

Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality

The Framingham Heart Study

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Background—Atrial fibrillation (AF) and congestive heart failure (CHF) frequently occur together, but there is limited information regarding their temporal relations and the combined influence of these conditions on mortality.

Methods and Results—We studied participants in the Framingham Study with new-onset AF or CHF. Multivariable Cox proportional hazards models with time-dependent variables were used to evaluate whether mortality after AF or CHF was affected by the occurrence and timing of the other condition. Hazard ratios (HRs) were adjusted for time period and cardiovascular risk factors. During the study period, 1470 participants developed AF, CHF, or both. Among 382 individuals with both conditions, 38% had AF first, 41% had CHF first, and 21% had both diagnosed on the same day. The incidence of CHF among AF subjects was 33 per 1000 person-years, and the incidence of AF among CHF subjects was 54 per 1000 person-years. In AF subjects, the subsequent development of CHF was associated with increased mortality (men: HR 2.7; 95% CI, 1.9 to 3.7; women: HR 3.1; 95% CI, 2.2 to 4.2). Similarly, in CHF subjects, later development of AF was associated with increased mortality (men: HR 1.6; 95% CI, 1.2 to 2.1; women: HR 2.7, 95% CI, 2.0 to 3.6). Preexisting CHF adversely affected survival in individuals with AF, but preexisting AF was not associated with adverse survival in those with CHF.

Conclusions—Individuals with AF or CHF who subsequently develop the other condition have a poor prognosis. Additional studies addressing the pathogenesis, prevention, and optimal management of the joint occurrence of AF and CHF appear warranted. (*Circulation*. 2003;107:2920-2925.)

Key Words: arrhythmia ■ fibrillation, atrial ■ heart failure ■ mortality

Atrial fibrillation (AF) and congestive heart failure (CHF) have been called the “two new epidemics of cardiovascular disease.”¹ Both conditions are responsible for substantial economic cost, morbidity, and mortality. These conditions also disproportionately affect the elderly, the incidence of each doubling for every successive decade of age.^{2,3} Hence, the burden associated with these disorders is expected to grow as the population ages.

An important feature of AF and CHF is their propensity to coexist, in part because they share antecedent risk factors, but also because one may directly predispose to the other.^{4,5} It is widely perceived that the combination of these conditions carries a worse prognosis than either alone. Thus, medical and mechanical therapies aimed at treating this combination have gained increasing attention.^{6,7} The data regarding the joint prognosis of AF and CHF are conflicting, however. For instance, AF has been reported to have a deleterious,^{8–10}

neutral,^{11,12} or beneficial^{13,14} impact on survival among patients with CHF.

Disparities among prior studies may reflect a focus on prevalent rather than incident disease,^{9,11,12} varying durations of AF and CHF,^{8,10,11} and the characteristics of different referral populations.^{8,11,13} The joint time course of AF and CHF and the sequence in which they occur may have a marked influence on prognosis; however, to our knowledge, this has not been studied in a general population. Accordingly, the purpose of this study was to characterize the joint epidemiology of AF and CHF in a large, community-based cohort that has been monitored for decades.

Methods

Subjects

The selection criteria and study design of the Framingham Heart Study have been described elsewhere.^{15,16} The original cohort has

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been followed up with biennial examinations since 1948. The offspring cohort was initiated in 1971 and has been examined quadrennially. All protocols are approved by the Boston Medical Center Institutional Review Board.

We studied individuals with new-onset AF or CHF between 1948 and 1995, excluding those with a history of AF or CHF at the time of study entry (n=30). We excluded participants whose first event occurred after 1995 (n=279) to ensure that follow-up was long enough to allow the occurrence of a second event. We also restricted analyses to individuals ≥ 50 years old, because both conditions were rare in younger individuals. Participants were followed up through 1998.

Clinical Evaluation

Medical history, physical examination, and electrocardiography were routinely administered at each Framingham Heart Study examination.^{15,16} Baseline risk factor data were derived from the closest examination cycle at or before the initial condition.

Records were obtained for all medical encounters related to cardiovascular disease and were adjudicated by a committee of 3 investigators. AF was diagnosed if AF or atrial flutter was present on an ECG obtained from the Framingham clinic or outside hospital or physician chart. The ECG interpretation of AF was confirmed by 1 of 2 Framingham Study cardiologists. The diagnosis of CHF was based on clinical criteria that have been in use since the study's inception. The presence of 2 major or 1 major and 2 minor criteria was used to establish a diagnosis of CHF. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, distended neck veins, rales, radiographic cardiomegaly, pulmonary edema, third heart sound, increased venous pressure, hepatojugular reflux, and weight loss on diuretic therapy. Minor criteria were ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, pulmonary vascular redistribution, decrease in vital capacity, and tachycardia.

On the basis of review of hospitalization records, physician office records, and information from the Framingham clinic visit, a date of onset was assigned to all new AF or CHF events. If individuals presented with AF and CHF on the same day, the events were considered concurrent and the same date was assigned to both events. For individuals developing AF, CHF was referred to as the comorbid condition and vice versa.

Statistical Analyses

Among participants with AF or CHF, incidence rates for developing the comorbid condition were calculated. Cumulative incidence curves were derived using the Kaplan-Meier methods (truncated at 10 years of follow-up for display) to depict the development of CHF after AF and AF after CHF.

The joint influence of AF and CHF on mortality was analyzed using sex-specific Cox proportional hazards models, with the development of the comorbid condition modeled as a time-dependent variable. Hence, we examined whether survival after AF was affected by the occurrence of CHF in those who were initially free of CHF and vice versa. In a second set of analyses, we examined whether survival after AF or CHF was affected by the preexistence of the comorbid condition. The comorbid condition was treated as a categorical predictor, and the reference group consisted of those who were free of the comorbid condition at the time of the index diagnosis. Thus, we evaluated if survival after CHF was affected by a prior diagnosis of AF or AF diagnosed on the same day and vice versa.

All models were adjusted for the following covariates: age, time period, prior or concurrent myocardial infarction, history of stroke or transient ischemic attack, diabetes, valvular disease on physical examination, ECG left ventricular hypertrophy, systolic blood pressure, use of antihypertensive therapy, and smoking. Time period (1948 to 1969, 1970 to 1979, 1980 to 1989, 1990 or later) was included in the model to account for possible secular trends in mortality after AF or CHF. All models were stratified for age (<75 and ≥ 75 years old).

TABLE 1. Baseline Characteristics by Initial Event

	AF* (n=683)	CHF† (n=708)	Concurrent AF and CHF‡ (n=79)
Mean age, y	74±10	73±11	75±10
Mean systolic blood pressure, mm Hg	144±23	153±27	149±23
Hypertension therapy, %	41	41	41
Myocardial infarction, %	18	45	27
Stroke/transient ischemic attack, %	12	12	10
Diabetes, %	12	23	24
Smoking, %	27	34	28
Significant murmur,§ %	13	18	26
ECG left-ventricular hypertrophy, %	7	15	4

The initial event occurred before 1970 for 18% of the sample, between 1970 and 1979 for 23%, between 1980 and 1989 for 36%, and after 1989 for 23%.

*Without concurrent or prior CHF.

†Without concurrent or prior AF.

‡AF and CHF diagnosed on the same day.

§ \geq Grade III/VI systolic murmur, or any diastolic murmur; missing for 35 (2%) subjects.

||Increased voltage and lateral repolarization abnormalities.

Secondary analyses were performed excluding subjects prescribed antiarrhythmics or anticoagulants for the index AF episode and excluding subjects with atrial flutter. We also tested time period interaction terms to evaluate whether the influence of comorbid AF or CHF differed in the 1990s compared with earlier decades.

Results

Subject Characteristics and Sequence of Events

Between 1948 and 1995, 1470 participants developed AF, CHF, or both. Characteristics of subjects at the time of their initial event are shown in Table 1. The mean follow-up was 5.6 years (5061 person-years) after the development of AF and 4.2 years (3823 person-years) after the development of CHF. The proportion of subjects dead at the end of follow-up was 86%.

A total of 382 participants developed both AF and CHF. Of these, 38% had AF first, 41% had CHF first, and 21% had both disorders diagnosed on the same day (Figure 1). Among those who had AF and CHF diagnosed on the same day, 7 (9%) had a myocardial infarction within the preceding 15 days.

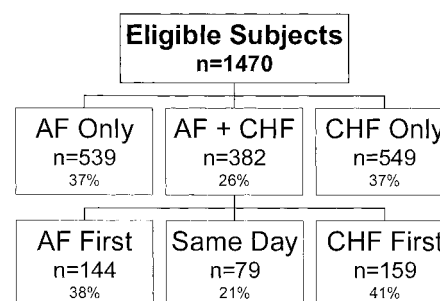


Figure 1. Timing and distribution of subjects with AF, CHF, or both.

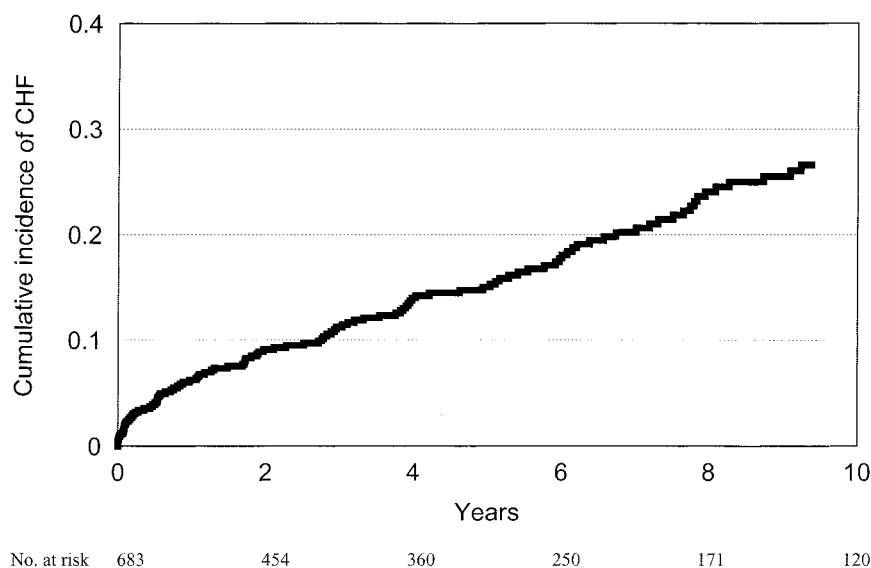


Figure 2. Unadjusted cumulative incidence of first CHF in individuals with AF.

Incidence Rates for Developing the Comorbid Condition

Of the 921 subjects diagnosed with AF, 238 (26%) had a prior or concurrent diagnosis of CHF and 144 (16%) developed it subsequently. Among those free of CHF at AF onset, the unadjusted incidence of CHF was 33 per 1000 person-years. Of 931 subjects diagnosed with CHF, 223 (24%) had prior or concurrent AF and 159 (17%) developed AF subsequently. The unadjusted incidence of AF, for those free of AF at CHF onset, was 54 per 1000 person-years. The cumulative incidence curves for the development of CHF after AF and AF after CHF are shown in Figures 2 and 3, respectively.

Impact of Developing the Comorbid Condition on Mortality

We used multivariable models to evaluate the impact of CHF on mortality in AF subjects, restricting our analyses to those who were free of CHF at the time of AF diagnosis (Table 2). The subsequent development of CHF (time-dependent vari-

able) was associated with a multivariable-adjusted hazard ratio for mortality of 2.7 (95% CI, 1.9 to 3.7) in men and 3.1 (95% CI, 2.2 to 4.2) in women.

Similarly, we examined the impact of AF on mortality in CHF subjects, restricting our analyses to those who were free of AF at the time of CHF diagnosis (Table 2). The development of subsequent AF (time-dependent variable) was associated with an adjusted hazard ratio for mortality of 1.6 (95% CI, 1.2 to 2.1) in men and 2.7 (95% CI, 2.0 to 3.6) in women.

Impact of Prior Diagnosis of the Comorbid Condition on Mortality

Additional multivariable analyses were performed to examine the influence of a prior diagnosis of the comorbid condition (Table 2). We estimated separate hazard ratios corresponding to whether the comorbid condition was diagnosed previously or on the same day as the index condition (with subjects without the comorbid condition as the reference group). In AF subjects, prior CHF and concurrent CHF were associated

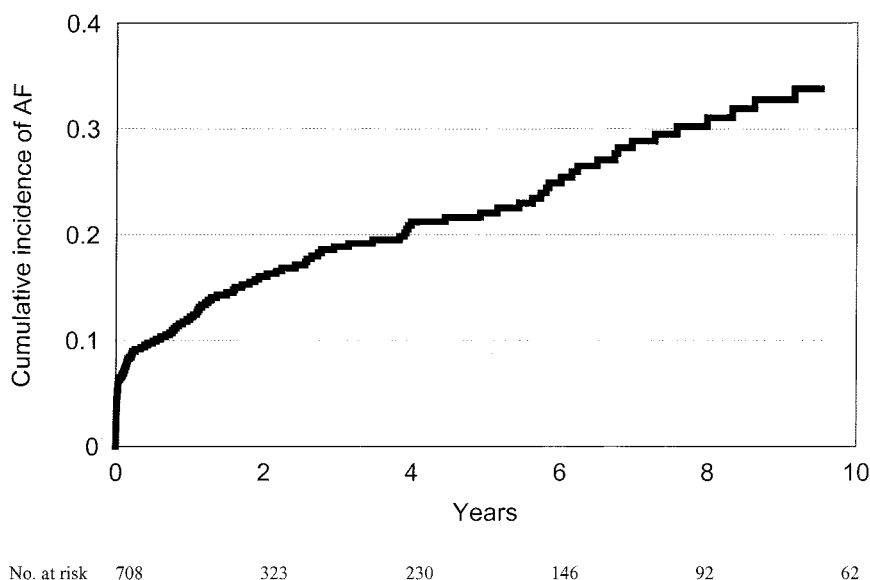


Figure 3. Unadjusted cumulative incidence of first AF in individuals with CHF.

TABLE 2. Cox Multivariable Proportional Hazards Models Examining the Impact of the Comorbid Condition on Mortality

Models	Men, Adjusted HR (95% CI)	Women, Adjusted HR (95% CI)
Comorbid condition as a time-dependent variable		
(A) Mortality after AF		
Impact of incident CHF	2.7 (1.9 to 3.7)*	3.1 (2.2 to 4.2)*
(B) Mortality after CHF		
Impact of incident AF	1.6 (1.2 to 2.1)†	2.7 (2.0 to 3.6)*
Comorbid condition as a categorical variable		
(C) Mortality after AF		
Impact of prior CHF	2.2 (1.6 to 3.0)*	1.8 (1.3 to 2.3)*
Impact of concurrent CHF‡	2.4 (1.6 to 3.5)*	1.4 (1.0 to 1.9)
(D) Mortality after CHF		
Impact of prior AF	0.8 (0.6 to 1.0)	1.2 (0.9 to 1.6)
Impact of concurrent AF‡	1.0 (0.7 to 1.4)	1.1 (0.8 to 1.5)

* $P \leq 0.0001$, † $P < 0.01$.

‡Diagnosed on same day. Each letter (A through D) denotes a separate model. Models with the comorbid condition as a time-dependent variable (A and B) are restricted to those without the comorbid condition at the index event. Hazard ratios (HR) are adjusted for age, time period, myocardial infarction, stroke/transient ischemic attack, diabetes, valvular disease, ECG left ventricular hypertrophy, systolic blood pressure, antihypertensive therapy, and smoking.

with increased mortality (Table 2). For men with AF, unadjusted median survival times for those with prior CHF, concurrent CHF, or no CHF (at the time of AF diagnosis) were 1.4, 2.1, and 6.6 years, respectively. Corresponding survival times in women were 1.8, 3.5, and 5.0 years.

In CHF subjects, neither prior AF nor concurrent AF was associated with increased mortality after multivariable adjustment (Table 2). Median unadjusted survival times for men with prior AF, concurrent AF, or no AF (at the time of CHF diagnosis) were 2.0, 2.1, and 1.7 years, respectively. For women, corresponding survival times were 2.1, 3.5, and 3.4 years.

Secondary Analyses

Results were similar in secondary analyses excluding subjects on antiarrhythmic therapy or anticoagulant therapy for the index AF or subjects with atrial flutter (data not shown). In women only, the adverse influence of incident CHF on AF mortality was less in the 1990s compared with earlier decades ($P=0.016$ for interaction). In men, there was marginal evidence of a stronger influence of incident AF on CHF mortality in the 1990s ($P=0.047$ for interaction).

Discussion

The goal of this study was to examine the complex relations between AF and CHF using observations from a large, prospective community-based cohort. We provide new information regarding the joint incidence of AF and CHF in the community. We also demonstrate that the temporal sequence of AF and CHF is important to consider when estimating the relative risk of mortality associated with having both conditions. For those with either AF or CHF, the development of the second condition has a deleterious impact on survival.

Our findings regarding the poor prognosis associated with AF and CHF are consistent with those of most^{8–10} but not all^{11,12} prior studies with >200 subjects. However, prior studies have been based on referral populations^{8,12} or retrospective analyses of randomized trial cohorts.⁹ Subjects in these studies have been predominantly male, with a mean age in the 50s and a high prevalence of idiopathic cardiomyopathy. Thus, they are not representative of individuals with AF or CHF in the community, who tend to be elderly and have a higher prevalence of hypertension.^{3,17} Furthermore, follow-up in most studies was less than a decade, which limited their ability to analyze incident AF or CHF events.

Interaction of AF and CHF

The reported prevalence of AF in various CHF series ranges from 13% to 27%.^{8,11,12,17,18} However, a single prevalence estimate may understate the overall frequency with which AF and CHF occur in the same individual. For instance, among 931 Framingham Study participants diagnosed with CHF, 223 (24%) had prior or concurrent AF. Another 159 (17%) had AF subsequently, however, so that the total proportion of CHF subjects with AF at some time was 41%. Similarly, 42% of AF subjects had CHF at some point during their lifetime.

Because all subjects in our study were free of AF and CHF at baseline, we had the opportunity to examine the chronology of these events. Interestingly, AF preceded CHF about as often as CHF preceded AF. In one fifth of subjects with AF and CHF, it was unclear which was the initial event, because both conditions were noted for the first time on the same day.

Several mechanisms may explain why AF and CHF occur together and may underlie the variability in their presentations. Animal studies and case reports indicate that AF with rapid ventricular response can lead to dilated cardiomyopathy.⁵ In addition, the loss of atrial transport may predispose to CHF by

causing a fall in cardiac output.¹⁹ Conversely, CHF may predispose to AF via acutely increased atrial filling pressures and atrial dilatation.⁶ Chronically, CHF causes atrial fibrosis and regional conduction abnormalities, which may provide a substrate for AF initiation.⁴ Furthermore, the sympathetic activation seen in chronic CHF may contribute to electrophysiologic changes, such as a shortened atrial refractory period, that promote AF.²⁰ A single event (such as myocardial infarction) may precipitate both AF and CHF. Additionally, common risk factors could influence both atrial and ventricular remodeling and predispose to subclinical left atrial and left ventricular dysfunction that can culminate in overt AF and CHF.

Impact of Developing the Comorbid Condition on Mortality

Although it is recognized that individuals with AF are at increased risk of death, prospective data regarding the predictors of mortality in AF are limited.²¹ We found that incident CHF had an adverse impact on prognosis in AF independently of other cardiovascular diagnoses and risk factors.

In contrast, the impact of AF on CHF mortality has been examined extensively but remains controversial. Carson et al¹¹ studied CHF patients in the V-HeFT trials and found that baseline AF was not related to overall mortality or sudden death. Another study, however, reported that AF was associated with increased mortality in the SOLVD trials.⁹ AF was also an independent predictor of mortality among patients in the AVID registry, most of whom had CHF or left ventricular dysfunction.²² Studies based on CHF patients at transplant centers have reached conflicting conclusions.^{8,12} Two studies have even reported that AF has a beneficial impact on prognosis in CHF.^{13,14}

We found that the development of new AF in individuals with CHF was associated with increased mortality. Our focus on subjects with new-onset AF and CHF (an incidence cohort) rather than subjects with prevalent disease may explain differences with prior studies. Several biases may occur in prevalence cohorts. The sickest subjects are less likely to be sampled, which may lead to survival bias.¹⁹ The apparent influence of AF is also confounded by disease duration, with AF being associated with more longstanding disease. Furthermore, prevalence studies are likely to underestimate of the overall impact of AF, because a substantial proportion of CHF patients are free of AF at baseline but develop it during follow-up. Two recent studies examined the impact of incident AF in CHF, with one suggesting an adverse effect¹⁹ and the other finding no effect.²³ Both studies, however, were based on a small number of incident AF cases and had limited power to examine mortality. It is also possible that variability in treatment and the adequacy of ventricular rate control in AF could contribute to differences between studies.

The adverse impact of AF in CHF patients is most likely multifactorial. The development of AF may be a marker of deterioration of ventricular function or increased neurohormonal activation. Alternately, AF may play a causal role via loss of atrial transport, accelerated ventricular response, or thromboembolism.^{9,19}

Impact of Prior Diagnosis of the Comorbid Condition on Mortality

We also examined the impact of a prior diagnosis of the comorbid condition on survival. Prior CHF had an adverse impact on prognosis in AF. However, antecedent AF was not a significant predictor of mortality in subjects with CHF. It is possible that the high mortality associated with CHF in the community overwhelmed the modest influence of preexisting AF, particularly after adjustment for other cardiovascular conditions.

Strengths and Limitations

The strengths of this investigation included the focus on incident AF and CHF cases with time-dependent models, routine ascertainment of antecedent risk factors, and uniform diagnostic criteria for AF and CHF. The large sample size allowed the use of sex-specific multivariable analyses. Furthermore, the availability of 5 decades of longitudinal data permitted complete follow-up (to time of death) on nearly all subjects.

Several limitations should be acknowledged. The unavailability of echocardiographic data during the first 3 decades of the study restricted us from drawing conclusions regarding the mechanism of heart failure (for instance, the presence of systolic versus diastolic dysfunction). Also, we did not distinguish between chronic and paroxysmal AF; the prognosis of these conditions may differ. The use of antiarrhythmic therapy for ventricular arrhythmias was not accounted for in these analyses. However, use of these medications was uncommon.

It is important to emphasize that treatment for AF and CHF has changed substantially in the last decade. These changes may have contributed to improved survival after CHF.²⁴ We found some evidence in women that the adverse impact of CHF after AF may have been less in the 1990s compared with earlier time periods. However, this result should be regarded as exploratory, because this was a secondary analysis and the probability value was not highly significant. Additionally, treatment has continued to evolve since our last year of follow-up (1998). Accordingly, much of the experience in this cohort represents the natural history of AF and CHF before the advent of contemporary therapies.

Clinical Implications

Because AF and CHF frequently occur together, there has been interest in understanding whether interventions to address this combination may favorably impact prognosis.²⁵ For instance, it has been speculated that restoring sinus rhythm may improve survival in patients with AF and CHF. The value of this strategy is unproven in AF²⁶ and has not been studied prospectively in CHF,¹⁸ although enrollment for a mortality trial of patients with both conditions is presently underway.⁷

Prior observational and treatment studies have focused on individuals with already established AF and CHF. Our study underscores the potential importance of intervening at an earlier stage in the clinical course of these patients. In individuals with AF or CHF alone, the development of the second condition carries a particularly poor prognosis. This

finding raises the possibility that prophylactic therapies to reduce the incidence of the second condition in high-risk patients with AF or CHF may confer clinical benefit.^{19,25,27} In light of the increasing burden of both conditions and the availability of new therapies, additional studies addressing the pathogenesis, prevention, and optimal management of the joint occurrence of AF and CHF seem warranted.

Acknowledgments

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