

## Atrial Fibrillation Begets Heart Failure and Vice Versa Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction

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**Background**—Atrial fibrillation (AF) and heart failure (HF) frequently coexist and together confer an adverse prognosis. The association of AF with HF subtypes has not been well described. We sought to examine differences in the temporal association of AF and HF with preserved versus reduced ejection fraction.

**Methods and Results**—We studied Framingham Heart Study participants with new-onset AF or HF between 1980 and 2012. Among 1737 individuals with new AF (mean age, 75±12 years; 48% women), more than one third (37%) had HF. Conversely, among 1166 individuals with new HF (mean age, 79±11 years; 53% women), more than half (57%) had AF. Prevalent AF was more strongly associated with incident HF with preserved ejection fraction (multivariable-adjusted hazard ratio [HR], 2.34; 95% confidence interval [CI], 1.48–3.70; no AF as referent) versus HF with reduced ejection fraction (HR, 1.32; 95% CI, 0.83–2.10), with a trend toward difference between HF subtypes (*P* for difference=0.06). Prevalent HF was associated with incident AF (HR, 2.18; 95% CI, 1.26–3.76; no HF as referent). The presence of both AF and HF portended greater mortality risk compared with neither condition, particularly among individuals with new HF with reduced ejection fraction and prevalent AF (HR, 2.72; 95% CI, 2.12–3.48) compared with new HF with preserved ejection fraction and prevalent AF (HR, 1.83; 95% CI, 1.41–2.37; *P* for difference=0.02).

**Conclusions**—AF occurs in more than half of individuals with HF, and HF occurs in more than one third of individuals with AF. AF precedes and follows HF with both preserved and reduced ejection fraction, with some differences in temporal association and prognosis. Future studies focused on underlying mechanisms of these dual conditions are warranted. (*Circulation*. 2016;133:484-492. DOI: 10.1161/CIRCULATIONAHA.115.018614.)

**Key Words:** atrial fibrillation ■ epidemiology ■ heart failure ■ mortality ■ ventricular function, left

Heart failure (HF) and atrial fibrillation (AF) have emerged as 2 new epidemics of cardiovascular disease in the last 20 years.<sup>1</sup> The prevalence of both conditions is expected to increase with the aging of the population. By the year 2030, there will be 12 million Americans with AF and >8 million with HF.<sup>2,3</sup> Beyond sharing common predisposing risk factors such as hypertension, diabetes mellitus, ischemic heart disease, and valvular heart disease,<sup>4</sup> AF and HF clearly are

closely intertwined, with each disease predisposing to the other. When present in combination, AF and HF portend a worse prognosis than either condition alone.<sup>5-7</sup>

### Clinical Perspective on p 492

AF coexists with both HF with preserved and reduced ejection fraction (HFpEF and HFrfEF).<sup>8</sup> However, previous studies have noted differences among HF subtypes in atrial

Received July 22, 2015; accepted December 23, 2015.

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Guest Editor for this article was Gregg C. Fonarow, MD.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.018614/-/DC1>.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.115.018614

remodeling and prognosis associated with AF. For example, left atrial (LA) remodeling appears distinct between subtypes, with greater eccentric LA remodeling in HFrEF and increased LA stiffness in HFpEF predisposing to AF.<sup>9</sup> Additionally, cardiovascular outcomes after AF appear to be influenced by HF subtype.<sup>10</sup> In light of these differences, we hypothesized that the temporal association between AF and HF subtypes would be distinct.

Prior studies focused on the association of AF and HF subtypes were conducted largely in hospital-based cohorts<sup>11</sup> in which the onset of 1 condition compared with the other is unclear. We sought to investigate the association of AF with HFpEF and HFrEF in a large, community-based cohort in which incident AF and HF events were ascertained longitudinally, enabling accurate chronicity of HF and AF events. We sought to leverage these study characteristics to examine differences in the temporal associations between HFpEF and HFrEF events in relation to incident AF and to characterize the risk of mortality among participants with various AF and HF subtypes.

## Methods

### Study Participants

The study design of the Framingham Heart Study is described elsewhere.<sup>12</sup> Briefly, participants enrolled in the original (n=5209) and offspring (n=5124) cohorts underwent periodic clinical examinations and medical history updates once every 2 to 4 years. The Framingham Heart Study was reviewed by the Boston University Medical Center Institutional Review Board, and all participants signed written consent.

Participants with new-onset AF (n=1737) or HF (n=1166) between 1980 and 2012 were included because echocardiography became more widely available after 1980 for the determination of HF subtype. For incident AF and HF analyses, participants attending 1 of 3 baseline examinations per cohort were included: original cohort examinations 16 (1979–1982), 20 (1986–1990), and 24 (1995–1998) and offspring cohort examinations 2 (1979–1983), 4 (1987–1991), and 6 (1995–1998; Figure 1 in the online-only Data Supplement). From this sample, 14864 observations were included in the incident AF analyses after the exclusion of prevalent AF (n=554), missing covariates (n=551), or no follow-up (n=28; Figure IIA in the online-only Data Supplement). For the incident HF analyses, observations with prevalent HF (n=217), missing covariates (n=575), or missing follow-up (n=2) were excluded, leaving 15203 observations for analysis (Figure IIA in the online-only Data Supplement). Follow-up was truncated at 8 years for incident AF and HF analyses.

### Clinical Examination

All participants underwent comprehensive clinical evaluations during the examination cycles that included blood pressure measurements, ECG, and blood tests. Diabetes mellitus was defined as a fasting glucose level  $\geq 126$  mg/dL, nonfasting glucose  $\geq 200$  mg/dL, or the use of hypoglycemic drugs or insulin. Fasting total cholesterol and high-density lipoprotein cholesterol were measured. Left ventricular (LV) hypertrophy on ECG was defined with the use of published criteria.<sup>13</sup> Current smoking was based on self-reported use of  $\geq 1$  cigarettes per day in the year before the examination. Valvular heart disease was defined as any diastolic murmur or systolic murmur  $\geq 3/6$  grade.

### Definition of Clinical End Points

All cardiovascular end points were adjudicated by a panel of 3 physicians using established protocols after systematic review of all available medical records. HF was defined with the established Framingham criteria.<sup>4</sup> HF subtype was determined after review of

records based on LV ejection fraction obtained by echocardiogram or radionuclide study performed at or near the HF event date (during HF admission or within 1 year of HF onset, provided that no intervening myocardial infarction occurred), as previously described.<sup>4</sup> HF events were classified as HFpEF (LV ejection fraction  $\geq 45\%$ ) or HFrEF (LV ejection fraction  $<45\%$ ). The presence of AF was determined after review of all available ECGs from examination cycles, outpatient and inpatient hospital records, or ambulatory ECG monitoring.

### Statistical Analysis

To examine the temporal association of AF and HF subtypes, we inspected the occurrence of prevalent AF, concurrent AF, and incident AF (after HF) in all individuals with new-onset HF between 1980 and 2012. Concurrent AF and HF were defined as the diagnosis of new AF and HF within 30 days of one another. Similarly, the occurrence of prevalent, concurrent, and incident HF by subtype (after AF) was examined in all individuals with new-onset AF between 1980 and 2012.

The cumulative incidences of AF, HFpEF, and HFrEF were estimated with a Kaplan-Meier–like method accounting for competing risk of death.<sup>14</sup> Separate curves were estimated for those with and without HF (for incident AF) and those with and without AF (for incident HF). We calculated directly standardized rates (sex and age adjusted with 10-year age strata) using the relevant baseline sample (free of AF or HF) for incidence rates or the sample that developed a specified condition (AF or HF) for postevent mortality rates. Multivariable Cox proportional hazards regression was used to examine the associations of prevalent and interim HF and incident AF. Analyses were first adjusted for age and sex and then further adjusted for established risk factors of AF (height, weight, systolic and diastolic blood pressures, current smoking, use of antihypertensive medication, diabetes mellitus, and history of myocardial infarction).<sup>15</sup> In secondary analyses, multivariable models were further adjusted for prevalent cardiovascular disease other than myocardial infarction and for estimated glomerular filtration rate (available in 9521 individuals in incident AF and 9737 individuals in incident HF analyses). To account for participants eligible for  $>1$  observation period, we used the sandwich estimator to generate robust standard error estimates clustered on the individual participant.<sup>16</sup>

To relate AF to incident HFpEF and HFrEF, Cox models were used and adjusted for age and sex and then further adjusted for body mass index, systolic blood pressure, heavy alcohol use, smoking, diabetes mellitus, LV hypertrophy, hypertension treatment, valvular heart disease, and history of myocardial infarction. Interim events were modeled as time-varying covariates. In secondary analyses, we compared the  $\beta$  coefficients of AF as predictors of incident HFpEF and HFrEF using the Lunn-McNeil method.<sup>17</sup>

Next, the association of HF and AF individually and conjointly on mortality was assessed with Cox models. The hazards of prevalent and interim AF for mortality among participants with newly diagnosed HF between 1980 to 2012 were assessed (Figure IIB in the online-only Data Supplement). The Kaplan-Meier method was used to calculate cumulative incidence plots of mortality. Similarly, the hazards of prevalent and interim HF for mortality among participants with newly diagnosed AF were assessed. Interim events were modeled as time-varying covariates, and follow-up was truncated at 10 years. Models were first adjusted for age and sex and then further adjusted for systolic blood pressure, body mass index, antihypertensive treatment, smoking, diabetes mellitus, and history of myocardial infarction. Covariates were taken from the most proximal Framingham Heart Study examination attended within 8 years preceding HF or AF diagnosis. HF subtype was examined with the use of a 4-level class variable (no HF, HFpEF, HFrEF, and unclassified HF). We considered a 2-sided value of  $P < 0.05$  statistically significant. To check the proportional hazard assumption, we tested for interactions with variables and log time, and we also used the “assess” statement in PHREG. Neither approach showed violation of the proportional hazard assumption. All statistical analyses were conducted with SAS version 9.3 for Windows (SAS Institute Inc, Cary, NC).

## Results

### Temporal Association of AF and HF Subtypes

Between 1980 and 2012, 1166 participants developed new-onset HF. Of these, 479 (41%) were classified as having HFpEF, and 516 (44%) were classified as having HFrEF (171 [15%] could not be classified). Of participants with HF, 38% had no AF at baseline or during follow-up, 32% had prevalent AF, 18% had AF diagnosed within 30 days of their incident HF diagnosis, and 12% developed incident AF after their incident HF diagnosis (Figure 1 and Table I in the online-only Data Supplement). The time distribution among prevalent, concurrent, and incident AF by HF subtypes is displayed in Table II in the online-only Data Supplement. Compared with people with HFrEF, individuals with HFpEF were more likely to have AF at any time (62% versus 55%;  $P=0.02$ ). Participants with HFpEF carried a much greater burden of prevalent AF compared with individuals with HFrEF (32% versus 23%;  $P=0.002$ ).

Over the same period, 1737 individuals developed new-onset AF. Of these, 1101 (63%) had no HF at any point, 145 (8%) had HF previously diagnosed at the time of their

AF diagnosis, 214 (12%) had HF diagnosed concomitantly or within 30 days of their incident AF event, and 277 (16%) developed incident HF after their AF diagnosis. Among participants with HF diagnosed before or concomitant with their AF diagnosis, the rates of HFrEF and HFpEF did not vary significantly. Among individuals with HF diagnosed after their AF event, 50% developed HFpEF, 40% developed HFrEF, and 10% were unclassified (Figure 1 and Table I in the online-only Data Supplement). The time intervals between AF diagnosis and HFpEF versus HFrEF events among 644 individuals who had both AF and HF during follow-up are presented in Figure III in the online-only Data Supplement.

### Prevalent HF and Interim HF Predict Incident AF

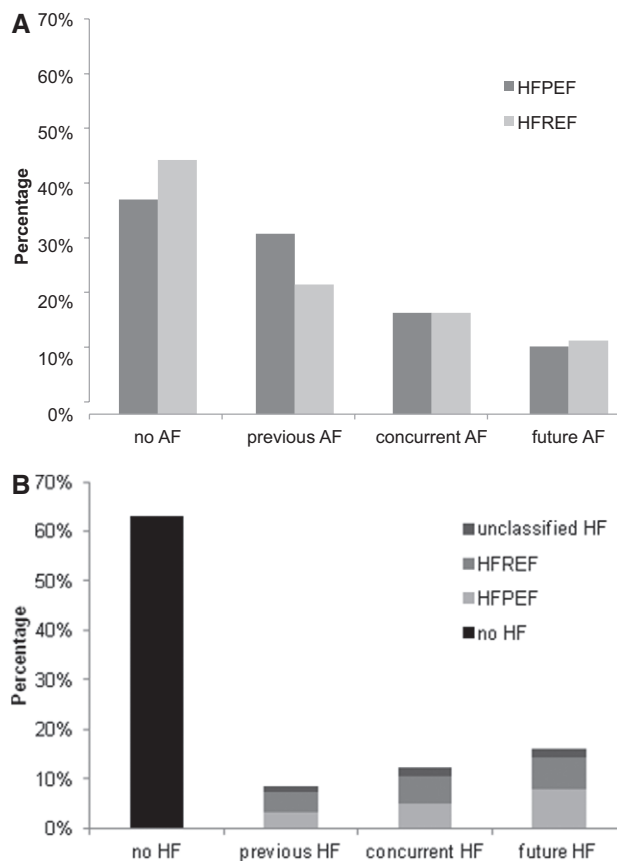
Among 14 864 observations included in the incident AF analysis, the mean age of participants was 58 years, and 55% were women. Baseline characteristics are displayed in Table 1. A total of 90 participants had prevalent HF (28 with HFpEF, 32 with HFrEF, and 30 with unclassified HF). There were 795 AF events during a mean follow-up of  $7.5\pm 1.6$  years. Those with prevalent HF had a higher cumulative incidence of AF compared with those free of HF (log-rank  $P<0.0001$ ; Figure 2A). The age- and sex-standardized incidence rate of AF was nearly 10-fold higher in those with prevalent HF compared with those without HF (Table 2).

In age- and sex-adjusted Cox models, prevalent HF was significantly associated with incident AF (hazard ratio [HR], 3.42; 95% confidence interval [CI], 2.10–5.56;  $P<0.0001$ ). Similarly, interim HF events predicted incident AF with a hazard of 2.41 (95% CI, 1.89–3.08;  $P<0.0001$ ). Prevalent and interim HF remained significantly associated with an  $\approx 2$ -fold increased hazard of incident AF after multivariable adjustment (Table 3). There were too few prevalent HF events to examine HF subtypes separately. After additional adjustment for prevalent cardiovascular disease (other than myocardial infarction) and kidney function, results remained similar, except the association of prevalent HF with incident AF, which was attenuated ( $P=0.11$ ).

### AF as a Predictor of Incident HF by HF Subtype

A total of 15 203 observations were included in the incident HF analysis. The participants' mean age was 58 years; 55% were women; and 403 participants had prevalent AF (Table 1). Over a mean follow-up of  $7.5\pm 1.5$  years, there were 215 incident HFpEF and 272 incident HFrEF events. The incidence rates of both HFpEF and HFrEF were higher in those with AF compared with those without AF (Table 2). Those with prevalent AF had a higher cumulative incidence of both HFpEF and HFrEF compared with those without prevalent AF (log-rank  $P<0.0001$  for both; Figure 2).

Prevalent AF predicted incident HFpEF (HR, 2.34; 95% CI, 1.48–3.70;  $P=0.0003$ ) but not HFrEF (HR, 1.32; 95% CI, 0.83–2.10;  $P=0.23$ ) in multivariable-adjusted analyses. In contrast, interim AF was significantly associated with incident HFrEF (HR, 1.71; 95% CI, 1.19–2.45;  $P=0.003$ ) but not HFpEF in multivariable-adjusted analyses ( $P=0.05$ ; Table 3). When the Lunn-McNeil method was used to compare  $\beta$  coefficients between the 2 subtypes of HF, there was a marginally significant difference in prevalent AF as a predictor of HFpEF versus HFrEF ( $P=0.06$ ), whereas interim AF did not appear to



**Figure 1.** Temporal association of atrial fibrillation (AF) and heart failure (HF) subtypes. **A**, Data for 995 participants with new HF and whether participants had previous, concurrent, or future AF or no AF (for 479 with HF with preserved ejection fraction [HFpEF]: 154, 88, 56, and 181, respectively; for 516 with HF with reduced ejection fraction [HFrEF]: 121, 94, 67, and 234, respectively). **B**, Data for 1737 participants with new AF, of whom 1101 had no HF ( $n=1101$ ) and others had previous, concurrent, or future HF (for 284 with HFpEF: 57, 88, and 139, respectively; for 272 with HFrEF: 67, 94, and 111, respectively; for 80 with unclassified HF: 21, 32, and 27, respectively).

**Table 1. Baseline Clinical Characteristics for Participants Free of Prevalent AF or HF**

	Free of Prevalent AF (n=14 864)	Free of Prevalent HF (n=15 203)
Age, y	57±15	58±15
Women, n (%)	8222 (55)	8322 (55)
Height, cm	166±10	166±10
Weight, kg	74±16	74±16
Body mass index, kg/m <sup>2</sup>	26.7±4.8	26.7±4.8
Systolic blood pressure, mm Hg	130±20	130±20
Diastolic blood pressure, mm Hg	77±10	77±10
Hypertension treatment, n (%)	3622 (25)	3778 (25)
Prevalent myocardial infarction, n (%)	628 (4)	655 (4)
Total cholesterol, mg/dL	211±41	210±41
HDL cholesterol, mg/dL	50±15	50±15
Heavy alcohol use, n (%)	943 (6)	963 (6)
Smoking, n (%)	3491 (23)	3540 (23)
Diabetes mellitus, n (%)	890 (6)	927 (6)
LV hypertrophy, n (%)	183 (1)	194 (1)
Valvular heart disease, n (%)	399 (3)	418 (3)
Prevalent HF, n (%)	90 (1)	...
Prevalent AF, n (%)	...	403 (3)

Values are mean±SD unless otherwise noted. AF indicates atrial fibrillation; HDL, high-density lipoprotein; HF, heart failure; and LV, left ventricular.

have differential association with incident HFpEF or HFrEF ( $P=0.66$ ). Results were not materially different after adjustment for cardiovascular disease (other than myocardial infarction) and kidney function.

### Prevalent AF and Interim AF as Predictors of Mortality After New HF

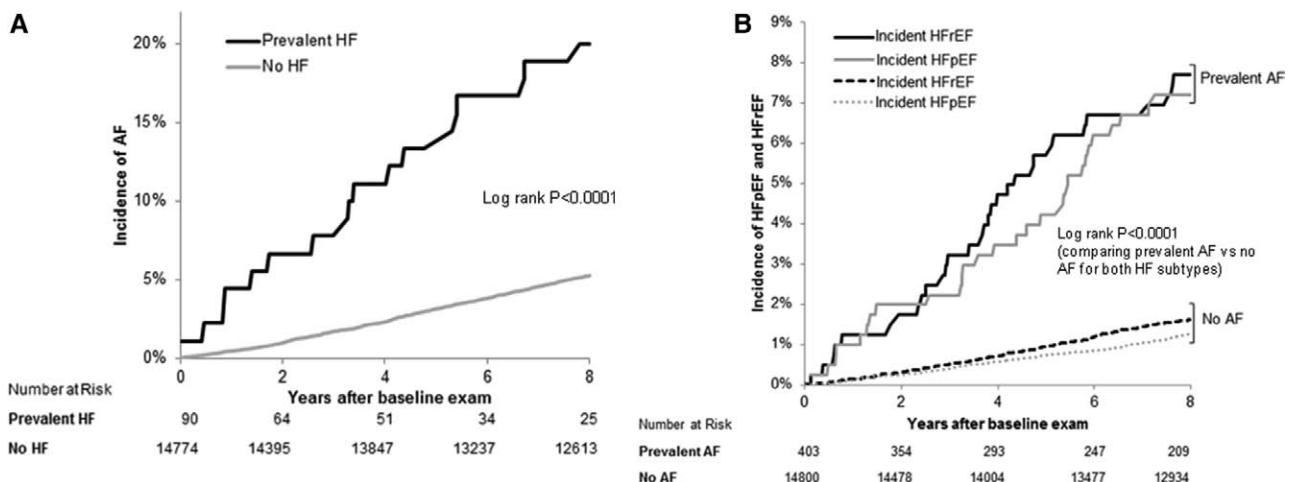
Of 759 participants with new-onset HF between 1980 and 2012 and available baseline examination data, 309 were classified as HFpEF, 360 as HFrEF, and 90 as unclassified HF. The

mean age was 79±11 years in the HFpEF group and 77±10 years in the HFrEF group. Other baseline characteristics are presented in Table II in the online-only Data Supplement. Over a mean follow-up of 3.6±3.4 years, there were 221 deaths among individuals with HFpEF and 289 among those with HFrEF. Cumulative incidence plots of mortality after HF are presented in Figure 3A. Incidence rates of all-cause mortality among those with HFpEF and HFrEF with versus without prevalent AF are displayed in Table 2.

Prevalent AF was not significantly associated with mortality among individuals with new-onset HFpEF or HFrEF after multivariable analyses (Table 4 and Figure 3). In contrast, interim AF (159 events) was significantly associated with mortality among individuals with both new HFpEF and HFrEF (multivariable-adjusted HR, 1.58; 95% CI, 1.08–2.30;  $P=0.02$ ; and HR, 2.02; 95% CI, 1.46–2.79;  $P<0.0001$ , respectively).

### Prevalent HF and Interim HF as Predictors of Mortality After New AF

Of 1191 individuals with new AF between 1980 and 2012 and available baseline covariates (Table II in the online-only Data Supplement), a total of 214 (91 HFpEF, 99 HFrEF, 24 unclassified) had prevalent HF. Over a mean follow-up period of 5.1±3.8 years, 683 participants (57%) died. Cumulative incidence plots by prevalent HF and HF subtype are shown in Figure 3B. The incidence rates of mortality in AF were highest in participants with prevalent HFrEF, followed by those with prevalent HFpEF and lowest in those without HF (Table 2). Among participants with AF, incidence rates of HF were similar in men and women (50.7 and 56.0 events per 1000 person-years, respectively), with a higher incidence of HFpEF in women (35.1 versus 21.2 events per 1000 person-years) and lower incidence of HFrEF in women (12.4 versus 27.2 events per 1000 person-years; Table III in the online-only Data Supplement). In exploratory analyses, we examined the association of the CHADS<sub>2</sub>-VAsc score<sup>18</sup> and incident HF events in those with AF and found that each 1-point increment in the score was associated with a 1.36-fold increased hazard



**Figure 2.** Cumulative incidence of atrial fibrillation (AF) and heart failure (HF) among those with and without the other condition. **A**, Cumulative incidence of AF ( $n=795$ ) in participants with and without prevalent HF. **B**, Cumulative incidence of HF with preserved ejection fraction (HFpEF;  $n=215$ ) and HF with reduced ejection fraction (HFrEF;  $n=272$ ) in participants with and without prevalent AF. For 95% confidence interval estimates, please see Table V in the online-only Data Supplement.

**Table 2. Incidence Rates for Incident Disease and Mortality With and Without AF and HF**

Outcome	Group	Incidence Rate (per 1000 patient-y)*	95% CI†
Incident AF (n=795)	Prevalent HF	47.8	24.1–71.6
	No HF	7.9	7.3–8.4
Incident HF (n=549)	Prevalent AF	31.4	24.0–38.8
	No AF	4.8	4.4–5.3
Incident HFpEF (n=215)	Prevalent AF	12.9	8.2–17.6
	No AF	1.9	1.6–2.1
Incident HFrEF (n=272)	Prevalent AF	13.2	8.5–18.0
	No AF	2.4	2.1–2.7
Mortality after new HF (n=598)	Prevalent AF	290	251–329
	No AF	244	218–270
Mortality after new HFpEF (n=221)	Prevalent AF	259	203–315
	No AF	188	154–222
Mortality after new HFrEF (n=289)	Prevalent AF	249	201–297
	No AF	262	221–304
Mortality after new AF (n=683)	Prevalent HFpEF	257	192–323
	Prevalent HFrEF	302	231–373
	No HF	120	109–131

AF indicates atrial fibrillation; CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.

\*Age (10-year interval) and sex standardized.

†The 95% CI estimates assume a constant incidence rate over time.

of HF (95% CI, 1.26–1.48;  $P<0.0001$ ), with modest discriminatory capability (c statistic, 0.62; 95% CI, 0.59–0.66).

In multivariable analyses, both prevalent HFrEF and HFpEF were associated with adverse outcomes in individuals with new AF (Table 4). However, those with prevalent HFrEF appeared to have a worse prognosis compared with those with HFpEF (prevalent HFrEF: HR, 2.72; 95% CI, 2.12–3.48;  $P<0.0001$ ; prevalent HFpEF: HR, 1.83; 95% CI,

1.41–2.37;  $P<0.0001$ ;  $P$  for comparison=0.02). In contrast, interim HFpEF (n=105) and HFrEF (n=98) appeared to have similar adverse associations with mortality ( $P=0.98$  for comparison; Table 4). Results were not materially different after accounting for the presence of pacemakers/implantable defibrillators at baseline (data not shown). In exploratory analyses, we examined cause-specific death in participants with AF. Age- and sex-standardized incidence rates of coronary heart disease and other cardiovascular deaths were higher compared with cerebrovascular deaths among those without HF (Table IV in the online-only Data Supplement).

## Discussion

Our findings highlight the close association of AF and HF, with some distinct differences in timing between HFpEF and HFrEF. More than half of the participants with HF had AF at some point, with AF more likely to antedate than to follow HF. Specifically, AF appeared to precede incident HFpEF more frequently than it did incident HFrEF events. Similarly, more than one third of participants with AF had HF, with most developing HF onset after AF rather than beforehand. These proportions emphasize the close association between these 2 conditions. In fact, previous data show that incidence of HF after AF is nearly double that of stroke<sup>19</sup> and emphasize the need for future HF prevention strategies similar to stroke prevention strategies that are currently implemented after AF. The incidence rates of both subtypes of HF after AF in our study approach that of incident HF in individuals with mild asymptomatic LV systolic dysfunction,<sup>20</sup> for which preventive therapies exist. Furthermore, AF and HF conjointly appear to portend a poor prognosis, with a higher risk among those with HFrEF compared with HFpEF and new AF.

A previous study examined the temporal association of AF and HF in the Framingham Heart Study in cases occurring between 1948 and 1995.<sup>7</sup> We now extend these findings to a more contemporary sample between 1980 and 2012 and, more important, examine the specific association with HFpEF and HFrEF. Compared with the previous analysis, a greater proportion of individuals have AF without HF, and AF more commonly precedes HF now. These differences may be attributable to enhanced surveillance, detection, prevalence, or

**Table 3. AF and HF as Predictors of Incident Disease**

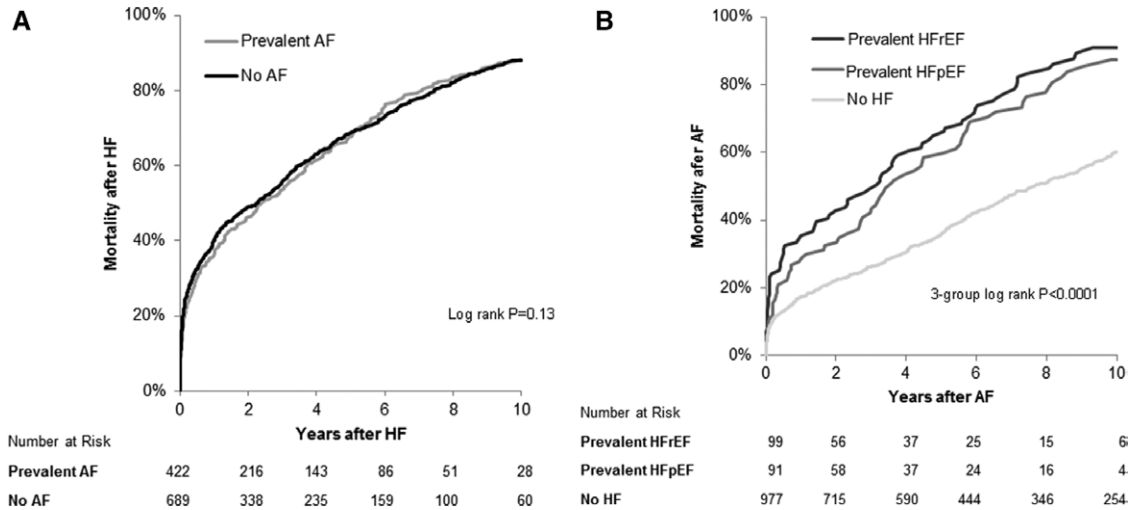
Outcome	Predictor	Age and Sex Adjusted		Multivariable Adjusted	
		HR (95% CI)‡	P Value	HR (95% CI)‡	P Value
Incident AF (n=795)*	Prevalent HF	3.42 (2.10–5.56)	<0.0001	2.18 (1.26–3.76)	0.005
	Interim HF	2.41 (1.89–3.08)	<0.0001	1.91 (1.48–2.46)	<0.0001
Incident HFpEF (n=215)†	Prevalent AF	3.11 (2.02–4.79)	<0.0001	2.34 (1.48–3.70)	0.0003
	Interim AF	1.78 (1.18–2.70)	0.006	1.52 (0.99–2.31)	0.05
Incident HFrEF (n=272)†	Prevalent AF	2.22 (1.47–3.34)	0.0001	1.32 (0.83–2.10)	0.23
	Interim AF	1.96 (1.37–2.81)	0.0002	1.71 (1.19–2.45)	0.003

AF indicates atrial fibrillation; CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.

\*Adjusted for age, sex, height, weight, systolic and diastolic blood pressures, diabetes mellitus, smoking, hypertension treatment, and history of myocardial infarction.

†Adjusted for age, sex, body mass index, hypertension treatment, smoking, alcohol, systolic blood pressure, history of myocardial infarction, heart murmur, diabetes mellitus, and left ventricular hypertrophy.

‡HR referent group is “no HF” in incident AF analyses and “no AF” in incident HF analyses.



**Figure 3.** Kaplan–Meier curves for all-cause death in those with heart failure (HF) and atrial fibrillation (AF). **A**, Cumulative incidence of all-cause mortality (n=598) after new HF by AF status. **B**, Cumulative incidence of all-cause mortality after new AF (n=683) by HF subtype status. For 95% confidence interval estimates, please see Table V in the online-only Data Supplement.

incidence of AF over time.<sup>21</sup> Another recent population-based study examined the temporal relationship of AF and HFpEF in the Olmsted County cohort.<sup>22</sup> Similar to our results, AF was found to occur in more than half of individuals with HFpEF, with incident AF after HFpEF bearing a worse prognosis compared with AF before or concurrent with HFpEF presentation. Our study expands these results to directly compare HFpEF and HFrEF in relation to AF among the same study sample.

Other previous studies examining the association of AF and HFpEF<sup>5,8,10,22–24</sup> versus HFrEF<sup>5,8,10,23,25–28</sup> with mortality were focused largely on hospital-based cohorts with some exceptions and showed variable results. A recent meta-analysis demonstrated a worse prognosis of AF with HFpEF compared with HFrEF.<sup>11</sup> Our findings show lower survival rates among participants with conjoint AF and HF, with lowest rates among participants with HFrEF and AF compared with

HFpEF and AF. Our study also suggests that timing matters: Prevalent AF appears to be less associated with mortality once HF has developed, likely as a result of a much higher mortality rate with HF regardless of prevalent AF status. Similar findings were previously described.<sup>7</sup> It may also be that prevalent AF results in an earlier presentation of HF owing to poor tolerance of this arrhythmia, making lead-time bias a potential explanation for our findings. Differences in our study compared with other prior studies may be attributable to limitations of studies without long-term follow-up, in which the timing of incident AF relative to incident HF may be unclear. Furthermore, HF disease severity appears to influence AF,<sup>29</sup> and prior studies focused on participants with existing HFpEF and HFrEF may have had variable disease severity or assessment at different time points of HF progression. In contrast, our study had the unique opportunity to examine timing from

**Table 4. Concomitant AF and HF as Predictors of All-Cause Mortality**

Outcome	Predictor	Age and Sex Adjusted		Multivariable Adjusted	
		HR (95% CI)†	P Value	HR (95% CI)†	P Value
Mortality after new HF (n=598)	Prevalent AF	1.18 (0.98–1.42)	0.09	1.25 (1.04–1.51)	0.02
	Interim AF	1.88 (1.50–2.35)	<0.0001	1.89 (1.51–2.38)	<0.0001
Mortality after new HFpEF (n=221)	Prevalent AF	1.23 (0.90–1.68)	0.19	1.33 (0.97–1.83)	0.08
	Interim AF	1.66 (1.15–2.39)	0.007	1.58 (1.08–2.30)	0.02
Mortality after new HFrEF (n=289)	Prevalent AF	1.19 (0.91–1.56)	0.2	1.18 (0.90–1.56)	0.23
	Interim AF	2.03 (1.47–2.80)	<0.0001	2.02 (1.46–2.79)	<0.0001
Mortality after new AF (n=683)	Prevalent HFpEF	1.85 (1.43–2.40)	<0.0001	1.83 (1.41–2.37)	<0.0001
	Prevalent HFrEF	2.77 (2.18–3.51)	<0.0001	2.72 (2.12–3.48)	<0.0001
	Prevalent HFpEF vs HFrEF	0.67 (0.49–0.92)	0.01	0.67 (0.48–0.94)	0.02
	Interim HFpEF	2.11 (1.57–2.83)	<0.0001	2.31 (1.72–3.11)	<0.0001
	Interim HFrEF	2.43 (1.82–3.24)	<0.0001	2.36 (1.76–3.16)	<0.0001
	Interim HFpEF vs HFrEF	0.87 (0.59–1.26)	0.46	0.98 (0.67–1.43)	0.91

AF indicates atrial fibrillation; CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.

\*Adjusted for age, sex, systolic blood pressure, antihypertensive treatment, body mass index, diabetes mellitus, smoking, and history of myocardial infarction.

†HR referent group is “no AF” in mortality after HF analyses and “no HF” in mortality analyses after AF.

the first presentation of AF relative to incident HF and may be less heterogeneous with respect to timing along disease course.

Although overall differences are modest given the strong association of AF with both HF subtypes, we show that prevalent AF precedes HFpEF in a higher proportion than HFrEF (32% versus 23%, respectively). The mechanisms by which AF may be different among HF subtypes remain incompletely characterized. Melenovsky et al<sup>9</sup> studied individuals with existing HF and found that LA remodeling was distinct among HF subtypes. Specifically, they observed eccentric LA remodeling in HFrEF and greater LA stiffness in HFpEF, and they suggested that greater LA stiffness may contribute to the greater AF burden seen in HFpEF. Other studies have demonstrated that diastolic dysfunction, a precursor of HFpEF, also appears to predict incident AF.<sup>30,31</sup> This association may be attributable to similar underlying mechanisms driving AF and HFpEF development, including myocardial inflammation and fibrosis, leading to atrial interstitial fibrosis and AF,<sup>32</sup> as well as HFpEF.<sup>33–38</sup> It also may be that AF is less well tolerated in individuals predisposed to HFpEF particularly with exertion and thereby may trigger clinical recognition of HF.<sup>4,39,40</sup> Interestingly, we found that individuals with HFpEF and those with HFrEF are at similar risk of developing future AF, which may reflect elevation in atrial pressures and remodeling in both types of HF.

Several limitations of our analyses deserve mention. First, AF was ascertained from all available ECGs and Holter monitor readings. We may have missed clinically unrecognized AF cases secondary to our reliance on medical records plus periodic study examinations for the diagnosis of AF. Although the majority of HF cases were classified as HFpEF versus HFrEF, 15% remained unclassified because of the unavailability of LV functional assessment at the time of HF, and differential misclassification could have influenced our results. Furthermore, HF adjudication was based on Framingham criteria,<sup>4</sup> which did not take into account biomarkers or echocardiographic data. This may have resulted in HF being underdiagnosed compared with other HF criteria. In addition, once a participant was diagnosed with AF or HF, more frequent routine medical surveillance may have resulted in ascertainment bias of the other condition. Whereas we describe associations, we acknowledge that our study is observational; we cannot rule out residual confounding or prove causal relations. Specifically, we were not able to account for emerging risk factors, including obstructive sleep apnea, and did not account for interim development of other risk factors. We were able to account for the use of antihypertensive medications, including  $\beta$ -blockers and calcium channel blockers; however, antiarrhythmics were not taken into account and are known to have potential adverse effects, particularly among individuals with HF.<sup>41</sup> The cause of HF was not formally adjudicated; specifically, the contribution of tachycardia-induced cardiomyopathy to HF incidence in participants with AF in our sample remains unknown. We classified HF on the basis of imaging at the first presentation, and subsequent transitions between HF subtypes after the first presentation were not examined. Lastly, our sample is predominantly white,

limiting the generalizability of our finding, particularly in light of racial differences in both AF and HF.<sup>42,43</sup>

Our data indicate that more than one third of individuals with AF have HF at some point, with most developing HF onset after AF rather than before their AF diagnosis. The finding that HF follows rather than predates AF highlights an opportunity for future studies focused on HF prevention in AF. Clinically, the focus in patients with AF is largely directed toward stroke prevention, with less focus on HF prevention. The incidence rates of both subtypes of HF after AF are comparable to the rate of incident HF among individuals with asymptomatic LV dysfunction, classified as American College of Cardiology/American Heart Association stage B HF. Identifying those at greatest risk of HF using established risk factors may help identify a population to target for future intervention strategies.<sup>44</sup>

## Conclusions

We show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF at some point in time. AF precedes and follows both HFpEF and HFrEF, with some differences in temporal association. Lastly, AF and HF conjointly portend a poor prognosis, with a higher risk among those with HFrEF. Future studies focused on underlying mechanisms of these dual conditions and potential therapeutic strategies are warranted.

## Sources of Funding

This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (contracts N01-HC-25195 and HHSN268201500001I). This work was supported by the National Institutes of Health (K23-HL116780 to Dr Ho, 1R01HL128914 to Dr Benjamin, 2R01HL092577 and 3R01HL092577-06S1 to Drs Benjamin and Ellinor). Dr Ho is supported by a Boston University School of Medicine, Department of Medicine Career Investment Award (Boston, MA). Dr Lubitz is supported by National Institutes of Health/National Heart, Lung and Blood Institute K23HL114724 and Doris Duke Charitable Foundation Clinical Scientist Development Award 2014105.

## Disclosures

None.

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### CLINICAL PERSPECTIVE

Atrial fibrillation (AF) and heart failure (HF) frequently coexist and together confer an adverse prognosis. However, the association of AF with HF subtypes has not been well-described. We studied the temporal association of new-onset AF and HF with preserved versus reduced ejection fraction in participants of the Framingham Heart Study. We show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF at some point of time. We found that AF precedes and follows both HF with preserved ejection fraction and HF with reduced ejection fraction, with some differences in temporal association: Prevalent AF was more strongly associated with incident HF with preserved ejection fraction. Lastly, AF and HF conjointly portend a poor prognosis, with a higher risk among those with reduced ejection fraction. These findings shed light on the complex association of AF and HF, and future studies focused on underlying mechanisms of these dual conditions and potential therapeutic strategies are warranted.