Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.10.062

Mortality Trends in Patients Diagnosed With First Atrial Fibrillation

A 21-Year Community-Based Study

Yoko Miyasaka, MD, PhD, FACC,* Marion E. Barnes, MSc,* Kent R. Bailey, PhD,† Stephen S. Cha, MS,† Bernard J. Gersh, MB, ChB, DPhil, FACC,* James B. Seward, MD, FACC,* Teresa S. M. Tsang, MD, FACC*

Rochester, Minnesota

Objectives The purpose of this study was to assess the mortality trends of atrial fibrillation (AF) in a community.

Background Limited data exist regarding the mortality trends of patients diagnosed with first AF.

Methods A community-based cohort of adult residents of Olmsted County, Minnesota, who had electrocardiogram-confirmed first-documented AF in the years 1980 to 2000 were identified and followed to 2004 or death. The primary outcome was all-cause mortality.

Results Of a total of 4,618 residents (mean age 73 ± 14 years) diagnosed with first AF, 3,085 died during a mean follow-up of 5.3 ± 5.0 years. Relative to the age- and gender-matched general Minnesota population, the mortality risk was increased ($p < 0.0001$) with a hazard ratio (HR) of 9.62 (95% confidence interval [CI] 8.93 to 10.32) within the first 4 months and 1.66 (95% CI 1.59 to 1.73) thereafter. Cox proportional hazards modeling showed no change in overall age- and gender-adjusted mortality (HR for the year 2000 vs. 1980: 0.99; 95% CI 0.86 to 1.13; $p = 0.84$), even after adjustment for comorbidities. In secondary analyses, no changes in mortality were seen for early (within first 4 months) or late (after 4 months) mortality for the entire group or within the subgroup of patients who did not have cardiovascular disease at baseline.

Conclusions In this cohort of patients newly diagnosed with AF, mortality risk was high, especially within the first 4 months. There was no evidence for any significant changes over the 21 years in terms of overall mortality, early or late mortality, or mortality among patients without pre-existing cardiovascular disease. (J Am Coll Cardiol 2007;49:986–92) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a growing public health problem (1), which has reached epidemic proportions (2–4). Our recent data provided evidence for a progressive increase in age-adjusted prevalence (5) as well as age-adjusted incidence over the past few decades (6). We projected that the number of persons with AF in the U.S. will exceed 10 million by the year 2050 (6). Atrial fibrillation is a well established risk factor for stroke (7–12), congestive heart failure (13–15), and premature death (14–18).

Considering the numerous changes in the management of AF patients over the last 2 decades, both in terms of treatment of AF itself (increased use of class 3 antiarrhythmic drugs, use of warfarin for prophylaxis against thromboembolic events, and introduction of various device therapies including AF ablation) as well as increased aggressiveness in coronary risk reduction in general, it is conceivable that the mortality risk of AF patients may have changed over time. Indeed, some studies have reported a decline in mortality risk after AF (19–23). However, these studies were largely hospital-based series of patients with any AF, and the findings would not provide an understanding of whether the overall mortality risk of patients has changed over time when followed longitudinally from first diagnosis. In the present study, we analyzed the mortality trends in a well defined community-based cohort followed longitudinally from the first documented AF episode.

Methods

Study setting. This community-based cohort study was approved by the Mayo Foundation Institutional Review Board. Olmsted County, Minnesota, is well suited for the

From the *Division of Cardiovascular Disease and Internal Medicine, and the †Section of Biostatistics, Mayo Clinic, Rochester, Minnesota. Dr. Tsang was supported by an American Heart Association National Scientist Development Grant, National Institutes of Health grant RO1 AG 22070, and an American Society of Echocardiography Outcomes Research Grant.

Manuscript received March 27, 2006; revised manuscript received October 19, 2006, accepted October 23, 2006.

conduct of studies with long-term follow up because of a number of unique features (24). Geographically, the community is relatively isolated from other urban centers, and medical care is delivered by only a few health care providers. Most of the Olmsted County residents return to the Mayo Clinic regularly, allowing capturing of events. An earlier study has shown that 96% of Olmsted County women residents age 65 to 74 years returned to the Mayo Clinic within a 3-year period (24). For each patient at the Mayo Clinic, a unified medical record containing details of all inpatient and outpatient encounters is maintained. Within each medical record, diagnoses made during office visits, clinic consultations, emergency room visits, hospital admissions, nursing home care, and autopsy examinations, as well as surgical procedures, are listed on a master sheet and coded. Coded diagnoses are then transferred to a central diagnostic index. This diagnostic index allows all patients with a diagnosis of interest to be readily identified. An electronic electrocardiogram database has been established at Mayo since 1976, allowing rapid identification of the coded interpretation and diagnoses for each electrocardiogram. All electrocardiograms can also be retrieved for direct review.

Incident AF cohort. The medical records of Olmsted County adult residents who had first AF documented between January 1, 1980, and December 31, 2000, in any of the Mayo administrative databases (medical index, surgical index, and electrocardiographic and echocardiographic databases) were reviewed and followed forward in medical records to March 2004 or death. We additionally confirmed that the presence of a 12-lead electrocardiogram showing AF was the very first documentation for each subject. Because the unit record system at Mayo dated back to the early 1900s, any electrocardiogram performed on any patient was contained within the unit record. Any AF that occurred before the establishment of the electronic databases would have been identified from the chart review process. Patients with atrial flutter alone and without any evidence of AF, were not included. For the purpose of this study, we did not specifically distinguish paroxysmal from persistent or permanent AF. All diagnoses, covariates, and outcomes were defined a priori, and the same definitions were applied to all patients throughout the 21-year study period.

Outcome ascertainment. Ascertainment of death was accomplished through comprehensive review of medical records and through the use of the following resources: death certificates, Vital Status Information from Mayo Registration, Minnesota State Death Tapes, and Social Security Death Index.

Statistical analyses. TRENDS IN BASELINE CHARACTERISTICS. Baseline characteristics were summarized by means and standard deviations or frequency percentages and assessed for trends across the calendar year of AF diagnosis using linear regression analyses for continuous variables and logistic regression analyses for binary variables, adjusting for age and gender. Calendar year of AF diagnosis was treated as a continuous variable. Only linear or linear logistic trends in calendar year of AF were considered.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio

MORTALITY AFTER FIRST AF DIAGNOSIS. The cumulative survival after AF was estimated using the Kaplan-Meier method. Based on Kaplan-Meier analyses, the mortality rate was highest in the initial 4 months after the diagnosis of first AF but decreased progressively and appeared to plateau at around the fifth month following first diagnosis. Therefore, we chose the cut point of 4 months after first AF diagnosis (early mortality period) for the purpose of analyses owing to the temporal profile and changes in mortality risk. The relative mortality risk associated with incident AF, defined as the hazard ratio (HR) between those with a diagnosis of AF and those in the Minnesota white population of the same age, gender, and calendar year, was analyzed both in terms of overall mortality as well as separately in terms of early mortality period (within first 4 months) and late mortality. First, observed and expected mortality were plotted and compared using the 1-sample log rank test, with expected mortality calculated using the Vital Statistics databases and an in-house SAS macro (SAS Institute, Cary, North Carolina). Second, the relative hazard was estimated, both overall and within the 2 time periods (early mortality period and late mortality), as the ratio of observed to expected deaths, with the numerator considered as a Poisson variable with expected value equal to the denominator, for the purpose of constructing confidence intervals (CI).

TRENDS IN MORTALITY AFTER FIRST AF DIAGNOSIS. For display purposes, Kaplan-Meier survival curves were estimated for each of the 4 periods 1980 through 1984, 1985 through 1989, 1990 through 1994, and 1995 through 2000. The primary formal analyses examined the effects of age and gender on mortality after AF diagnosis, and then the effect of calendar year of AF diagnosis on mortality, controlling for age and gender, using the Cox proportional hazards model for time to death, with age, gender, and calendar year in the model. Two models were considered: a main effects model with age, gender, and calendar year entering additively, and a second model that considered, in addition, all 3 possible 2-way interactions among the 3 variables, with only significant interactions being retained.

Next, to explore trends in mortality adjusting for patient baseline characteristics, multivariable Cox regression models were used, further adjusting the main effects model for a set of baseline clinical variables. Clinical covariates selected for adjustment included age; gender; body mass index; heart rate at AF diagnosis; and history of myocardial infarction, congestive heart failure, peripheral vascular disease, carotid artery disease, stroke, systemic hypertension, diabetes mellitus, smoking, regular alcohol use, chronic renal disease, chronic obstructive pulmonary disease, hyperthyroidism,

JACC Vol. 49, No. 9, 2007
March 6, 2007:986–92

and malignancy. We did not use valvular heart disease for adjustment in the multivariate models for the purpose of assessing trends in mortality. This was because the prevalence of valvular heart disease increased markedly over time, despite the same definition used throughout the study period, reflecting the major changes in practice with the use of echocardiography.

Finally, to allow for the pronounced difference between early high mortality and late mortality, 3 supplementary analyses were performed, adjusting for baseline characteristics. In the first, analysis was limited to the early high mortality period of follow-up by censoring all patients at the early high mortality period. In the second, analysis was limited to subjects who survived and were followed beyond the early high mortality period. In the third supplementary analysis, with the goal of removing patients who were more likely to have early events, analysis was restricted to those without earlier or concurrent cardiovascular history (congestive heart failure, ischemic stroke, angina, angiographically confirmed coronary artery disease, or myocardial infarction).

PREDICTORS OF DEATH IN PATIENTS WITH AF. In an attempt to understand the factors associated with mortality risk, we evaluated the relationship between selected clinical variables and time to death by Cox modeling. The following variables were considered: age; gender; body mass index; heart rate at AF diagnosis; and history of myocardial infarction, congestive heart failure, echocardiographically confirmed valvular heart disease, coronary revascularization, peripheral vascular disease, carotid artery disease, stroke, systemic hypertension, diabetes mellitus, dyslipidemia, smoking, regular alcohol use, chronic renal disease, chronic obstructive pulmonary disease, hyperthyroidism, and malignancy . First, an overall model was estimated, describing the HR associated with each variable throughout time. In addition, a 2-phase time-dependent model was estimated,

Table 1 Baseline Characteristics of the Study Population, Stratified by Calendar Year of AF Diagnosis

Variable	Overall (n = 4,618)	Calendar Year of AF Diagnosis				p Value*
		1980–1984 (n = 826)	1985–1989 (n = 938)	1990–1994 (n = 1,209)	1995–2000 (n = 1,645)	
Age (yrs)	73.1 ± 14.4	72.9 ± 14.5	72.8 ± 14.1	73.0 ± 14.7	73.4 ± 14.3	0.07
Men	2,365 (51)	412 (50)	469 (50)	629 (52)	855 (52)	0.08
BMI (kg/m^2)	27.1 ± 6.2	25.8 ± 5.3	26.2 ± 5.5	27.2 ± 6.3	28.0 ± 6.6	<0.0001
Systolic BP (mm Hg)	138 ± 21	137 ± 22	143 ± 21	140 ± 20	135 ± 19	<0.0001
Diastolic BP (mm Hg)	78 ± 11	78 ± 11	80 ± 10	79 ± 11	75 ± 11	<0.0001
Heart rate at AF (beats/min)	112 ± 32	113 ± 32	115 ± 32	111 ± 31	112 ± 32	0.12
History of CAD	1,776 (38)	315 (38)	400 (43)	441 (36)	620 (38)	0.15
Prior myocardial infarction	962 (21)	189 (23)	194 (21)	246 (20)	333 (20)	0.08
Prior CHF	446 (9.7)	59 (7.1)	82 (8.7)	131 (11)	174 (11)	<0.01
Concurrent CHF	884 (19)	206 (25)	223 (24)	220 (18)	235 (14)	<0.0001
Clinically diagnosed VHD	1,128 (24)	131 (16)	217 (23)	304 (25)	476 (29)	<0.0001
Echocardiographically confirmed VHD	969 (21)	46 (5.6)	160 (17)	292 (24)	471 (29)	<0.0001
Coronary revascularization	575 (12)	44 (5.3)	83 (8.8)	154 (13)	294 (18)	<0.0001
Peripheral artery disease	605 (13)	105 (13)	139 (15)	161 (13)	200 (12)	0.16
Carotid artery disease	208 (4.5)	26 (3.1)	43 (4.6)	56 (4.6)	83 (5.0)	<0.05
Stroke	437 (9.5)	86 (10)	85 (9.1)	128 (11)	138 (8.4)	0.09
Systemic hypertension	3,694 (80)	580 (70)	754 (80)	982 (81)	1,378 (84)	<0.0001
Diabetes mellitus	844 (18)	154 (19)	148 (16)	227 (19)	315 (19)	0.28
Dyslipidemia	1,706 (37)	128 (15)	245 (26)	451 (37)	882 (54)	<0.0001
Smoking	2,592 (56)	431 (52)	533 (57)	679 (56)	949 (58)	<0.05
Regular alcohol use	539 (12)	89 (11)	119 (13)	151 (12)	180 (11)	0.79
Chronic renal disease	782 (17)	150 (18)	140 (15)	188 (16)	304 (18)	0.39
COPD	1,000 (22)	192 (23)	230 (25)	244 (20)	334 (20)	<0.05
Hyperthyroidism	47 (1.0)	10 (1.2)	18 (1.9)	8 (0.7)	11 (0.7)	<0.05
History of malignancy	1,237 (27)	171 (21)	242 (26)	315 (26)	509 (31)	<0.0001
Angiotensin-converting enzyme inhibitor	504 (11)	5 (0.6)	27 (2.9)	157 (13)	315 (19)	<0.0001
Angiotensin receptor blocker	34 (0.7)	0 (0)	0 (0)	0 (0)	34 (2.1)	<0.0001
Calcium-channel blocker	666 (14)	25 (3.0)	98 (10)	198 (16)	345 (21)	<0.0001
Beta-blocker	687 (15)	89 (11)	115 (12)	147 (12)	336 (20)	<0.0001
Diuretics	1,705 (37)	335 (41)	364 (39)	429 (35)	577 (35)	<0.01
Lipid-lowering therapy	222 (4.8)	2 (0.2)	6 (0.6)	30 (2.5)	184 (11)	<0.0001

Values are given as mean ± SD or number (%). *p value for trends across calendar-year of AF diagnosis by linear regression analysis for continuous variables and logistic regression analysis for binary variables, with adjustment for age and gender.

AF = atrial fibrillation; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; VHD = valvular heart disease.

in which each variable's HR was allowed to vary between the early high mortality period and late mortality. The HRs in each time period were tested for departure from the null hypothesis of no association, and the 2 HRs were further tested for equality to each other. All tests of significance were 2 tailed, and a p value of <0.05 was considered to be statistically significant.

Results

The study population consisted of 4,618 subjects (mean age 73 ± 14 years, range 18 to 107 years, 51% men) who were confirmed to have AF for the first time in the years 1980 to 2000. Baseline characteristics stratified by calendar-year of AF diagnosis are displayed in Table 1.

Mortality after first AF diagnosis. During a mean follow-up time of 5.3 ± 5.0 years, 3,085 died. Of these, 761 died within the first 4 months and 2,324 thereafter. The Kaplan-Meier estimates of survival at 4 months, 1 year, 3 years, and 5 years were 83% (95% CI 82% to 85%), 77% (95% CI 76% to 78%), 63% (95% CI 62% to 65%), and 52% (95% CI 51% to 54%), respectively. A high early mortality rate (within first 4 months) followed by a flatter survival curve after 4 months was evident (Fig. 1). Relative to age- and gender-matched general Minnesota population, the mortality risk for AF patients was substantially higher (log rank $p < 0.0001$). The HRs were as follows: overall: 2.08 (3,085 vs. 1,481.8 expected, 95% CI 2.01 to 2.16); within the first 4 months: 9.62 (761 observed vs. 79.07 expected, 95% CI 8.93 to 10.32); and after the first 4 months: 1.66 (2,324 observed vs. 1,402.8 expected, 95% CI 1.59 to 1.73) (Fig. 1). The most common causes of cardiovascular death were coronary artery disease, congestive heart failure, and ischemic stroke, accounting for 22%, 14%, and 10%, respectively, of the early deaths (within first 4 months) and 15%, 16%, and 7%, respectively, of the late deaths. The most common noncardiovascular cause of death was malignancy, accounting for 18% and 14% of the early and late deaths, respectively.

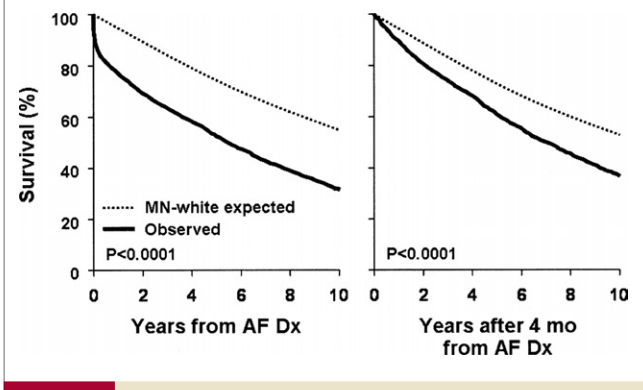

Figure 1 Survival for AF Patients Compared With the Age- and Gender-Matched General MN Population

Survival for the entire study population of patients diagnosed with first atrial fibrillation (AF) **(left)** and for the subgroup of survivors who lived beyond the first 4 months after the initial AF diagnosis (Dx) **(right)**, compared with the age- and gender-matched general Minnesota (MN) population.

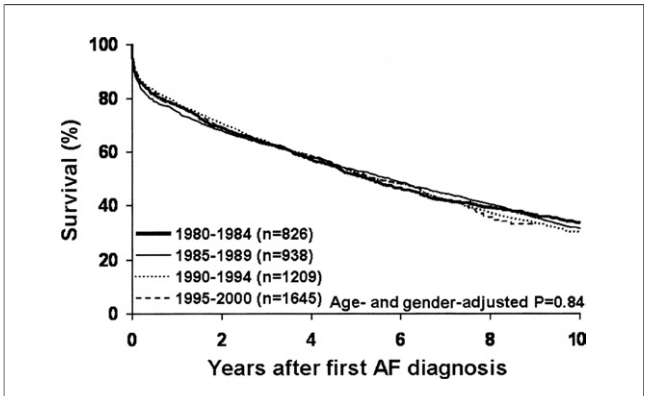

Figure 2 Mortality Trend of Patients Diagnosed With First AF, Stratified by Calendar Year of AF Diagnosis

AF = atrial fibrillation.

Trends in mortality after first AF diagnosis. Kaplan-Meier survival curves by 5-year periods are essentially superimposable (Fig. 2). Advancing age (HR per 10 years: 1.95; 95% CI 1.88 to 2.03; $p < 0.0001$) and male gender (HR 1.25; 95% CI 1.16 to 1.35; $p < 0.0001$) were associated with increased mortality risk in Cox regression analysis. When calendar year of AF diagnosis was added to the model, and a main effects model was estimated, there was no change in the overall trend in age- and gender-adjusted mortality after first AF was diagnosed observed over the 2 decades (HR for the year 2000 vs. 1980: 0.99; 95% CI 0.86 to 1.13; $p = 0.84$).

Analysis of 2-way interactions. When the 2-way interactions among the 3 variables (age, gender, and calendar year of AF diagnosis) were added to the model, there was no significant interaction between gender and calendar year of AF diagnosis but a significant negative interaction between age and calendar year of AF diagnosis ($p = 0.003$). To further understand this interaction, the incidence cohort was divided into 4 age strata (<60 years, 60 to 69 years, 70 to 79 years, and ≥80 years), and a main effects model was fit within each of these strata. A significant increasing trend in mortality was observed in patients under 60 years of age (HR 1.92; 95% CI 1.04 to 3.56; $p = 0.03$), but no significant trends could be demonstrated in the other 3 age groups. In subjects over 60 years of age, no overall trend in age- and gender-adjusted mortality was observed (HR 0.98; 95% CI 0.83 to 1.09; $p = 0.48$). Therefore, all supplementary analyses were done both overall and within 2 age strata (<60 years and ≥60 years) (Table 2).

Supplementary analyses. MORTALITY TRENDS STRATIFIED BY AGE. For the overall group and for those over age 60, the mortality trends were similar when adjusted for age and gender only or when multiple clinical variables were included in the model. In contrast, for the group under 60 years of age, adjustment for multiple baseline clinical vari-

JACC Vol. 49, No. 9, 2007
March 6, 2007:986–92

Table 2 Mortality Risk of Calendar Year 2000 Relative to 1980, Stratified by Age for the Overall Population and Various Subgroups

		Overall		Age <60 yrs		Age ≥60 yrs	
Model	Subject at Risk	n	HR* (95% CI)	n	HR* (95% CI)	n	HR* (95% CI)
Age- and gender-adjusted	All eligible	4,618	0.99 (0.86–1.13)	707	1.92† (1.04–3.56)	3,911	0.98 (0.83–1.09)
Adjusted for clinical variables‡	All eligible	4,618	0.99 (0.86–1.14)	707	1.56 (0.80–3.03)	3,911	0.97 (0.84–1.12)
Adjusted for clinical variables‡	All eligible (censored at 4 months)	4,618	0.95 (0.73–1.22)	707	4.09† (1.12–40.9)	3,911	0.86 (0.66–1.12)
Adjusted for clinical variables‡	4-month survivors	3,796	1.07 (0.91–1.26)	635	0.96 (0.43–2.14)	3,161	1.08 (0.91–1.28)
Adjusted for clinical variables‡	No CV disease§	2,064	0.95 (0.75–1.21)	502	1.78 (0.63–5.02)	1,562	0.88 (0.69–1.13)

*Hazard ratio (HR) is for calendar year 2000 compared with that in 1980; †$p < 0.05$ for HR different from 1.0; ‡clinical covariates selected for adjustment included age, gender, body mass index, heart rate at atrial fibrillation diagnosis, and history of myocardial infarction, congestive heart failure, peripheral vascular disease, carotid artery disease, stroke, systemic hypertension, diabetes mellitus, smoking, regular alcohol use, chronic renal disease, chronic obstructive pulmonary disease, hyperthyroidism, and malignancy; §analysis restricted to those without cardiovascular (CV) disease including prior or concurrent congestive heart failure, ischemic stroke, angina, angiographically confirmed coronary artery disease, and myocardial infarction.
CI = confidence interval.

ables removed the statistical significance of the increasing trend in mortality (HR 1.56: 95% CI 0.80 to 3.03; p = 0.27).

MORTALITY TRENDS STRATIFIED BY EARLY VERSUS LATE MORTALITY AND BY PRE-EXISTING CARDIOVASCULAR DISEASE. When analysis was restricted to the high-mortality period (within first 4 months), to a late period (after the first 4 months), or to the subjects who were free of cardiovascular diseases at the time of diagnosis of AF, there were no significant trends in mortality in the overall group or in the over-60 age group. The only significant change identified was an increasing trend in the under-60 age group (HR 4.09; 95% CI 1.12 to 40.9; p = 0.03) in the high-mortality period (within first 4 months) (Table 2). Among those who were under 60 years of age, malignancy was the cause in 1 out of 13 (8%) of the early deaths (within first 4 months) for the period of 1980 to 1989, and 11 out of 36 (31%) of the early deaths for the period 1990 to 2000 (p = 0.10). This observation suggested that the upward trend in early mortality in the younger group might have been limited to the subset with malignancy. To test this possibility, analysis of early mortality in the younger age group was further stratified by the presence or absence of a history of malignancy. The result was a significant upward trend in early mortality in those with malignancy (n = 70), accounting for 21 early deaths (HR 16.02; 95% CI 1.95 to 131.4; p = 0.008). There was no significant trend in early mortality in those without malignancy (n = 637), accounting for 28 early deaths (HR 1.75; 95% CI 0.47 to 6.61; p = 0.39).

PREDICTORS OF OVERALL, EARLY, AND LATE MORTALITY. The predictors of overall, early (within first 4 months), and late (after 4 months) mortality are shown in Table 3. Age, but not gender, was an important predictor of death for overall, early, and late mortality. A number of cardiovascular risk factors and chronic disease, including pulmonary and renal disease as well as malignancy, were predictors of

Table 3 Multivariable Models for Prediction of Early (Within 4 Months) or Late Death (After 4 Months)

	Overall Death		Early Death (≤4 Months)		Late Death (>4 Months)	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (per 10 yrs)*	1.79 (1.71–1.86)	<0.0001	1.33 (1.23–1.44)	<0.0001	1.98 (1.88–2.09)	<0.0001
Men	1.06 (0.98–1.15)	0.17	0.99 (0.84–1.18)	0.99	1.09 (0.99–1.20)	0.07
BMI (per 5 kg/m^2)*	0.90 (0.87–0.93)	<0.0001	0.80 (0.74–0.86)	<0.0001	0.93 (0.89–0.97)	<0.001
Heart rate at AF (per 10 beats/min)*	1.02 (1.01–1.03)	<0.001	1.08 (1.05–1.10)	<0.0001	1.00 (0.99–1.02)	0.70
Prior myocardial infarction*	1.39 (1.27–1.52)	<0.0001	1.75 (1.47–2.07)	<0.0001	1.27 (1.15–1.42)	<0.0001
Prior CHF*	1.34 (1.19–1.50)	<0.0001	0.90 (0.72–1.13)	0.35	1.60 (1.41–1.83)	<0.0001
Echo-confirmed VHD	1.26 (1.16–1.38)	<0.0001	1.31 (1.10–1.55)	<0.01	1.27 (1.15–1.41)	<0.0001
Coronary revascularization	0.76 (0.67–0.86)	<0.0001	0.64 (0.49–0.83)	<0.001	0.80 (0.69–0.92)	<0.01
Peripheral vascular disease	1.25 (1.13–1.38)	<0.0001	1.14 (0.94–1.38)	0.19	1.30 (1.16–1.47)	<0.0001
Carotid artery disease	1.19 (1.01–1.40)	0.03	1.13 (0.84–1.53)	0.41	1.23 (1.01–1.49)	0.04
Stroke	1.29 (1.15–1.44)	<0.0001	1.31 (1.06–1.62)	0.01	1.27 (1.11–1.45)	<0.001
Systemic hypertension	1.28 (1.14–1.44)	<0.0001	1.14 (0.89–1.45)	0.29	1.30 (1.14–1.48)	<0.0001
Diabetes mellitus	1.51 (1.38–1.66)	<0.0001	1.52 (1.28–1.82)	<0.0001	1.50 (1.35–1.67)	<0.0001
Dyslipidemia	0.91 (0.84–0.99)	0.02	0.82 (0.69–0.97)	0.02	0.95 (0.86–1.05)	0.29
Smoking	1.17 (1.07–1.27)	<0.001	1.30 (1.09–1.55)	<0.01	1.12 (1.02–1.24)	0.02
Chronic renal disease*	1.57 (1.43–1.72)	<0.0001	1.89 (1.60–2.24)	<0.0001	1.49 (1.33–1.66)	<0.0001
COPD*	1.41 (1.29–1.53)	<0.0001	1.14 (0.96–1.35)	0.14	1.49 (1.35–1.65)	<0.0001
History of malignancy*	1.43 (1.32–1.55)	<0.0001	1.88 (1.62–2.19)	<0.0001	1.29 (1.17–1.41)	<0.0001

*$p < 0.05$ for HR different in 2 time periods of early (within first 4 months) and late (after 4 months) death.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

overall mortality. Of note, malignancy and chronic renal disease were associated with almost a 2-fold increase in risk of early mortality, although age remained the most significant factor for late mortality (Table 3).

Discussion

The present study showed that there was no change in the overall age- and gender-adjusted mortality in patients diagnosed with first AF over the 21-year period, even after adjustment for comorbidities. Our secondary analyses further demonstrated that there were no significant changes in early (within first 4 months) or late mortality or in the mortality of the patients who did not have history of cardiovascular disease at baseline.

Trends in mortality over 2 decades. The present study was not an intervention study but a longitudinal cohort study with all participants selected based on first documented AF event. Most published series which reported an improvement in survival have been hospital-based studies (21–23), often specifically of AF complicating another event such as myocardial infarction or congestive heart failure (19,20). Thus, the AF events in those studies were not incident AF but represent a mixture of first and recurrent AF, usually surrounding specific comorbid conditions. We found that there was no change in the overall age- and gender-adjusted mortality, even after adjusting for multiple clinical risk factors. Additionally, we did not find any significant change in mortality trend when we limited the analyses to those who died within the first 4 months of AF diagnosis, survived the first 4 months, or did not have pre-existing cardiovascular disease. The impact on mortality trends was likely complex and multifactorial. We speculate that AF itself was probably not the primary cause of death in the majority of patients but a result of an underlying cascade of pathologic changes and events to which conventional AF treatment would not make a positive impact. Therefore, although the management of AF and complications, as well as our aggressiveness in treatment of risk factors of AF, might have changed over time, we were unable to detect a change in the overall mortality.

In an exploratory analysis of mortality trends stratified by age that was motivated by the presence of a highly significant age by calendar-year interaction term, we observed an increase over time in early mortality among patients under 60 years of age which was limited to the subset of those with a history of malignancy. In addition to a significant increase in the proportion of incident AF cases with a history of malignancy during this period (Table 1), the proportion of early deaths attributable to malignancy increased from 8% to 31% in the group under 60 years of age. Whether these observations were related to increased survival of certain malignancies over time, with development of AF as a preterminal event, warrants further investigations.

Predictors of overall, early, and late mortality. Atrial fibrillation has previously been shown to be associated with premature death (14–18), and this was further confirmed in the present study. We evaluated the temporal distribution of death, and found a clustering of death in the early period (within first 4 months), followed by an attenuated but nonetheless increased mortality risk thereafter. From our multivariable models, faster heart rate at AF diagnosis, lower body mass index, history of chronic renal disease, and malignant disease were all strongly associated with early death. In patients who died early after AF diagnosis, AF represented a preterminal event, marking the severe illness of these patients. In contrast, cardiovascular comorbidities, as well as chronic illness, were important predictors for late death, as expected to be associated with age-related AF.

Study limitations. There were inherent biases associated with the retrospective design. It was possible that some incident AF cases were been missed, because some patients may not have been seen at the Mayo Clinic and some asymptomatic cases may not have come to medical attention. Detailed data with respect to cardiac function and the use of medical therapy were not readily available, and how these factored into the mortality trends could not be determined. Also, the assessment of changes in the comorbid conditions was difficult in part because of the changing definitions over time and missing laboratory data. The population of Olmsted County is predominantly white, and whether similar mortality rates and trends are present in other ethnic and racial groups is unknown.

Conclusions

In this community-based cohort study, the mortality risk of patients diagnosed with first AF was substantially higher than that of the same age- and gender-matched general population, especially within, but not limited to, the first 4 months. The overall trend in age- and gender-adjusted mortality did not change over the 21-year period, even after multiple adjustments. Further, we could not identify any significant change in the trends of early or late mortality or mortality of patients without pre-existing cardiovascular disease.

Reprint requests and correspondence: Dr. Teresa S. M. Tsang, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: tsang.teresa@mayo.edu.

REFERENCES

1. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol 2001;37:371–8.
2. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997;337:1360–9.
3. Scheinman MM. Atrial fibrillation and congestive heart failure: the intersection of two common diseases. Circulation 1998;98:941–2.
4. Alpert JS. Atrial fibrillation: a growth industry in the 21st century. Eur Heart J 2000;21:1207–8.
5. Tsang TS, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in

Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:93–100.
6. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota 1980–2000, and implications on the projections for future prevalence. Circulation 2006;114:119–25.
7. Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation. Risk of stroke and role of antithrombotic therapy. Circulation 1991;84: 469–81.
8. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the Elderly. Stroke 1998;29:1341–6.
9. Whisnant JP, Wiebers DO, O'Fallon WM, Sicks JD, Frye RL. A population-based model of risk factors for ischemic stroke: Rochester, Minnesota. Neurology 1996;47:1420–8.
10. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. Neurology 1978;28:973–7.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22: 983–8.
12. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290: 1049–56.
13. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107: 2920–5.
14. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley Study. Am J Med 2002;113:359–64.
15. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476–84.
16. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
17. Vidaillet H, Granada JF, Chyou PH, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med 2002;113:365–70.
18. Gajewski J, Singer RB. Mortality in an insured population with atrial fibrillation. JAMA 1981;245:1540–4.
19. Goldberg RJ, Yarzebski J, Lessard D, Wu J, Gore JM. Recent trends in the incidence rates of and death rates from atrial fibrillation complicating initial acute myocardial infarction: a community-wide perspective. Am Heart J 2002;143:519–27.
20. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with atrial fibrillation and advanced heart failure. J Am Coll Cardiol 1996;28:1458–63.
21. Stewart S, MacIntyre K, Chalmers JW, et al. Trends in case-fatality in 22968 patients admitted for the first time with atrial fibrillation in Scotland, 1986–1995. Int J Cardiol 2002;82:229–36.
22. Frost L, Engholm G, Moller H, Husted. Decrease in mortality in patients with a hospital diagnosis of atrial fibrillation in Denmark during the period 1980–1993. Eur Heart J 1999;20:1592–9.
23. Frost L, Vestergaard P, Mosekilde L, Mortensen LS. Trends in incidence and mortality in the hospital diagnosis of atrial fibrillation or flutter in Denmark, 1980–1999. Int J Cardiol 2005;103: 78–84.
24. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996;71:266–74.

APPENDIX

For the definition of covariates, please see the online version of this article.