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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;■:■–■) © 2017 by the American College of Cardiology Foundation.

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

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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

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.

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]).

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 pre-defined 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.

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