Atrial Fibrillation and Mortality in Heart Failure
A Community Study

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Background—Heart failure (HF) and atrial fibrillation (AF) share common risk factors and often coexist. The combination of HF and AF may carry a worse prognosis than either condition alone; however, the magnitude of this risk remains controversial and it is not known whether the timing of AF influences the risk of death.

Methods and Results—We determined the risk of all-cause mortality in relation to the presence of AF prior to or after HF diagnosis in a community-based cohort of persons diagnosed as having HF between 1983 and 2006. Of 1664 individuals with HF, 553 had a history of AF and 384 developed AF after HF. During a median follow-up of 4.0 years, 450 deaths occurred among persons with prior AF, 314 among those with AF after HF, and 572 among patients without AF. In fully adjusted models, compared with patients without AF, those with AF prior to HF had a 29% increased risk of death, whereas those who developed AF after HF exhibited a 2-fold increased risk of death.

Conclusions—In the community, AF is frequent in the setting of HF and is associated with a large excess risk of death. The magnitude of this excess risk differs markedly according to the timing of AF, with AF developing after HF conferring the largest increased risk of death compared with HF patients without AF.

Key Words: arrhythmia ♦ atrial fibrillation ♦ heart failure ♦ mortality ♦ survival

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and affects >2.2 million Americans.1 Atrial fibrillation often coexists with heart failure (HF), and the 2 conditions share many common risk factors, such as older age, hypertension, valvular heart disease, myocardial infarction (MI), and diabetes mellitus.2 Patients with HF have >3-fold increased risk of developing AF3;4; however, the effect of AF on the prognosis in HF patients remains controversial.

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Recently, 2 meta-analyses have summarized the published literature on the risk of death in HF patients with AF compared with those in sinus rhythm, indicating that the coexistence of AF in HF patients increases the odds of mortality 14% to 57% compared with HF alone.5,6 Unfortunately, these meta-analyses did not distinguish whether the AF associated with HF was chronic or recent AF, and the populations studied and follow-up were heterogeneous. However, observational studies7,8 have indicated that, compared with HF patients without AF, new-onset AF during a hospitalization for HF corresponds to an increased risk of death and in-hospital death, whereas prior AF was not associated with worse survival. In contrast, among outpatients with HF due to left ventricular systolic dysfunction, neither baseline nor new-onset AF developing during a median follow-up of 1.8 years, was associated with all-cause mortality.9 Among HF clinical trial populations, mixed results have been reported as to whether baseline or new-onset AF are associated with increased mortality compared with patients without AF.10–13 The major limitations of these studies are as follow: AF was not captured during follow-up7,12 and when AF was captured during follow-up, a time-dependent analysis considering this was not conducted.9–11,13 Furthermore, these studies enrolled patients with active HF and, thus, are not representative of a cohort of incident HF patients. These previously mentioned methodological limitations are important because they leave uncertainties about the clinical implications of AF in HF. Because the timing of AF in relation to HF diagnosis may play a role in the prognosis of HF patients, we aimed to describe the risk of all-cause mortality among HF patients who had AF prior to HF and AF that developed after HF in a community-based study in Olmsted County, Minnesota.

Methods

Study Setting
This study was conducted in Olmsted County. Population-based epidemiological research is feasible in Olmsted County because it is relatively isolated from other urban centers and only a few providers
deliver nearly all healthcare to local residents. Each provider uses a comprehensive medical record system in which the details of every encounter are entered and can be easily retrieved. Medical records are reviewed under the auspices of the Rochester Epidemiology Project, a record-linkage system that allows the indexing of all medical records of Olmsted County residents according to clinical and pathological diagnoses, surgical procedures, and billing information. This indexing system enables the retrieval of all medical records for use in epidemiological studies and ensures complete capture of all healthcare-related events occurring in Olmsted County.14 This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Identification of the Study Cohort

Possible HF diagnoses among Olmsted County residents between 1983 and 2006 were identified by International Classification of Diseases-9th Revision, Clinical Modification (ICD-9-CM) code 428, assigned during either outpatient visits or hospitalizations. A random sample of residents was selected for validation of incident HF diagnosis based on the Framingham criteria18 and data abstraction from the medical records.19 Incidence status was determined after review of the entire medical record, which, on average, spans 4 decades for patients with cardiovascular disease.17 After validation, 1664 cases of HF met the Framingham criteria and were included in this study.

Clinical Data Collection

The characteristics of patients at HF diagnosis were determined from medical records. Body mass index was calculated as weight (in kilograms from the last outpatient value before HF diagnosis) divided by height (in meters from a first available outpatient value) squared. Medications, current (within the past 6 months) and former cigarette smoking status, along with documented alcohol abuse or occasional or former use of alcohol were obtained from medical records associated with the HF diagnosis. Anemia was defined by World Health Organization criteria18 (hemoglobin <8.1 mmol/L in men and 7.5 mmol/L in women) using the hemoglobin level closest to and within 1 year of HF diagnosis. Glomerular filtration rate was estimated using the closest serum creatinine value within 1 year of HF diagnosis with the Modification of Diet in Renal Disease Study equation.19 Left ventricular ejection fraction (LVEF; in percentage) was determined using values collected from any ECG, angiogram, multigated acquisition scan, or sestamibi scan performed within 1 year of HF diagnosis. The value closest in time to HF diagnosis was used when multiple values were available, and the average value was used when multiple values were measured on the same day. More than 26% of patients were missing LVEF value; thus, multiple imputation methods were used for those with missing values.20 An ejection fraction ≥50% defined HF with a preserved ejection fraction, whereas a reduced ejection fraction was defined as an ejection fraction <50%.21 Because <5% of patients were assigned a New York Heart Association (NYHA) class by a physician to describe the severity of HF, an algorithm was used to derive NYHA class using the Framingham criteria. Based on our algorithm, patients were classified as class IV if acute pulmonary edema, paroxysmal nocturnal dyspnea, or orthopnea was present; class II or III if the patient exhibited dyspnea on exertion; or class I if none of the previously described symptoms were present.

Clinicians’ diagnoses were used to identify history of hyperthyroidism and chronic obstructive pulmonary disease (COPD) before the index date of HF. A history of hypertension was defined as ≥2 ambulatory blood pressure readings of ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic, a physician diagnosis of hypertension, or treatment with antihypertensive medication. Prevalent diabetes was defined according to the American Diabetes Association criteria.22 A previous MI was ascertained by validated epidemiological criteria.23

AF Ascertainment

To provide as complete a capture of AF events as possible, the first date of AF or atrial flutter, as documented by an ECG or an ICD-9-CM code of 427.31 or 427.32 during either hospitalizations or outpatient visits identified incident AF events. ECG documentation is the clinical gold standard to ascertain AF. However, even though 97% of the cohort had at least 1 ECG, averaging 26 ECGs per person, we found that an approach based on ECG alone misses >10% of cases. Indeed, of the 937 identified incident AF events, 682 (73%) had both an ECG and diagnostic code, 142 (15%) had an ECG only, and 113 (12%) had a diagnostic code only. Most of the 12% missing ECGs had documented AF by another source, such as a rhythm strip or Holter monitor that is not captured in our ECG database. Atrial fibrillation was divided into prior AF and AF after HF, with individuals diagnosed as having incident AF and HF on the same day considered to have prior AF. Individuals with no documented evidence of AF were categorized as having no AF.

Ascertainment of Death

Participants were followed through December 31, 2009, for deaths from any cause. Deaths among Olmsted County residents were obtained from inpatient and outpatient medical records, and death certificates were obtained on a yearly basis from the county and the state (Minnesota). In addition, the Mayo Clinic registration office records the obituaries and notices of death in the local newspapers. The underlying causes of death were categorized into cardiovascular (ICD-9 codes 390–459 and ICD-10 codes 100-199) and noncardiovascular, based on American Heart Association classifications.3 Cardiovascular deaths were further categorized into coronary heart disease (CHD), cardiac non-CHD, and noncardiac circulatory diseases.24

Statistical Analysis

Statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC) and Splus statistical software, version 8 (TIBCO Software, Inc, Palo Alto, CA). The follow-up was calculated from the index date of HF until death, last follow-up, or December 31, 2009, whichever came first.

The distribution of AF events in relation to HF diagnosis was plotted in a histogram. Means and proportions for participant characteristics were given overall and by AF category. Unadjusted and age- and sex-adjusted Cox proportional hazards models, with an indicator for prior AF and AF after HF modeled as a time-dependent variable, were modeled to examine the effects of AF prior to and AF after HF in relation to all-cause mortality. Fully adjusted Cox models again with an indicator for prior AF and AF after HF, modeled as a time-dependent variable, were modeled adjusting for age, sex, year of HF diagnosis, body mass index, smoking status (current, former, or never), derived NYHA class, estimated glomerular filtration rate, anemia, medications at the index visit (β-blockers, angiotensin-converting enzyme inhibitors, and diuretics), and history of hypertension, MI, COPD, and diabetes before the date of HF diagnosis. We also computed hazard ratios (HRs) for death with AF after HF modeled as a time-dependent covariate, with indicator variables for those with AF developing ≤1 year after HF and those with AF occurring >1 year after HF. The proportional hazards assumption was tested using scaled Schoenfeld residuals and found to be valid.

A stratified proportional hazards regression model, which allows for multiple strata with distinct baseline hazard functions for each cause of death but common coefficient values, was used to analyze the various causes of death.25 The use of strata by AF interactions allowed the testing of differences in the HRs across the cause of death strata within AF categories.

In sensitivity analyses, we separated those with AF and HF occurring on the same day and modeled this group with an indicator variable. Furthermore, we excluded those who had atrial flutter and ran analyses among those with AF only. In addition, we ran models further adjusting for history of CHD and LVEF to determine whether these variables also confound the association of AF with death. Finally, we tested for the presence of multiplicative interactions by sex and preserved versus reduced LVEF. In
models adjusting for LVEF and testing for the interaction between AF status and LVEF, both a complete case analysis and a multiple imputation analysis were run. To impute missing LVEF values, 5 data sets were created and analyzed with results combined using Rubin rules.20

Results

Of 1664 individuals with HF diagnosed between 1983 and 2006 (mean age at HF diagnosis, 76.2 years; 45.6% men), 553 had a history of AF and 384 developed AF after HF diagnosis. Included in the 553 individuals categorized as having prior AF were 134 with AF and HF diagnosed on the same day. The development of AF in relation to the index date of HF ranged from 47 years before to 24 years after HF diagnosis (Figure). The means and proportions of participant characteristics in the full cohort, and by AF status, are shown in Table 1. Those who developed AF prior to HF were older at HF diagnosis; had less severe HF, as determined by the derived NYHA classification; were more likely to be taking β-blockers; and were less likely to be a current smoker or to have prevalent diabetes compared with those without AF or with AF after HF. Those with AF after HF were more likely to be taking angiotensin-converting enzyme inhibitors and diuretics, had the highest prevalence of hypertension and hyperthyroidism, and had the lowest prevalence of COPD, MI, and anemia of all AF groups.

Over a median (25th–75th percentile) follow-up of 4.0 (1.6–7.1) years, 450 deaths occurred among persons with...

**Table 1. Participant Characteristics Overall and by AF Status**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>No AF (n=727)</th>
<th>Prior AF (n=553)</th>
<th>AF after HF (n=384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HF onset, y*</td>
<td>76.2 (12.7)</td>
<td>74.6 (13.9)</td>
<td>79.4 (9.9)</td>
<td>74.7 (12.9)</td>
</tr>
<tr>
<td>Male sex</td>
<td>45.6</td>
<td>42.8</td>
<td>46.8</td>
<td>49.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>27.7 (7.6)</td>
<td>27.6 (7.6)</td>
<td>27.4 (7.5)</td>
<td>28.5 (7.5)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>44.2</td>
<td>40.0</td>
<td>50.1</td>
<td>43.5</td>
</tr>
<tr>
<td>Former</td>
<td>41.3</td>
<td>41.4</td>
<td>41.4</td>
<td>40.9</td>
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<tr>
<td>Current</td>
<td>14.5</td>
<td>18.6</td>
<td>8.5</td>
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<td>Alcohol drinking</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33.7</td>
<td>35.2</td>
<td>34.0</td>
<td>30.2</td>
</tr>
<tr>
<td>Occasional or prior</td>
<td>53.8</td>
<td>51.9</td>
<td>52.3</td>
<td>59.9</td>
</tr>
<tr>
<td>Abuse</td>
<td>12.5</td>
<td>12.9</td>
<td>13.7</td>
<td>9.9</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min/1.73 m²*</td>
<td>54.3 (20.0)</td>
<td>55.2 (20.3)</td>
<td>53.1 (18.1)</td>
<td>54.4 (21.7)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %*†</td>
<td>45.3 (17.6)</td>
<td>43.0 (18.1)</td>
<td>48.6 (16.3)</td>
<td>44.5 (17.9)</td>
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<tr>
<td>Derived NYHA class</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9.9</td>
<td>11.7</td>
<td>8.3</td>
<td>8.6</td>
</tr>
<tr>
<td>II-III</td>
<td>32.7</td>
<td>31.5</td>
<td>36.7</td>
<td>29.4</td>
</tr>
<tr>
<td>IV</td>
<td>57.4</td>
<td>56.8</td>
<td>55.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Diagnoses before HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>73.0</td>
<td>69.2</td>
<td>74.3</td>
<td>78.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23.5</td>
<td>25.6</td>
<td>19.5</td>
<td>25.3</td>
</tr>
<tr>
<td>COPD</td>
<td>23.1</td>
<td>22.8</td>
<td>24.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21.2</td>
<td>23.1</td>
<td>20.8</td>
<td>18.2</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3.4</td>
<td>3.2</td>
<td>3.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>47.6</td>
<td>48.6</td>
<td>49.4</td>
<td>43.2</td>
</tr>
<tr>
<td>Medications at the index visit</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>35.1</td>
<td>31.8</td>
<td>39.6</td>
<td>34.9</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>44.5</td>
<td>42.4</td>
<td>43.0</td>
<td>50.8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>72.8</td>
<td>71.3</td>
<td>72.5</td>
<td>76.0</td>
</tr>
</tbody>
</table>

Data are given as percentages unless otherwise indicated.
*Data are given as mean (SD).
†Only among those with LVEF measured within 1 year of HF diagnosis (n=1225).
Table 2. Data for Mortality by AF Categorization

<table>
<thead>
<tr>
<th>Variable</th>
<th>No AF*</th>
<th>Prior AF</th>
<th>AF after HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.48 (1.31–1.68)</td>
<td>2.35 (2.04–2.71)</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.00</td>
<td>1.22 (1.08–1.38)</td>
<td>2.07 (1.79–2.38)</td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td>1.00</td>
<td>1.29 (1.13–1.46)</td>
<td>2.22 (1.93–2.57)</td>
</tr>
</tbody>
</table>

Data are given as HR (95% CI). *Reference.
†Adjusted for age, sex, body mass index, year of heart failure diagnosis, smoking status, derived NYHA class, estimated glomerular filtration rate, anemia, hypertension, diabetes mellitus, COPD, MI, and β-blockers, angiotensin-converting enzyme inhibitors, and diuretics at the index visit.

Prior AF, 314 among those with AF after HF, and 572 among patients without AF. Compared with those without AF, individuals who had prior AF and those who developed AF after HF had unadjusted HRs for death of 1.48 (95% CI, 1.31–1.68) and 2.35 (95% CI, 2.04–2.71), respectively (Table 2). In models adjusted for age, sex, body mass index, year of HF diagnosis, smoking status, derived NYHA class, estimated glomerular filtration rate, anemia, hypertension, diabetes, COPD, MI, and β-blockers, angiotensin-converting enzyme inhibitors, and diuretics at the index visit, AF prior to HF corresponded to a 29% increased risk of death and AF after HF conferred a 2.2-fold increased risk of death. However, further stratification of the AF after HF group revealed that those who developed AF ≤1 year of HF diagnosis exhibited a 54% (HR, 1.54; 95% CI, 1.25–1.89) increased risk of death, whereas those who developed AF >1 year after HF exhibited a 3-fold (HR, 3.04; 95% CI, 2.56–3.61) increased risk of death compared with those without AF.

When the underlying causes of death were categorized into cardiovascular (54%) and noncardiovascular (46%), the associations of AF status with death did not differ between cardiovascular and noncardiovascular deaths for AF prior to or after HF compared with no AF (Table 3). However, when the cardiovascular deaths were further categorized into CHD, cardiac non-CHD, and noncardiac circulatory deaths, the HRs for cause of cardiovascular death were similar only among those with AF after HF. Among those with AF prior to HF, the strongest association observed was for noncardiac circulatory deaths, with an HR of 2.48 (95% CI, 1.61–3.83) compared with the no AF group. Within each category of cardiovascular death, however, those with AF after HF exhibited a larger risk of death compared with those with AF prior to HF, particularly for CHD and cardiac non-CHD deaths.

Several sensitivity analyses were also conducted. First, acknowledging uncertainties regarding the exact timing of AF in relation to HF diagnosis, AF that occurred on the same day as HF (n=134) was modeled separately from the prior AF group; AF on the same day as HF did not confer an excess risk of death (HR, 1.18; 95% CI, 0.95–1.46), whereas results for AF prior to and after HF did not change. Second, associations remained the same after the exclusion of those with atrial flutter (n=139) (data not shown). Third, adjustment for history of CHD did not alter our results (data not shown). Fourth, HRs were unchanged in sensitivity analyses further adjusting for LVEF. In the complete case model, the HRs were 1.22 (95% CI, 1.05–1.42) and 2.01 (95% CI, 1.69–2.38) for prior AF and AF after HF, respectively; the corresponding HRs using the 5 data sets with imputed LVEF were 1.29 (95% CI, 1.14–1.46) and 2.21 (95% CI, 1.92–2.56), respectively. Finally, the associations of AF with all-cause mortality did not differ by sex or ejection fraction (data not shown).

### Discussion

In this community-based cohort of individuals with HF, the timing of AF in relation to HF diagnosis differentially affected the risk of all-cause mortality. Compared with those without AF, AF after HF conferred the highest risk of death, with more than a doubling of risk over a median follow-up of 4.0 years and 3 times the risk among the subset of individuals developing AF >1 year after HF diagnosis. Those with AF prior to HF exhibited a 29% increased risk of death. Furthermore, the associations of AF status with death did not differ between cardiovascular and noncardiovascular causes of death. However, a higher risk of death was apparent among cardiovascular deaths categorized as noncardiac circulatory for AF developing prior to HF, whereas similar risks were found for all types of cardiovascular death among those with AF after HF.

### Relationship Between AF and HF

AF may facilitate the development of HF through increased resting heart rate and an exaggerated heart rate response, which reduces cardiac output; irregularity of the ventricular response; loss of effective atrial contractile function; and the effects of antiarrhythmic therapy.26 Furthermore, left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular function are also common in both AF and HF.27 Aside from sharing common risk factors, either condition may predispose to the other through several potential mechanisms.

Atrial fibrillation may facilitate the development of HF through increased resting heart rate and an exaggerated heart rate response, which reduces cardiac output, irregularity of
the ventricular response, loss of effective atrial contractile function, and the effects of antiarrhythmic therapy. Likewise, HF may predispose to AF through atrial stretch; increased interstitial fibrosis; neurohormonal activation, which promotes structural remodeling and AF; and dysregulation of intracellular calcium. Several reviews discussing the relationship between AF and HF have been published. Furthermore, the nature of the relationship between HF and AF can be seen in data from the Framingham Heart Study. Of participants who developed both AF and HF during follow-up, 38% had AF first, 41% had HF first, and 21% had both conditions diagnosed the same day.

**Timing of AF Onset in Relation to HF**

The impact of the timing of AF development compared with HF diagnosis has rarely been reported. The results of 2 recent meta-analyses indicate that the coexistence of AF in HF patients increases the odds of mortality compared with HF alone; however, the timing of AF onset in relation to HF has not been adequately addressed in most studies. Several clinical trials of HF patients compared all-cause mortality in relation to AF that was present at baseline and AF that developed during either hospitalization or follow-up with patients without AF. In the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Congestive Heart Failure (CHF) trial, baseline AF was not associated with all-cause mortality; however, new-onset AF that developed during hospitalization was associated with a 28% (95% CI, 9%–50%) increased risk of all-cause mortality after multivariable adjustment compared with those without AF.

In the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program, baseline AF was associated with a 80% and 38% increased risk of all-cause mortality compared with no AF among those with preserved and low LVEF, respectively; after adjustment for baseline covariates, baseline AF remained associated with an increased risk of death (37% and 22%, respectively). Regardless of LVEF, AF that developed during follow-up conferred a 2-fold increased risk of death in unadjusted models; adjusted associations were not reported. However, those that developed AF during follow-up were analyzed as an indicator variable and the timing in relation to HF was not analyzed using a time-dependent variable. The Carvedilol or Metoprolol European Trial (COMET) reported a similar increased risk of all-cause mortality among those developing AF during follow-up (adjusted HR, 1.90; 95% CI, 1.54–2.35) but modeled AF occurring during follow-up as a time-dependent variable. Unlike the CHARM trial, however, after adjustment for covariates, baseline AF did not confer an increased risk of all-cause mortality compared with those without AF in the COMET trial.

In the second Prospective Randomized study of Ibopamine on Mortality and Efficacy (PRIME-II), however, neither baseline AF nor AF that developed during follow-up was associated with survival.

Among observational studies, prior AF has not been predictive of all-cause mortality compared with HF patients without AF. However, among hospitalized HF patients, new-onset AF during hospitalization conferred a 1.5-fold (95% CI, 1.1- to 2.0-fold) increased risk of in-hospital mortality compared with patients without AF during hospitalization. A similar increased risk was reported among HF patients >65 years who were discharged from the hospital with a primary diagnosis of HF, in whom new-onset AF during hospitalization was associated with a 40% (95% CI, 7%–82%) increased risk of all-cause mortality after adjustment for important demographic and clinical variables. In contrast, among outpatients with HF, new-onset AF occurring during follow-up was not associated with survival; however, limited power and the use of an indicator variable, instead of a time-dependent variable, for AF developing during follow-up may have potentially masked a positive association of new-onset AF with all-cause mortality in this study.

The Framingham Heart Study reported that later development of AF in HF corresponded to an increased risk of mortality, whereas preexisting AF did not adversely affect survival. The HRs for death among HF patients who subsequently developed AF were 1.6 (95% CI, 1.2–2.1) and 2.7 (95% CI, 2.0–3.6) among men and women, respectively. Our results are congruent with those of the Framingham Heart Study because we found the highest risk among individuals who developed AF after HF. Indeed, our results indicated >2-fold increased risk of all-cause mortality for those who developed AF after HF compared with those without AF, although we did not find that the association of AF with death differed by sex. Our data amplify the analysis reported by the Framingham Heart Study by demonstrating that persons with AF prior to HF also have an increased risk of death, although smaller than for those with AF after HF. Differences in sample size, event classification, and analytical methods may explain these partially diverging results, underscoring the importance of examining questions in several populations. Taken altogether, the results presented herein emphasize that the timing of AF development compared with HF diagnosis is critically important to consider clinically because it affects survival differentially, with AF developing later in the course of disease corresponding to a large excess risk of death. This excess risk among those who develop AF after HF may be related to many different plausible mechanisms. For example, AF that develops after HF may be due to medication use, heart rate control, fluid status, or underlying HF cause. However, in our cohort, the additional adjustment for medications or CHD did not affect our estimates. In addition, AF after HF may be a marker of worsening HF; however, future studies will need to be conducted to test these hypotheses.

**Limitations and Strengths**

Limitations of this study must be acknowledged. First, although we used both ECGs and ICD-9 diagnostic codes to identify AF events, some events may have been missed among asymptomatic individuals or those who did not seek medical attention. Atrial fibrillation can be discovered in the presence of a heart rate abnormality or for an unrelated reason (eg, a preanesthesia examination). There is no apparent reason for symptomatic AF to be detected differentially before and after HF; however, we cannot
exclude that this might be the case for asymptomatic AF. Second, we did not have information on treatment for AF or on categorizing AF as paroxysmal, persistent, or permanent. Thus, we could not adjust for these variables in our models or report stratified analyses by type of AF. Third, many patients were missing data on NYHA class and LVEF (95% and 26%, respectively). Underdocumentation of NYHA class in medical records is a pervasive issue; thus, to adjust for the severity of HF in our fully adjusted models, we created an algorithm to derive NYHA class using the Framingham criteria. For LVEF, we used multiple imputation methods to run a model adjusted for LVEF in the full cohort; however, we found that results were similar when using the imputed data compared with the complete case analysis. Finally, although the characteristics of the Olmsted County population are similar to those of US whites, the generalizability of our results to other racial groups may be limited.

The strengths of this study include the defined community-based incidence cohort of patients with HF; thus, this is of optimal relevance to clinical practice. The validation of each event was rigorous, as was the approach to AF classification, using both ECGs and diagnostic codes, which optimizes the validity of our results. Finally, unlike most studies that have examined the impact of AF in HF on survival, we were able to categorize the onset of AF in relation to HF to determine associations of AF prior to and after HF diagnosis with overall and cause-specific mortality. In doing so, we uncovered that the timing of AF in relation to HF diagnosis substantially modified the excess risk of death.

Conclusions
Among community subjects with HF, AF occurs frequently and is associated with a large excess risk of death, which is strongly influenced by the timing of AF. Atrial fibrillation that developed after the diagnosis of HF had a worse impact on survival, conferring more than twice the risk of death compared with HF patients without AF. These data identify AF as an adverse prognostic indicator in HF and underscore the importance of its management in HF patients.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Atrial fibrillation (AF) often coexists with heart failure (HF), and the combination of AF with HF may carry a worse prognosis than either condition alone. The purpose of this study was to determine how the timing of AF development in relation to HF diagnosis affected survival among 1664 community patients with HF diagnosed between 1983 and 2006. Among these 1664 incident HF patients, 553 had a history of AF and 384 developed AF after HF. During a median follow-up of 4.0 years, 450 deaths occurred among persons with prior AF, 314 occurred among those with AF after HF, and 572 occurred among patients without AF. Compared with those without AF, AF that occurred before HF was associated with a 29% increased risk of all-cause mortality, whereas AF that developed after HF conferred >2-fold increased risk of death. Thus, the risk of death in HF patients associated with AF differs markedly according to the timing of AF development, with AF developing later in the course of HF conferring the greatest risk of all-cause mortality.
Atrial Fibrillation and Mortality in Heart Failure: A Community Study
Alanna M. Chamberlain, Margaret M. Redfield, Alvaro Alonso, Susan A. Weston and Véronique L. Roger

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