JACC: HEART FAILURE
VOL. 5, NO. 8, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.04.004

CLINICAL RESEARCH

Modifiable Risk Factors for Incident Heart Failure in Atrial Fibrillation

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ABSTRACT

OBJECTIVES This study sought to identify modifiable risk factors and estimate the impact of risk factor modification on heart failure (HF) risk in women with new-onset atrial fibrillation (AF).

BACKGROUND Incident HF is the most common nonfatal event in patients with AF, although strategies for HF prevention are lacking.

METHODS We assessed 34,736 participants in the Women's Health Study who were free of prevalent cardiovascular disease at baseline. Cox models with time-varying assessment of risk factors after AF diagnosis were used to identify significant modifiable risk factors for incident HF.

RESULTS Over a median follow-up of 20.6 years, 1,495 women developed AF without prevalent HF. In multivariable models, new-onset AF was associated with an increased risk of HF (hazard ratio [HR]: 9.03; 95% confidence interval [CI]: 7.52 to 10.85). Once women with AF developed HF, all-cause (HR: 1.83; 95% CI: 1.37 to 2.45) and cardiovascular mortality (HR: 2.87; 95% CI: 1.70 to 4.85) increased. In time-updated, multivariable models accounting for changes in risk factors after AF diagnosis, systolic blood pressure >120 mm Hg, body mass index ≥30 kg/m^2, current tobacco use, and diabetes mellitus were each associated with incident HF. The combination of these 4 modifiable risk factors accounted for an estimated 62% (95% CI: 23% to 83%) of the population-attributable risk of HF. Compared with women with 3 or 4 risk factors, those who maintained or achieved optimal risk factor control had a progressive decreased risk of HF (HR for 2 risk factors: 0.60; 95% CI: 0.37 to 0.95; 1 risk factor: 0.40; 95% CI: 0.25 to 0.63; and 0 risk factors: 0.14; 95% CI: 0.07 to 0.29).

CONCLUSIONS In women with new-onset AF, modifiable risk factors including obesity, hypertension, smoking, and diabetes accounted for the majority of the population risk of HF. Optimal levels of modifiable risk factors were associated with decreased HF risk. Prospective assessment of risk factor modification at the time of AF diagnosis may warrant future investigation. (J Am Coll Cardiol HF 2017;5:552–60) © 2017 by the American College of Cardiology Foundation.

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Manuscript received March 7, 2017; revised manuscript received March 30, 2017, accepted April 11, 2017.

The onset of atrial fibrillation (AF) has been consistently associated with increased mortality in diverse populations, including those with low cardiovascular disease burden (1). Improvements in thromboembolic risk prediction, coupled with the proliferation of anticoagulation agents, have led to important declines in stroke-related mortality for patients with AF (2). Despite these major advances, improvement in overall survival for patients with AF has been modest, with age-adjusted 5-year mortality rates of nearly 40% in a contemporary cohort (2). There remains a significant need to identify additional determinants of mortality in this population.

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To that end, recent studies have suggested a shifting epidemiology of cardiovascular risk after new-onset AF (3). In particular, HF now represents the most common incident cardiovascular event in patients with AF, occurring at a rate nearly twice that of stroke (4). AF and HF frequently coexist and the combination confers a greater mortality risk than either does alone (5). However, in contrast to stroke where established preventive approaches exist, there are few, if any, preventive strategies for reducing the incidence of HF in patients with AF.

We therefore used the WHS (Women's Health Study) (6)—a large, longitudinal cohort of women without prevalent cardiovascular disease at baseline—to examine the population risk, prognostic implications, and risk factors for incident HF in women with new-onset AF. We hypothesized that modifiable risk factors might account for a significant proportion of population and individual HF risk in AF and thus might provide important targets for prevention.

METHODS

STUDY COHORT. The study cohort comprised 39,876 female health care professionals in the United States enrolled in the WHS, an ongoing observational follow-up study that began in 1993 as a 2 × 2 randomized controlled trial of vitamin E and low-dose aspirin for the primary prevention of cardiovascular disease and cancer (6). Women were age 45 years or older and free of cardiovascular disease and cancer at study entry. After the end of randomized treatment on March 31, 2004, participants were invited to participate in an observational follow-up study including serial questionnaires about cardiovascular risk factors and updated health outcomes. All participants provided written, informed consent, and the study was approved by the institutional review board of Brigham and Women's Hospital.

RISK FACTOR ASCERTAINMENT. Participants self-reported cardiovascular risk factors and interval health events at baseline and on annual questionnaires. Covariates of interest included baseline demography (age, race/ethnicity, height, weight) as well as time-updated assessment of both clinical risk factors (diabetes mellitus, systolic blood pressure, antihypertensive medication use, hyperlipidemia, lipid-lowering medication use, use of hormone replacement therapy) and lifestyle habits (smoking status [never, former, current], physical activity [metabolic equivalents per week], alcohol consumption [number of drinks per day]).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BMI = body mass index
CI = confidence interval
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
PAF = population-attributable fraction
SBP = systolic blood pressure

ASCERTAINMENT OF AF AND CARDIOVASCULAR ENDPOINTS. Details regarding AF ascertainment have been previously described (1). Briefly, at study entry, 48 months, and annually thereafter, women were asked to report diagnoses of incident AF. Medical records pertaining to the AF diagnosis, electrocardiograms, and rhythm strips were reviewed by an endpoint committee of cardiologists. Confirmation of AF required the presence of electrocardiographic evidence or a medical report clearly indicating a history of AF.

Ascertainment of cardiovascular endpoints (HF, stroke, myocardial infarction [MI]) and death in WHS has been previously described (1). Women reported new physician diagnoses of cardiovascular endpoints via annual follow-up questionnaires. Similar to AF, women were first asked to report HF on the 48-month questionnaire. Information on MI and stroke was collected from the beginning of the study. Deaths were usually reported by family members or postal authorities or ascertained through the National Death Index. All events were adjudicated according to predefined criteria in a blinded fashion by an endpoint committee of physicians. HF was confirmed if either Framingham Heart Study (7) or Cardiovascular Health Study (8) criteria were met. Incident HF was further categorized by left ventricular ejection fraction within 3 months of HF diagnosis (9). HF subtypes were classified as heart failure with preserved ejection fraction (HFpEF) if left ventricular ejection fraction was ≥50% or heart failure with reduced ejection fraction (HFrEF) if left ventricular ejection fraction was <50%. Deaths were confirmed to be from cardiovascular causes on the basis of autopsy reports, death certificates, medical records, and information obtained from family members.

TABLE 1 Baseline Characteristics of Total Cohort at Enrollment and New-Onset AF Without HF at AF Diagnosis

	Total Cohort at Enrollment (N = 34,736)	New-Onset AF Without HF at AF Diagnosis (n = 1,495)
Age, yrs	55 ± 7	69 ± 8
Race/ethnicity		
White	32,759 (94.0)	1,454 (97.0)
Black	720 (2.0)	12 (1.0)
Hispanic	348 (1.0)	4 (<1.0)
Other	909 (3.0)	25 (2.0)
BMI, kg/m^2	26 ± 5	28.1 ± 6.1
Diabetes mellitus	938 (3.0)	172 (12.0)
Hypertension	9,176 (26.0)	1,140 (76.0)
SBP, mm Hg		
<120	15,324 (45.0)	314 (21.0)
120–139	14,604 (43.0)	826 (55.0)
140–159	3,970 (11.0)	311 (21.0)
≥160	406 (1.0)	43 (3.0)
Hyperlipidemia	10,505 (30)	954 (64)
History of coronary revascularization	0 (0.0)	67 (5.0)
History of MI	0 (0.0)	24 (2.0)
History of stroke	0 (0.0)	36 (2.0)
Chronic kidney disease	7 (<1.0)	12 (1.0)
Smoking status		
Never	17,920 (52.0)	720 (48.0)
Past	12,484 (36.0)	696 (47.0)
Current	4,306 (12.0)	79 (5.0)
EtOH ≥2 drinks/day	1,360 (4.0)	91 (6.0)
Physical activity, ≥7.5 METS/week	18,923 (55.0)	856 (57.0)
Anticoagulation use		663 (44.0)
CHADSVASc score*		
1		159 (11.0)
2		392 (26.0)
3		523 (35.0)
4		349 (23.0)
5		55 (4.0)
6		16 (1.0)
7–9		1 (<1.0)

Values are mean ± SD or n (%). *CHADSVASc score reflects thromboembolic risk: hypertension (1 point), age (65 to 74 years: 1 point; ≥75 years: 2 points), diabetes mellitus (1 point), history of stroke, transient ischemic attack, or thromboembolism (2 points), vascular disease (1 point), female (1 point).

AF = atrial fibrillation; BMI = body mass index; EtOH = alcohol; HF = heart failure; METS = metabolic equivalents; MI = myocardial infarction; SBP = systolic blood pressure.

POPULATION FOR ANALYSIS. For the present analysis, women with a history of AF at study entry (n = 876) or the presence of a cardiovascular event before randomization (stroke, MI, HF; n = 59) were excluded. We also excluded women who were either lost to follow-up during the initial trial (n = 1,246) or opted out of observational follow-up (n = 2,959) at the end of the trial in 2004 because incident AF and subsequent cardiovascular events could not be reliably confirmed. The final study cohort included 34,736 women.

STATISTICAL ANALYSIS. First, we quantified the relative and absolute risk of incident HF associated with the development of incident AF in the entire study population. Person-years of follow-up were defined from the date of return of the baseline questionnaire until the first occurrence of HF, death, loss to follow-up or December 31, 2014. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Incident AF was entered into the model as time-varying covariates. Models were initially adjusted for age and randomization assignment (vitamin E, aspirin) with subsequent multivariable, time-varying adjustment for HF risk factors. In secondary analyses, we assessed the association between AF and incident HF subtypes (HFpEF, HFrEF). In addition, as the association between AF and HF may differ by the proximity of their temporal relationship (5,10), we performed sensitivity analyses that censored HF events <30 days after AF diagnosis (n = 61).

To quantify the association between modifiable risk factors and the development of incident HF in those with new-onset AF, we used Cox models incorporating time-varying HF risk factors limited to the subpopulation of women with new-onset AF and without prevalent HF (n = 1,495). In these models, each woman contributed person-years of follow-up from the date of AF diagnosis to the first occurrence of HF, death, loss to follow-up, or December 31, 2014. Baseline covariates in the AF subpopulation were updated to reflect the assessment most proximate to the date of AF diagnosis, followed by subsequent time-varying adjustment of HF risk factors after AF diagnosis. To estimate the joint risk reduction associated with risk factor modification, we constructed a risk factor score composed of significant modifiable risk factors (1 point each for: systolic blood pressure [SBP] >120 mm Hg, body mass index [BMI] ≥30 kg/m^2, current smoking, diabetes). Using a similar method for time-varying assessment as outlined for the individual risk factors, we then compared multivariable-adjusted HR for participants with the least favorable risk factor profile (3 or 4 points) to those with progressively favorable profiles (2, 1, and 0 points). Patients with 3 or 4 points were combined to maintain similarly sized risk factor strata given the rare prevalence of women with all 4 risk factors (i.e., 4 points).

We then assessed the absolute and relative risk of stroke, MI, and mortality associated with the development of HF in this AF subpopulation through the use of age-adjusted cumulative incidence curves and

proportional hazard models with incident HF as a time-varying covariate and cardiovascular endpoints (stroke, MI) and mortality (all-cause, cardiovascular) as outcomes. Person-years of follow-up were derived from the date of AF diagnosis to the first occurrence of death, stroke, MI, loss to follow-up, or December 31, 2014, as appropriate. Models included time-varying adjustment for established risk factors for cardiovascular morbidity and mortality. Mortality models (all-cause, cardiovascular) included additional time-varying adjustment for stroke and MI after AF diagnosis. To explore whether prognostic implications differed by timing of HF after AF, we repeated the mortality analyses excluding participants with HF <30 days after AF diagnosis (n = 61).

For all the above-mentioned outcomes, we calculated the population-attributable fraction (PAF) and 95% CI, which reflects the proportion of the outcome that would not have occurred if the risk factor were not present (assuming a causal relationship). To calculate the PAF, we estimated the relative risk from multivariable pooled logistic regression models, which allowed for updated assessment of risk factor prevalence and direct inclusion of age in the model. In this approach, each 2-year interval was treated as an independent follow-up study and observations over all intervals were pooled, as previously described (11). Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). A 2-tailed $p < 0.05$ indicated statistical significance.

RESULTS

STUDY COHORT. Baseline characteristics of the study cohort are shown in Table 1. In 34,736 women who were free of prevalent cardiovascular disease at baseline, 1,534 women developed new-onset AF (4.4% of the study cohort) and 687 developed HF (2.0% of the study cohort) over a median follow-up of 20.6 (interquartile range [IQR]: 19.6 to 21.1) years. Among 1,534 women with new-onset AF, there were 226 HF events, the majority of which occurred after AF diagnosis (n = 187; 82.7%). Excluding women with HF before AF (n = 39), the baseline characteristics of the 1,495 women with new-onset AF and without prevalent HF, updated to the time of AF diagnosis, are also shown in Table 1. Of women with new-onset AF and with available echocardiography at the time of AF diagnosis (n = 1,064), only a minority demonstrated structural heart disease as reflected by the presence of left ventricular hypertrophy (n = 419; 39%), mitral regurgitation (n = 157; 15%), or left atrial enlargement (n = 493; 46%).

TABLE 2 Risk Factors for Incident HF After AF Diagnosis

	Multivariable-Adjusted HR (95% CI)*	p Value
Diabetes mellitus	1.57 (1.07–2.32)	0.0001
Smoking status		
Never smoker	Reference	
Prior smoker	0.99 (0.73–1.34)	0.94
Current smoker	2.11 (1.11–4.03)	0.02
BMI, kg/m^2		
<25	Reference	
25–29	0.97 (0.66–1.43)	0.89
≥30	1.62 (1.10–2.40)	0.02
		trend = 0.011
SBP, mm Hg		
<120	Reference	
120–139	2.12 (1.33–3.36)	0.002
140–159	1.76 (1.02–3.02)	0.041
≥160	2.50 (1.10–5.71)	0.029
		trend = 0.044
Physical activity, ≥7.5 METS/week	0.95 (0.70–1.28)	0.71
EtOH ≥ 2 drinks/day	1.37 (0.75–2.50)	0.30
Hyperlipidemia	1.06 (0.73–1.54)	0.77
Age, per year	1.06 (1.04–1.08)	<0.0001
Race/ethnicity		
White	Reference	
Black	1.23 (0.30–5.02)	0.77
Hispanic	†	1.00
Other	0.72 (0.10–5.26)	0.72
History of MI at AF diagnosis	0.44 (0.15–1.27)	0.13
Medication use		
Vitamin E	0.79 (0.59–1.07)	0.12
Aspirin	1.23 (0.92–1.66)	0.17
HRT	0.73 (0.53–1.00)	0.05
Statin	0.72 (0.70–1.28)	0.06
Antihypertensive medication use	1.26 (0.89–1.76)	0.19
Chronic kidney disease	4.02 (2.31–7.00)	<0.0001
Incident coronary heart disease	2.44 (1.62–3.67)	<0.0001

*Multivariable adjustment was for age, race, randomization assignment (ASA, vitamin E), and history of MI at AF diagnosis as well as time-updated assessment of medication use (statin, antihypertensive, HRT), incident coronary heart disease (MI and/or revascularization), chronic kidney disease, and modifiable risk factors shown (diabetes mellitus, physical activity, alcohol consumption, smoking, BMI, SBP, hyperlipidemia). †HR were not calculable secondary to small sample size.

ASA = aspirin; CI = confidence interval; HRT = hormone replacement therapy; HR = hazard ratio; other abbreviations as in Table 1.

AF AS RISK FACTOR FOR INCIDENT HF. Following the diagnosis of AF, the age-adjusted cumulative incidence rate of HF was 17.4 cases/1,000 person-years (95% CI: 13.4 to 21.4) over a median follow-up of 6.8 (IQR: 3.7 to 10.3) years. The incidence of HF after new-onset AF was greater than age-adjusted incidences of stroke (9.0 cases/1,000 person-years; 95% CI: 6.6 to 11.3 person-years) and MI (4.4 cases/1,000 person-years; 95% CI: 2.6 to 6.1 person-years). In multivariable-adjusted analyses, AF was associated with 9-fold increased risk of incident HF (HR: 9.03; 95% CI: 7.52 to 10.84; $p < 0.0001$), with similar

TABLE 3 Modifiable Risk Factors and HF Risk in New-Onset AF

Modifiable Risk Factors at AF Baseline‡	Subgroup (n)	Incident HF Events	Person-Yrs Follow-Up	Age-Adjusted Incidence Rate* (95% CI)	Multivariable-Adjusted HR† (95% CI)	p Value
0	231	9	1,896.5	6.3 (2.2–10.4)	0.14 (0.07–0.29)	<0.0001
1	758	88	5,679.4	16.2 (12.1–20.4)	0.40 (0.25–0.63)	<0.0001
2	381	65	2,743.7	25.8 (17.3–34.2)	0.60 (0.37–0.95)	0.029
3–4	125	25	779.3	36.0 (17.4–54.6)	Reference	

*Incidence rates are age-adjusted, reported per 1,000 person-yrs, and reflect risk factor profiles at the time of AF diagnosis. †Multivariable models reflect time-updated assessment of risk factor profiles (i.e., allows for changes in risk factor profiles after AF diagnosis). Specifically, adjustment was for age, race, randomization assignment (ASA, vitamin E), and history of MI at AF diagnosis as well as time-updated assessment of medication use (statin, antihypertensive, HRT), MI, coronary revascularization, chronic kidney disease, and modifiable risk factors. ‡Modifiable risk factors as assessed at the time of AF diagnosis include: diabetes mellitus, current smoking, BMI ≥30 kg/m^2, and SBP >120 mm Hg.

Abbreviations as in Tables 1 and 2.

risk estimates for incident HFpEF (HR: 9.63; 95% CI: 7.67 to 12.86; p < 0.0001) and HFrEF (HR: 10.02; 95% CI: 7.38 to 13.61; p < 0.001). After censoring HF events occurring within 30 days of AF diagnosis (n = 61), the association between AF and incident HF was attenuated, but remained significant in multivariable-adjusted models (HR: 4.99; 95% CI: 4.05 to 6.13; p < 0.0001) (Online Table 1). Assuming a causal association between AF and incident HF and after accounting for population-level risk factors for HF, the population-attributable risk of new-onset AF for incident HF was 26% (95% CI: 15% to 37%).

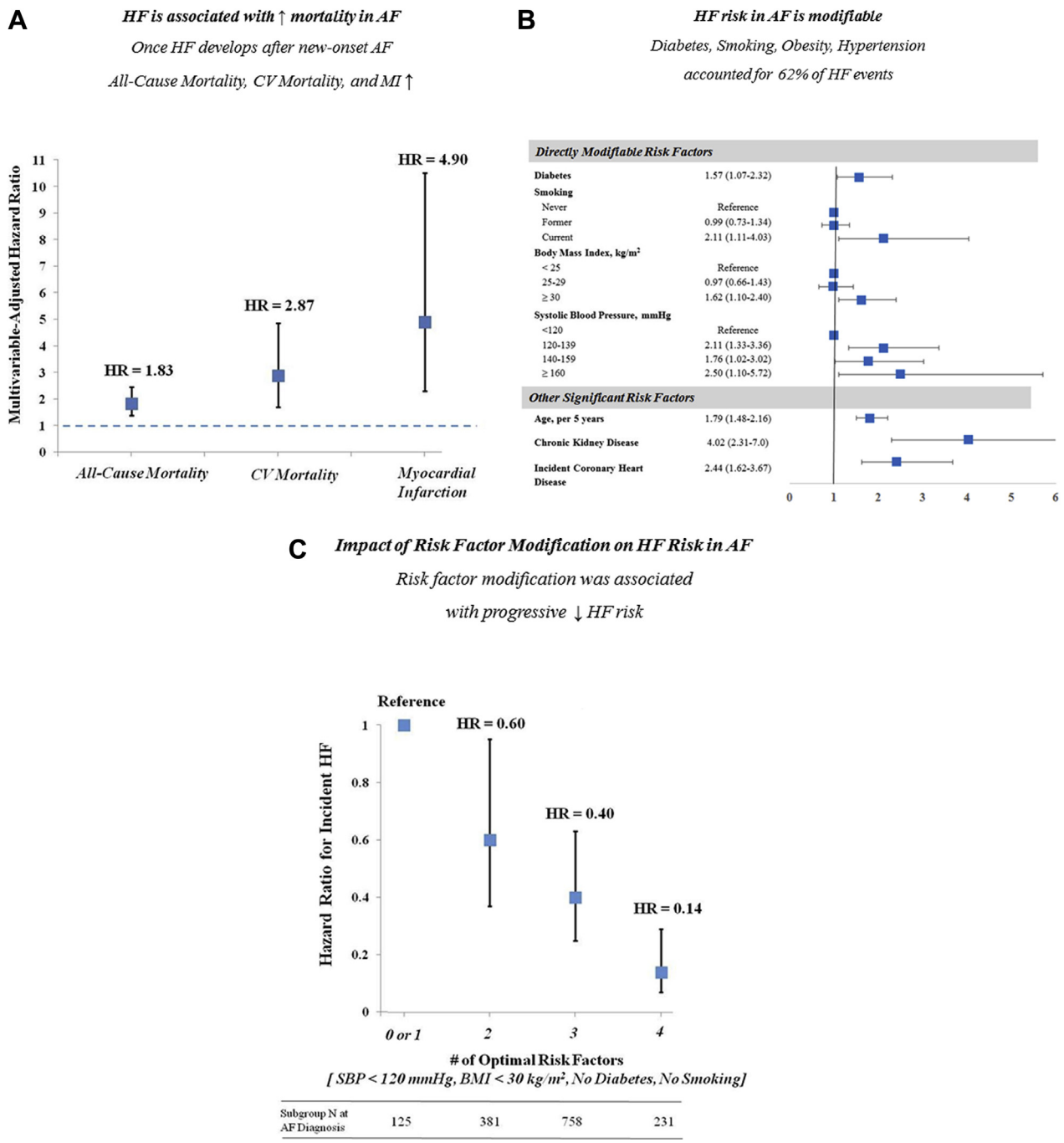
RISK FACTORS FOR INCIDENT HF AFTER NEW-ONSET AF. We next examined risk factors associated with incident HF in women with new-onset AF (Table 2). In multivariable and time-updated models accounting for changes in risk factors after AF diagnosis, 4 directly modifiable risk factors (diabetes mellitus, current smoking, obesity, and elevated SBP) were each significantly associated with the development of incident HF. Additional risk factors associated with HF in women with new-onset AF included age, chronic kidney disease, and incident myocardial infarction. Borderline significant inverse associations with HF risk were also observed for statin and hormone replacement therapy use.

At the time of AF diagnosis, 85% of women (1,264 of 1,495) had at least 1 directly modifiable risk factor associated with HF risk (diabetes, smoking, BMI ≥30 kg/m^2, or SBP >120 mm Hg) (Table 3). Increasing BMI was associated with a significant increased risk of incident HF (multivariable-adjusted HR: 1.15 per 5 kg/m^2; 95% CI: 1.01 to 1.28; continuous p = 0.04), with the most significant risk confined to those with BMI ≥30 kg/m^2 (HR: 1.62; 95% CI: 1.10 to 2.40; p = 0.02) when compared with normal-weight (BMI <25 kg/m^2) women. In addition, increasing SBP was associated with an increased risk of incident HF (HR: 1.16; 95% CI: 1.05 to 1.28 [per 10 mm Hg increase]; p = 0.003). When assessed categorically, the relative risk of incident HF was elevated even at mild elevations in SBP (HR: 2.12; 95% CI: 1.33 to 3.36; p = 0.002 for SBP 120 to 139 vs. <120 mm Hg) and persisted for higher values of SBP (trend across SBP categories, p = 0.044).

To assess the joint impact of these modifiable risk factors on incident HF, we used multivariable-adjusted models with time-updated assessment of risk factors after AF diagnosis (Table 3, Online Table 2). Compared with women with the least favorable risk factor profile (3 to 4 risk factors), women who maintained or achieved optimal risk factor levels were at significantly decreased risk of HF, with a graded reduction in risk across progressively more optimal risk factors levels (Table 3, Figure 1). For example, women with optimal levels of all 4 modifiable risk factors (SBP <120 mm Hg, BMI <30 kg/m^2, absent smoking, absent diabetes) were at 86% lower risk of incident HF (HR: 0.14; 95% CI: 0.07 to 0.29) compared with women with the least favorable risk factor profile (3 to 4 risk factors). Assuming a causal relationship between modifiable risk factors and HF, an estimated 62% (95% CI: 23% to 83%) of the population-attributable risk of incident HF after new-onset AF was attributable to these 4 directly modifiable risk factors, with the greatest contributing risk factor being SBP (Online Table 3).

IMPACT OF INCIDENT HF ON MORTALITY AND CARDIOVASCULAR EVENTS AFTER AF. Among the 1,495 women with new-onset AF without prevalent HF, 310 deaths, 96 strokes, and 51 MI occurred over a median follow-up of 7.4 (IQR: 4.4 to 11.0) years. Age- and multivariable-adjusted estimates for the association between incident HF and mortality (all-cause, cardiovascular), stroke, and MI in women with new-onset AF are shown in Table 4. In multivariable-adjusted models inclusive of time-updated accounting for stroke and myocardial infarction,

FIGURE 1 HF Risk in AF: Impact of Risk Factor Modification



This study estimated the influence of risk factor modification on heart failure (HF) risk in women with new-onset atrial fibrillation (AF). In women with new-onset AF, the onset of HF was associated with significant increases in mortality (all-cause, cardiovascular [CV]) and morbidity (myocardial infarction [MI]) **(A)**. Risk factors for incident HF in women with new-onset AF included directly modifiable factors (obesity, hypertension, smoking, diabetes) as well as other significant risk factors (age, chronic kidney disease, incident coronary heart disease [MI, revascularization]). All 4 directly modifiable risk factors accounted for 62% of the population attributable fraction of HF in the cohort **(C)**. Compared with women with the least favorable risk factor profile (3 to 4 modifiable risk factors), women who maintained or achieved more favorable risk factor profiles after new-onset AF were at progressively lower risk of incident HF **(B)**. BMI = body mass index; HR = hazard ratio; SBP = systolic blood pressure.

TABLE 4 Impact of Incident HF on Cardiovascular Mortality, Stroke, and MI in New-Onset AF

	No HF	HF	p Value
All-cause mortality			
Events, n	241	69	
Incidence rate (95% CI)*	25.2 (21.1–29.4)	42.3 (28.9–55.7)	
HR (95% CI)			
Age-adjusted	1.00 (Reference)	2.11 (1.60–2.77)	<0.0001
Multivariable-adjusted†	1.00 (Reference)	1.83 (1.37–2.45)	<0.0001
CV mortality			
Events, n	59	26	
Incidence rate (95% CI)	6.3 (4.3–8.3)	16.0 (7.6–24.4)	
HR (95% CI)			
Age-adjusted	1.00 (Reference)	3.47 (2.15–5.60)	<0.0001
Multivariable-adjusted	1.00 (Reference)	2.87 (1.70–4.85)	<0.0001
Stroke			
Events, n	81	15	
Incidence rate (95% CI)	8.8 (6.3–11.3)	9.9 (3.4–16.5)	
HR (95% CI)			
Age-adjusted	1.00 (Reference)	1.11 (0.53–2.32)	0.78
Multivariable-adjusted	1.00 (Reference)	0.89 (0.42–1.90)	0.76
MI			
Events, n	36	15	
Incidence rate (95% CI)	3.4 (1.8–5.1)	10.0 (3.2–16.8)	
HR (95% CI)			
Age-adjusted	1.00 (Reference)	4.96 (2.38–10.33)	<0.0001
Multivariable-adjusted	1.00 (Reference)	4.90 (2.29–10.50)	<0.0001

*Incidence rates are age-adjusted and reported per 1,000 person-yrs. †Multivariable adjustment was for demography (age, white race, education), randomization assignment (ASA, vitamin E), and anticoagulation use at the time of AF diagnosis with time-varying adjustment for BMI, coronary revascularization, diabetes mellitus, hypertension, hyperlipidemia, statin use, alcohol consumption, exercise, smoking status, and HRT. Mortality (all-cause, CV) models included additional time-varying adjustment for stroke and MI after AF diagnosis.

Abbreviations as in Tables 1 and 2.

incident HF was associated with a 2-fold increase in all-cause mortality (HR: 1.83; 95% CI: 1.37 to 2.45; $p < 0.0001$), with similar mortality risk associated with incident HFpEF and HFrEF (Online Table 4). Incident HF was also associated with an increased risk of cardiovascular mortality (HR: 2.87; 95% CI: 1.70 to 4.85; $p < 0.0001$) and MI (HR: 4.90; 95% CI: 2.29 to 10.50; $p < 0.0001$) in multivariable-adjusted models, but it was not associated with an increased risk of stroke. In our cohort, nearly every woman with subsequent HF (181 of 187; 97%) had a $CHADSVASc_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Age 65 to 74 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Sex) score of ≥2 at the time of AF diagnosis. After taking into account population-level risk factors for mortality and morbidity, we estimated that 9.9% (95% CI: 2.2% to 18.3%) of all deaths and 18.2% (95% CI: 1% to 35%) of cardiovascular deaths in women with new-onset AF could be attributed to incident HF.

DISCUSSION

In women with new-onset AF, HF was the most common nonfatal event and its onset was associated with increased all-cause and cardiovascular mortality. Directly modifiable risk factors—obesity, diabetes mellitus, elevated systolic blood pressure, and current tobacco smoking—were jointly associated with 62% of the population risk of incident HF. In time-updated models accounting for changes in risk factors after AF diagnosis, women who maintained or achieved an optimal risk factor profile were at significantly reduced risk of HF. Taken together, these findings highlight the potential population and individual level impact of risk factor modification on HF risk in new-onset AF.

Previous studies of incident HF in those with AF (12–14) have focused primarily on risk prediction and, as such, have incorporated both modifiable and non-modifiable risk factors assessed at AF baseline. The clinical impact of these studies is limited, however, by the absence of evidence for HF preventive therapies in AF. By incorporating time-updated assessments of directly modifiable risk factors after AF diagnosis, our study is the first to estimate the association between optimal levels of risk factors and HF risk in patients with AF. We identified a consistent decrement in HF risk associated with progressively optimal risk factor profiles, with a striking 86% lower HF risk among women with optimal levels of modifiable risk factors (obesity, hypertension, smoking, diabetes). These factors have also been associated with incident AF (15–17), and thus our study suggests that risk factor improvement even after the diagnosis of AF may decrease HF risk and improve outcomes. Though hypothesis-generating, our findings more firmly establish a necessary evidence base to support future investment in intervention trials aimed at risk factor modification in AF patients and further support the inclusion of HF as endpoint in such prospective assessments.

With respect to individual risk factors, we found that blood pressure elevations accounted for a large proportion of the population attributable risk of incident HF and observed individual increases in HF risk associated with even modestly elevated SBP (i.e., 120 to 139 mm Hg). These findings are consistent with previous reports of SBP and HF risk in the general population (18) that found increased HF risk at modest elevation in SBP with a generally fixed hazard across increasing SBP categories. Our findings may add to emerging reports supporting the salutary cardiovascular effects of lower SBP targets for antihypertensive

therapy (19). We would note that the lack of a clear gradation of HF risk in categories of SBP ≥140 mm Hg may also be due to the relatively low numbers of women with persistent elevations in SBP above this level in this health professional cohort. Further studies in hypertensive AF populations would be needed to fully evaluate this question. Other directly modifiable risk factors associated with HF risk included BMI ≥30 kg/m^2, a finding consistent with recent studies highlighting the pathophysiological relationship between obesity and HF (20). Finally, to the extent that incident MI likely mediates some of the association between our modifiable risk factors and HF, our adjusted estimates regarding the impact of risk factor modification on HF risk are conservative.

We additionally estimate the potential clinical impact of HF prevention on other adverse outcomes in our cohort. Consistent with recent estimates from contemporary cohorts of mixed sex (3,4,10), we find that HF was the most common nonfatal cardiovascular event after AF, reinforcing the predominant impact of HF on morbidity after AF even among women, who are known to be at elevated risk for stroke. Once HF developed in women with AF, we found that cardiovascular morbidity and mortality were increased. Whereas previous reports have identified similar relative risk elevations for cardiovascular and total mortality (5), we add to these previous reports by quantifying the potential impact of HF prevention on mortality in AF. Assuming a causal association between incident HF and mortality, we estimated that prevention of HF in women with new-onset AF could potentially lead to an estimated 10% reduction in total and 18% reduction in cardiovascular mortality. Similar to a recent report in patients with establish AF (14), incident HF was not associated with subsequent stroke risk in women with new-onset AF. This finding, which is seemingly contradictory to older reports (21), may reflect the successful real-world institution of anticoagulation either before or at the time of HF diagnosis. Finally, we observed a bidirectional association between HF and incident MI, which to our knowledge, has not been previously reported. Concordant with this finding, statin use was associated a numerically lower, albeit statistically insignificant, risk of HF. This finding is based on small numbers, and if confirmed in other cohorts, could provide further justification for aggressive risk factor modification (including lipids) in AF patients.

STUDY LIMITATIONS. Our study has several strengths including prospective assessment of risk factors, large sample size, adjudication of endpoints, and incorporation of time-updated risk factors of incident HF risk. Nonetheless, the findings of this study should be interpreted in the context of its design and limitations. First, the study population comprised healthy, middle-aged, and predominantly white female health professionals. The PAF estimates in this study, which are population-specific, may not generalize to men or nonwhite ethnicities. Second, risk factor modification was not randomized at the time of AF diagnosis, and the associations identified including PAF estimates cannot be directly taken as causal. Third, modifiable risk factors including BMI and SBP were self-reported, although nondifferential misclassification would have biased our findings toward the null. The prognostic value of self-reported BP and BMI in the WHS (15) has been previously reported. Fourth, the methodology of AF ascertainment may have underestimated asymptomatic cases of AF. In addition, the diagnosis of AF may have led to increased medical surveillance resulting in ascertainment bias for incident HF and thus magnifying AF-HF risk estimates. Fifth, information regarding some HF risk factors (e.g., sleep apnea, coronary disease without MI) were not available and could not be assessed. In addition, echocardiographic evaluation was not systematically performed in this cohort and therefore the contribution of potential cardiac structural risk factors (e.g., valvular heart disease) to HF risk could not be assessed. Sixth, although adjustment for multiple comparisons was not performed, the primary findings of the study would remain significant even with Bonferroni correction. Finally, as pharmacotherapy for AF was assessed 2 years after AF diagnosis, we were unable to assess the impact of pharmacotherapy strategies (e.g., antiarrhythmic use, β-blockade) strategies on HF risk.

CONCLUSIONS

In women free of prevalent cardiovascular disease at baseline, new-onset AF was associated with an increased risk of HF that, in turn, was associated with increased mortality and morbidity. Our data provide support for the concept that targeting modifiable risk factors, including obesity, smoking, elevated SBP, and diabetes mellitus, in patients with new-onset AF has the potential to significantly reduce the individual risk and population burden of HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Cardiovascular risk in AF is changing in the contemporary era of anticoagulation. In a large cohort of women with new-onset AF, HF was the most common incident cardiovascular event, occurring at a rate nearly twice that of stroke. The onset of HF was associated with a more than 2-fold increase in mortality and 4-fold increase risk of myocardial infarction. Directly modifiable risk factors—obesity, smoking, elevated SBP, and diabetes mellitus—accounted for 62% of the population burden of HF. Compared with women with the least favorable risk factor profile (3 to 4 modifiable risk factors), women who maintained or achieved optimal levels of risk factors after AF diagnosis (BMI <30 kg/m^2, SBP <120 mm Hg, nonsmoker, absent diabetes) had an 86% lower risk of incident HF.

TRANSLATIONAL OUTLOOK: Future studies are needed to examine the impact of risk factor modification at the time of AF diagnosis on incident HF risk. Prevention of HF may represent an important endpoint of AF intervention trials in the future and a relevant target for improving survival in AF.

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KEY WORDS atrial fibrillation, epidemiology, heart failure, prevention, risk factor

APPENDIX For supplemental tables, please see the online version of this paper.