0.5)	33 (5.1)

CHD indicates coronary heart disease; CVD, cardiovascular disease (not stroke or CHD). Percentages are the percentages of all subjects in the category (eg, male with AF, or male without AF) dying within the specified time interval unadjusted for clinical covariates. Matched cohort analysis (non-AF subjects matched to AF subjects by age, sex, and calendar year).

the pooled logistic regression analyses, 2149 men and 2714 women met eligibility criteria for inclusion at some point during follow-up. Age-adjusted ORs for death with AF were 2.4 in men and 3.5 in women. After multivariate adjustment, with risk factor status at each biennial examination taken into account, AF remained significantly associated with an increased risk of death; the OR with AF was 1.5 in men (95% CI, 1.2 to 1.8) and 1.9 in women (95% CI, 1.5 to 2.2).

Further tests failed to reveal a significant interaction between age and AF with respect to mortality. The multivariate coefficients for an age-AF interaction were 0.00811 ($P=0.49$) in men and -0.00419 ($P=0.69$) in women, suggesting that the risk of death with AF did not significantly vary over the 4 decades of age studied. However, the risk of death in the setting of AF did vary by sex. With men and women combined, in a full multivariate model, there was a significant interaction between sex and AF with regard to mortality. The presence of AF made the sexes look similar for mortality: an OR of 1.2 (95% CI, 0.98 to 1.49) for men versus women with AF compared with an OR of 1.6 (95% CI, 1.4 to 1.7) for men versus women without AF.

Secondary analyses explored the impact of AF in subsets of subjects with AF (Table 3). With subjects who died within the first 30 days of follow-up eliminated, AF remained significantly associated with greater mortality in women (OR, 1.5) but not in men (OR, 1.1). Lastly, in an analysis limited to subjects initially free of clinically evident cardiovascular disease and valvular heart disease, AF was associated with a doubling in mortality (multivariate OR, 2.4 [95% CI, 1.8 to 3.3] in men and 2.2 [95% CI, 1.6 to 3.1] in women).

Cause of Death

The mortality rate in the first 30 days and 1 year for the AF subjects and matched subjects without AF are listed in Table 4. The excess mortality observed with AF appeared early; about 15% of subjects with AF died within 30 days of diagnosis. The cause-specific mortality at 1 year suggests that the distribution of the causes of death for the AF subjects was similar to that of the matched subjects without AF (Table 4). However, compared with matched subjects without AF, for each of the causes of death, a higher percentage of the AF subjects died in the first year after AF was diagnosed.

Discussion

These population-based data indicate that subjects with AF have markedly reduced survival compared with subjects without AF, with risk factor–adjusted ORs for death of 1.5 and 1.9 in men and women, respectively. The multivariate analyses suggest that the greater mortality probably was attributable to AF, rather than reflecting the greater burden of risk factors and cardiovascular disease of AF subjects.

We performed secondary analyses to see whether the increased mortality risk was limited to subsets of subjects with AF. One possibility is that AF merely served as a marker for terminal illness. After elimination of 30-day mortality, AF remained associated with a 50% greater mortality in women. However, in men who survived 30 days after AF was diagnosed, AF was no longer significantly associated with increased mortality, suggesting that in men the worsened survival with AF was heavily influenced by early mortality. Another potential explanation is that the increased mortality of AF was confined to subjects with structural heart disease or more severe clinically evident cardiovascular events. When our analysis was limited to subjects free of baseline myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack, AF was still associated with about a doubling in mortality.

Comparison With Previous Literature

Although few would consider AF a benign condition, it has remained unclear whether AF is associated with mortality independent of the coexisting conditions with which it is often observed. The risk of subsets of AF subjects with cardiovascular disease remains controversial. For example, some investigators have reported that after myocardial infarction, AF is associated with excess mortality,[14,15] whereas others have not found an independent effect of AF on post–myocardial infarction mortality.[16,17] Similarly, whether AF is an independent predictor of mortality in subjects with heart failure or stroke is also unclear, with some investigators reporting[18–20] and others refuting[21–23] an independent contribution of AF to mortality.

Evidence of mortality risk in broader series of AF subjects comes from several sources. Gajewski and Singer[24] in 1981 examined insurance applicants and found that after 3.3 years

of follow-up, applicants with chronic AF or paroxysmal AF in the setting of mitral stenosis or coronary artery disease had increased mortality. In a 1982 hospital-based study, Godtfredsen[25] found that subjects with AF had a worse mortality compared with the general population. A number of cohort studies have also examined the issue, with samples ranging from male air force recruits[26] to male civil servants[27] to population-based samples.[28–32] Given the diverse study designs, it is not surprising that the reported 1-year mortality has varied widely, from 2.6% in the Gajewski and Singer[24] series describing insurance applicants with asymptomatic chronic AF to 16% in patients >70 years of age with AF detected on hospitalization.[33] While 1 study found that the 1.9-fold mortality risk was not statistically significant,[30] most studies have found that AF conferred excess risk of death,[24,26–29,31,32] with a risk of all-cause mortality ranging from an adjusted relative risk of 1.3[26] to an unadjusted relative risk of 2.6.[27]

However, the studies of broader samples of AF subjects have been limited by a number of factors, including a small number of AF cases[29–32] and the inclusion of prevalent AF cases.[24,25,27–30,32,34] Prior studies have also had the disadvantages of being retrospective,[24,25,34] case series,[25,34] or case-control in design.[28,30] Most of the prior studies have not shed light on possible sex differences in the mortality of AF because they have been all male cohorts[26,27] or lacked sex-specific analyses.[24,25,28,30,32,34] With regard to clarifying the independent impact of AF on mortality, the fundamental limitation of most prior studies was their lack of time-dependent or multivariate analyses.[24,25,27,28,30–32,34]

Study Strengths and Limitations

The Framingham Heart Study, by virtue of its longitudinal population-based design, has several advantages. The selection bias inherent in hospital-based series, prevalent AF series, or retrospective series was minimized. In the present series, ECGs were systematically ascertained on all subjects at each biennial examination and by review of outside hospital and physician records. Furthermore, the large number of subjects with AF contained in this series allowed us to analyze the mortality of AF over a broad age range and enabled the separate evaluation of the risk of death in men and women. To the best of our knowledge, the present investigation is the first to examine the relation between sex and AF mortality. We observed a significant interaction between AF mortality and sex, so that AF diminished the typical advantage women enjoy in survival. In addition, the routine collection of clinical history, physical examination, ECGs, and outside hospital records allowed multivariate adjustment for other factors, which may have contributed to the excess mortality seen with AF. A strength of the present study was that pooled logistic regression models were used so that the covariates in the multivariate model were updated at each biennial examination.

The study sample was largely white; our results may not be generalizable to other racial groups. Similarly, the results may not be relevant to subjects outside the age range studied (55 to 94 years of age), particularly younger subjects without any evidence of structural heart disease. In addition, we combined AF and atrial flutter, as well as chronic and paroxysmal AF; hence, we do not comment on differences in the prognosis of these AF subsets. Although the primary analysis controlled for covariates such as myocardial infarction, we were unable to control for infarct severity, which has been associated with risk for both AF and death. Most of the follow-up occurred before the availability of echocardiography and the widespread use of anticoagulants and antiarrhythmics for AF. The lack of routine echocardiography undoubtedly contributed to some misclassification of valvular heart disease. Moreover, we have insufficient data to comment on whether the mortality of AF is altered by anticoagulants[35] or antiarrhythmics,[36] as suggested by others. However, studies suggest that only about one third of eligible AF patients in the United States receive warfarin.[37,38] Therefore, we believe that our mortality data may have relevance to most subjects with AF, given current treatment practices.

Clinical Implications

Several observations suggest that the burden of AF might be expected to rise. The population is aging, and the incidence of AF increases with advancing age.[2] Furthermore, recently published data suggest that the prevalence of AF in the population is increasing even after accounting for age.[39] AF is known to result in substantial morbidity, with a risk factor–adjusted 2.6- to 4.5-fold risk of stroke.[4] The present study demonstrates that AF is independently associated with a 50% to 90% increase in the risk of death. The increased mortality was seen in men and women and was consistent across the 4 decades of age studied. Our investigation supports the contention that AF is associated with excess mortality, which persists after adjustment for coexisting cardiovascular conditions.

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