ORIGINAL RESEARCH

# Predisposing Factors Associated With Development of Persistent Compared With Paroxysmal Atrial Fibrillation

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***Background*—**Once atrial fibrillation (AF) progresses to sustained forms, adverse outcomes increase and treatment success rates decrease. Therefore, identification of risk factors predisposing to persistence of AF may have a significant impact on AF morbidity.

***Methods and Results*—**We prospectively examined the differential associations between traditional, lifestyle, and biomarker AF risk factors and development of paroxysmal versus nonparoxysmal AF (persistent/permanent) among 34 720 women enrolled in the Women's Health Study who were free of cardiovascular disease and AF at baseline. AF patterns were defined based on current guidelines and classified according to the most sustained form of AF within 2 years of diagnosis. During a median follow-up of 16.4 years, 690 women developed paroxysmal AF and 349 women developed nonparoxysmal AF. In multivariable time-varying competing risk models, increasing age (hazard ratio [HR] 1.11, 95% CI 1.10 to 1.13, versus HR 1.08, 1.07 to 1.09, per year), body mass index (HR 1.07, 1.05 to 1.09, versus HR 1.03, 1.02 to 1.05, per kg/m$^2$), and weight (HR 1.30, 1.22 to 1.39, versus HR 1.14, 1.08 to 1.20, per 10 kg) were more strongly associated with the development of nonparoxysmal AF compared with paroxysmal AF. Hemoglobin A1c levels at baseline were directly related to the development of nonparoxysmal AF but inversely associated with paroxysmal AF in multivariable competing risk models (*P* for nonequal association=0.01).

***Conclusions*—**In women without AF or CVD at baseline, increasing age, adiposity, and higher hemoglobin A1c levels were preferentially associated with the early development of nonparoxysmal AF. These data raise the hypothesis that efforts aimed at weight reduction or glycemic control may affect the proportion of the population with sustained AF. **(*J Am Heart Assoc*. 2014;3: e000916 doi: 10.1161/JAHA.114.000916)**

**Key Words:** atrial fibrillation • HbA1c • obesity • risk factors

Atrial fibrillation (AF) is a heterogeneous disorder with variable clinical profile and natural course.[1–3] Experimental models[4,5] have demonstrated the self-perpetuating nature of AF with recurring episodes becoming more progressive and eventually sustained. However, in clinical studies,[6–10] the majority of patients with AF remain paroxysmal, suggesting the electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal. In several studies, patients who develop these sustained forms of AF (persistent/permanent) also have higher rates of cardiovascular disease (CVD) morbidity, including cardiovascular hospitalizations and[7] heart failure[11,12]; recent studies suggest that thromboembolism rates may be higher as well.[7,13] There are data from recent prospective studies suggesting that patients who develop sustained forms of AF may have a higher subsequent mortality.[11,12] It is also well established that success rates associated with ablative or medical therapies aimed at maintenance of sinus rhythm are lower once AF becomes persistent or permanent.[1,14] Therefore, understanding factors that predispose to sustained forms of AF may lead to preventive and therapeutic approaches that may lower AF-related morbidity and improve response to traditional therapies.

Risk factors associated with incident AF have been well established; however, studies examining whether these AF risk factors differ with regard to the development of persistent and permanent AF rather than paroxysmal AF are limited.[6–10,15–17] Prior work has identified age,[6–8] body mass index (BMI),[9,18] underlying heart disease,[7,8,15] and other comorbidities such as

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chronic obstructive pulmonary disease and hypertension (HATCH score)[7,17]as risk factors for progression to more persistent forms of AF among patients with established paroxysmal AF and varying degrees of CVD. To date, studies have examined single baseline measures of traditional risk factors, and data on biomarker associations are lacking. The majority of studies have been performed in patients with established paroxysmal AF and varying degrees of CVD, and data in healthy populations without established AF or CVD remain sparse.[6,10] Rates of progression to sustained forms of AF are greatest within the first year of diagnosis,[8] suggesting that efforts aimed at preventing sustained AF may need to begin before the onset of clinically recognized disease.

To address these gaps, we prospectively examined the association between AF risk factors and the development of paroxysmal versus nonparoxysmal AF among a large prospective cohort of women without prior CVD or AF at baseline, by using traditional and lifestyle risk factors assessed and updated before the development of AF and using biomarkers measured at entry into the study before the development of disease.

## Methods

### Study Population

All subjects were participants of the Women's Health Study (WHS), a previously published,[19,20] randomized placebo-controlled trial evaluating the benefits and risks of low-dose aspirin, beta-carotene, and vitamin E in the primary prevention of CVD and cancer. Briefly, the WHS enrolled 39 876 female health professionals in 1993 who were 45 years of age or older without known CVD, cancer, and other major illnesses. Randomized treatment ended on March 31, 2004, and subsequently women were invited to participate in continued observational follow-up. We excluded women who did not participate in the observational follow-up period (n=4204), had a history of AF (n=897), or had a confirmed cardiovascular event (n=65) before study entry, leaving 34 720 women for our primary analysis. Blood samples were available for 28 345 women at the time of randomization. After applying exclusion criteria, 25 007 were eligible for the biomarker analyses. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston.

### Traditional and Lifestyle AF Risk Factors

Information on baseline characteristics, changes in covariates, and study outcomes were collected through the use of mailed questionnaires at baseline, 6 months, and every 12 months thereafter. Covariates examined include age (years), BMI (kg/m$^2$), BMI categories (<25, 25 to 29.9, and ≥30 kg/m$^2$), weight (per 10 kg), height (per 10 cm), history of diabetes mellitus, hypertension, hypercholesterolemia, ever smoker (current and past), alcohol intake (≥2 drinks per day), and physical activity (<7.5 or ≥7.5 metabolic equivalent hours per week).

### Biomarker Risk Factors

Selected available biomarkers previously associated with AF in this or other cohorts were analyzed for differential associations with AF including inflammatory markers,[21] hemoglobin (Hb)A1c (%),[22,23] glomerular filtration rate <60 mL/min per 1.73 m$^2$,[24,25] and lipids (low- and high-density lipoproteins and triglycerides [all mg/dL]).[4,26] Based on prior relationships with AF in this cohort,[21] inflammatory markers, high-sensitivity C-reactive protein, fibrinogen, and soluble intercellular adhesion molecule were combined into an inflammatory score. The inflammatory score ranged from 0 to 3, with 1 point added to the score of a woman for each marker of inflammation in the highest tertile.[21] HbA1c was analyzed in quartiles.[22]

### Ascertainment of AF Types

At baseline, 48 months, and annually thereafter, women were asked to report diagnoses of incident AF. Beginning on September 19, 2006, additional questionnaires were sent to women enrolled in the continued observational follow-up who reported an incident AF event on at least 1 annual questionnaire to confirm AF episodes and collect additional information. Available medical records, ECGs, rhythm strips, 24-hour ECG monitoring, and testing regarding cardiac structure and function were reviewed. For participants reporting AF during the trial and observational period who were deceased, family members were contacted to obtain consent for medical records. An incident AF event was confirmed if there was ECG evidence of AF (n=813) or if a medical report clearly indicated a personal history of AF (n=226). The earliest date in the medical records was set as the date of onset of AF. An end point committee of physicians reviewed medical records according to predefined criteria.[27]

AF was classified into subtypes according to definitions recommended by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conference.[1] Paroxysmal AF was defined as self-terminating within 7 days, persistent AF required cardioversion or lasted ≥7 days, and permanent AF lasted >1 year and/or attempts to convert rhythm were abandoned.[1] Women with persistent and permanent AF were categorized together as having nonparoxysmal AF because physician decision to not pursue cardioversion primarily

accounted for this distinction.[7] To consistently characterize AF type in women diagnosed with AF early and late in the study, we assigned the most sustained form (permanent>persistent>paroxysmal) of AF documented in the medical record within 2 years of initial AF diagnosis.

## Statistical Analysis

Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the first occurrence of AF, death, loss to follow-up, or March 2, 2011, whichever came first. Women in whom AF pattern could not be characterized were censored from the analysis at the time of their AF diagnosis (n=40). Baseline characteristics across groups of women were compared by using Wilcoxon rank sum test for continuous variables, $\chi^2$ tests for categorical variables, and Mantel–Haenszel trend test for ordinal variables.

To evaluate differential relationships for AF risk factors according to AF type, we used age- and multivariable-adjusted proportional hazards regression models stratified by paroxysmal and nonparoxysmal AF according to the competing risk model approach detailed by Lunn and McNeill.[28,29] Through this method, separate associations of risk factors and their relative hazards for the 2 AF types are evaluated simultaneously under a proportional hazards assumption, which assumes different associations of each study variable with paroxysmal and nonparoxysmal AF. To test whether risk estimates for each individual risk factor differ according to the 2 outcomes, we then fit a series of reduced models in which 1 risk factor at a time was forced to have a single effect estimate across both outcomes, while the effects of all other risk factors were allowed to be different. We used likelihood ratio tests to compare the full competing risk model with the individual reduced models.

For traditional and lifestyle risk factors, the primary analysis (n=34 720) consisted of time-varying competing risk models with updated covariates. The age-adjusted model further adjusted for aspirin, vitamin E, beta-carotene, BMI, history of diabetes mellitus, hypertension, hypercholesterolemia, ever smoker, alcohol intake, and physical activity. A second multivariable model (B) substituted height and weight for BMI and included all covariates in model A. For the biomarker analyses, we constructed age- and multivariable-adjusted competing risk models that adjusted for biomarker levels at baseline, as well as the covariates just described collected at the time of the baseline blood collection among 25 007 women in the biomarker cohort.

To evaluate the degree to which the association between risk factors and AF types may be mediated by development of cardiovascular events (CVE; myocardial infarction, stroke, revascularization, and heart failure), we refitted competing risk models to adjust for interim CVE events. We also performed additional models censoring women at the time they developed a CVE.

To explore how the presence of symptoms, rate control medications,[30] or left atrial (LA) enlargement may have influenced AF progression and our primary results, we also examined risk factor associations with nonparoxysmal versus paroxysmal AF in case-only logistic regression models that adjusted for symptom status, rate control medications (β-blocker, calcium channel blockers, or digoxin), and LA enlargement (LA diameter >40 mm or qualitative description of enlargement) documented on echocardiogram near the time of AF diagnosis.

Statistical analysis was performed by using SAS software version 9.1.3 (SAS Institute Inc). All *P* values were 2-sided and statistically significant at $P \leq 0.05$.

# Results

## Baseline Characteristics

During a median follow-up of 16.4 years (interquartile range 15.6 to 16.8 years), 1039 confirmed cases of incident AF occurred. Of those AF cases, 349 (33%) developed nonparoxysmal AF and 690 (67%) remained paroxysmal within 2 years of initial AF diagnosis. Women who developed nonparoxysmal AF were more likely to be older, heavier, and obese compared with women with paroxysmal AF. There were no significant differences in other traditional and lifestyle risk factors among women with paroxysmal and nonparoxysmal AF (Table 1). With respect to biomarkers, HbA1c and low-density lipoprotein levels were higher among women with nonparoxysmal compared with those with paroxysmal AF (Table 2).

## Traditional and Lifestyle Risk Factors and AF Type

In competing risk models, older age and higher BMI were more strongly associated with nonparoxysmal AF compared with paroxysmal AF ($P<0.001$ and $P=0.002$ for nonequal association, respectively; Table 3) after adjustment for updated covariates. For each year of age, the hazard of developing nonparoxysmal AF increased by 11% (95% CI 10% to 13%) compared with 8% (95% CI 7% to 9%) for paroxysmal AF. For BMI, the respective percentage increases were 7% (95% CI 5% to 9%) versus 3% (95% CI 2% to 5%) for nonparoxysmal AF versus paroxysmal AF. When compared with women with a BMI of <25 kg/m$^2$, obese women (≥30 kg/m$^2$) had a 2.56-fold (95% CI 1.93- to 3.40-fold) higher risk for the development of nonparoxysmal AF versus a 1.49-fold (95% CI 1.22- to 1.83-fold) higher risk for paroxysmal AF ($P=0.01$ for nonequal association). When height and

**Table 1.** Baseline Traditional and Lifestyle CVD Risk Factors According to the Development of Paroxysmal and Nonparoxysmal AF Among 34 720 Women in the Primary Analysis

| Traditional Lifestyle Factors | No AF (N=33 641) | Paroxysmal AF (N=690) | *P* Value* | Nonparoxysmal AF (N=349) | *P* Value† | *P* Value‡ |
|---|---|---|---|---|---|---|
| Age, median (IQR), y | 52.8 (48.8 to 58.5) | 57.7 (51.9 to 64.0) | <0.001 | 60.1 (53.8 to 65.5) | <0.001 | 0.001 |
| BMI, median (IQR), kg/m$^2$ | 24.9 (22.4 to 28.3) | 25.8 (23.2 to 29.8) | <0.001 | 26.6 (23.5 to 31.5) | <0.001 | 0.01 |
| BMI categories, % | | | | | | |
| <25 kg/m$^2$ | 51.4 | 43.0 | | 34.8 | | |
| 25 to <30 kg/m$^2$ | 30.8 | 33.0 | <0.001 | 32.5 | <0.001 | 0.001 |
| ≥30 kg/m$^2$ | 17.7 | 23.9 | | 32.8 | | |
| Weight, median (IQR), kg | 67.6 (59.9 to 77.1) | 70.8 (63.5 to 81.6) | <0.001 | 74.8 (63.5 to 86.6) | <0.001 | 0.004 |
| Height, median (IQR), cm | 165.1 (160.0 to 167.6) | 165.1 (162.6 to 170.2) | <0.001 | 165.1 (162.6 to 170.2) | <0.001 | 0.39 |
| Hypertension, % | 24.7 | 39.4 | <0.001 | 44.8 | <0.001 | 0.09 |
| Diabetes, % | 2.4 | 4.5 | <0.001 | 4.0 | 0.05 | 0.72 |
| Hypercholesterolemia, % | 29.0 | 31.7 | 0.11 | 37.5 | 0.001 | 0.06 |
| Current/past smoking, % | 48.3 | 49.7 | 0.46 | 54.7 | 0.02 | 0.13 |
| ≥2 Alcoholic drinks/day, % | 3.9 | 5.2 | 0.07 | 5.7 | 0.07 | 0.73 |
| Exercise | | | | | | |
| <7.5 MET-h per week | 45.4 | 50.3 | 0.01 | 47.9 | 0.36 | 0.46 |
| ≥7.5 MET-h per week | 54.6 | 49.7 | | 52.2 | | |

CVD indicates cardiovascular disease; AF, atrial fibrillation; IQR, interquartile range; BMI, body mass index; MET-h, metabolic equivalent hours.
**P* value comparing women with paroxysmal AF with women with no AF.
†*P* value comparing women with nonparoxysmal AF with women with no AF.
‡*P* value comparing women with paroxysmal AF with women with nonparoxysmal AF.

**Table 2.** Baseline Biomarker Levels According to the Development of Paroxysmal and Nonparoxysmal AF Among 25 007 Women Who Donated Blood Samples

| Baseline Biomarker | No AF (N=24 200) | Paroxysmal AF (N=530) | *P* Value* | Nonparoxysmal AF (N=277) | *P* Value† | *P* Value‡ |
|---|---|---|---|---|---|---|
| HbA1c | | | 0.06 | | <0.001 | 0.002 |
| ≤4.84% | 25.4 | 23.0 | | 15.2 | | |
| 4.84% to ≤5.00% | 24.8 | 22.2 | | 21.7 | | |
| >5.00% to 5.19% | 25.2 | 28.3 | | 27.4 | | |
| >5.19% | 24.6 | 26.6 | | 35.7 | | |
| GFR <60 mL/min per 1.73 m$^2$, % | 5.1 | 6.4 | 0.16 | 9.4 | 0.001 | 0.13 |
| Inflammatory score, % | | | <0.001 | | <0.001 | |
| 0 | 39.4 | 27.5 | | 25.3 | | |
| 1 | 31.8 | 32.6 | | 33.7 | | 0.70 |
| 2 | 19.6 | 25.4 | | 27.1 | | |
| 3 | 9.2 | 14.4 | | 13.9 | | |
| Lipids, median (IQR) | | | | | | |
| HDL, mg/dL | 52.1 (43.3 to 62.5) | 51.4 (42.3 to 61.9) | 0.30 | 52.3 (43.4 to 62.8) | 0.94 | 0.61 |
| LDL, mg/dL | 121.2 (100.3 to 144.1) | 118.9 (99.5 to 144.0) | 0.61 | 128.3 (105.2 to 149.2) | 0.01 | 0.02 |
| Triglycerides, mg/dL | 117.0 (83.0 to 173.0) | 127.0 (92.0 to 178.0) | 0.001 | 118.0 (86.0 to 181.0) | 0.12 | 0.43 |

AF indicates atrial fibrillation; HbA1c, hemoglobin A1c; GFR, glomerular filtration rate; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**P* value comparing women with paroxysmal AF with women with no AF.
†*P* value comparing women with nonparoxysmal AF with women with no AF.
‡*P* value comparing women with paroxysmal AF and women with nonparoxysmal AF.

**Table 3.** Traditional and Lifestyle CVD Risk Factors: Age- and Multivariable-Adjusted Hazard Ratios (95% CI) for Development of Paroxysmal Versus Nonparoxysmal AF Using Updated Covariates Among 34 720 Women in the Primary Analysis

| Risk Factor | Paroxysmal AF (N=690) | *P* Value | Nonparoxysmal AF (N=394) | *P* Value | *P* Value* |
|---|---|---|---|---|---|
| *Model A* | | | | | |
| Age, per year | | | | | |
| Age-adjusted model | 1.08 (1.07 to 1.09) | <0.001 | 1.11 (1.09 to 1.12) | <0.001 | |
| Multivariable-adjusted model 1† | 1.08 (1.07 to 1.09) | <0.001 | 1.11 (1.10 to 1.13) | <0.001 | <0.001 |
| Multivariable-adjusted model 2‡ | 1.08 (1.06 to 1.09) | <0.001 | 1.11 (1.10 to 1.13) | <0.001 | <0.001 |
| BMI, per kg/m$^2$ | | | | | |
| Age-adjusted model | 1.04 (1.03 to 1.06) | <0.001 | 1.08 (1.06 to 1.10) | <0.001 | |
| Multivariable-adjusted model 1† | 1.03 (1.02 to 1.05) | <0.001 | 1.07 (1.05 to 1.09) | <0.001 | 0.002 |
| Multivariable-adjusted model 2‡ | 1.03 (1.02 to 1.05) | <0.001 | 1.07 (1.05 to 1.09) | <0.001 | 0.003 |
| BMI categories§ | | | | | |
| Age-adjusted model | | | | | |
| 25 to <30 kg/m$^2$ | 1.37 (1.14 to 1.63) | 0.001 | 1.57 (1.20 to 2.05) | 0.001 | |
| >30 kg/m$^2$ | 1.71 (1.42 to 2.07) | <0.001 | 2.93 (2.25 to 3.81) | <0.001 | |
| Multivariable-adjusted model 1† | | | | | 0.01 |
| 25 to <30 kg/m$^2$ | 1.30 (1.08 to 1.55) | 0.005 | 1.51 (1.15 to 1.97) | 0.003 | |
| >30 kg/m$^2$ | 1.49 (1.22 to 1.83) | <0.001 | 2.56 (1.93 to 3.40) | <0.001 | |
| Multivariable-adjusted model 2‡ | | | | | 0.01 |
| 25 to <30 kg/m$^2$ | 1.30 (1.08 to 1.55) | 0.005 | 1.51 (1.15 to 1.97) | 0.003 | |
| >30 kg/m$^2$ | 1.50 (1.22 to 1.84) | <0.001 | 2.57 (1.93 to 3.40) | <0.001 | |
| Diabetes | | | | | |
| Age-adjusted model | 1.52 (1.19 to 1.95) | 0.001 | 1.86 (1.36 to 2.55) | <0.001 | |
| Multivariable-adjusted model 1† | 1.21 (0.93 to 1.56) | 0.15 | 1.26 (0.96 to 1.76) | 0.17 | 0.84 |
| Multivariable-adjusted model 2‡ | 1.15 (0.89 to 1.50) | 0.28 | 1.22 (0.87 to 1.70) | 0.25 | 0.80 |
| Hypertension | | | | | |
| Age-adjusted model | 1.66 (1.41 to 1.96) | <0.001 | 2.03 (1.58 to 2.60) | <0.001 | |
| Multivariable-adjusted model 1† | 1.49 (1.25 to 1.77) | <0.001 | 1.59 (1.23 to 2.06) | 0.001 | 0.66 |
| Multivariable-adjusted model 2‡ | 1.46 (1.23 to 1.74) | <0.001 | 1.57 (1.21 to 2.04) | 0.001 | 0.66 |
| Hypercholesterolemia | | | | | |
| Age-adjusted model | 0.97 (0.83 to 1.13) | 0.69 | 0.91 (0.73 to 1.13) | 0.40 | |
| Multivariable-adjusted model 1† | 0.87 (0.75 to 1.02) | 0.10 | 0.78 (0.63 to 0.98) | 0.03 | 0.43 |
| Multivariable-adjusted model 2‡ | 0.86 (0.73 to 1.00) | 0.06 | 0.77 (0.62 to 0.96) | 0.02 | 0.43 |
| Drinks >2 per day | | | | | |
| Age-adjusted model | 1.28 (0.92 to 1.76) | 0.14 | 1.42 (0.92 to 2.19) | 0.11 | |
| Multivariable-adjusted model 1† | 1.35 (0.97 to 1.88) | 0.07 | 1.55 (1.00 to 2.40) | 0.05 | 0.63 |
| Multivariable-adjusted model 2‡ | 1.36 (0.98-1.88) | 0.07 | 1.55 (1.00-2.41) | 0.05 | 0.63 |
| Current or past smoker | | | | | |
| Age-adjusted model | 1.05 (0.90 to 1.22) | 0.54 | 1.29 (1.04 to 1.59) | 0.02 | |
| Multivariable-adjusted model 1† | 1.03 (0.89 to 1.20) | 0.68 | 1.27 (1.03 to 1.58) | 0.03 | 0.12 |
| Multivariable-adjusted model 2‡ | 1.03 (0.89 to 1.20) | 0.73 | 1.27−(1.02 to 1.57) | 0.03 | 0.12 |
| Exercise, >7.5 MET-h per week | | | | | |
| Age-adjusted model | 0.91 (0.78 to 1.06) | 0.23 | 0.83 (0.67 to 1.02) | 0.07 | |

Continued

**Table 3.** Continued

| Risk Factor | Paroxysmal AF (N=690) | *P* Value | Nonparoxysmal AF (N=394) | *P* Value | *P* Value* |
|---|---|---|---|---|---|
| Multivariable-adjusted model 1† | 1.02 (0.87 to 1.19) | 0.81 | 1.02 (0.82 to 1.27) | 0.87 | 1.00 |
| Multivariable-adjusted model 2‡ | 1.03 (0.88 to 1.20) | 0.73 | 1.03 (0.83 to 1.28) | 0.81 | 1.00 |
| *Model B*‖ | | | | | |
| Height, per 10 cm | | | | | |
| Age-adjusted model | 1.34 (1.19 to 1.52) | <0.001 | 1.40 (1.18 to 1.67) | <0.001 | |
| Multivariable-adjusted model 1† | 1.38 (1.22 to 1.57) | <0.001 | 1.42 (1.19 to 1.70) | <0.001 | 0.78 |
| Multivariable-adjusted model 2‡ | 1.38 (1.22 to 1.57) | <0.001 | 1.43 (1.20 to 1.70) | <0.001 | 0.78 |
| Weight, per 10 kg | | | | | |
| Age-adjusted model | 1.18 (1.12 to 1.23) | <0.001 | 1.35 (1.27 to 1.43) | <0.001 | |
| Multivariable-adjusted model 1† | 1.14 (1.08 to 1.20) | <0.001 | 1.30 (1.22 to 1.39) | <0.001 | 0.001 |
| Multivariable-adjusted model 2‡ | 1.14 (1.08 to 1.20) | <0.001 | 1.31 (1.22 to 1.39) | <0.001 | 0.001 |

CVD indicates cardiovascular disease; AF, atrial fibrillation; BMI, body mass index; MET-h, metabolic equivalent hours.
**P* value from likelihood ratio tests of the null hypothesis that a risk factor has an equal effect on development of paroxysmal vs nonparoxysmal AF.
†Model 1: additionally adjusted for aspirin, vitamin E, beta-carotene, BMI, hypertension, diabetes, cholesterol, alcohol consumption, smoking, and exercise, using time-varying covariates.
‡Model 2: additionally adjusted for interim development of myocardial infarction, stroke, revascularization, and heart failure using time-varying covariates.
§Hazard ratios are for categories; however, likelihood ratio tests are based on comparison of models that use continuous values.
‖Model B: adjusted for height and body weight using time-varying covariates instead of BMI.

weight were substituted for BMI in the multivariable analyses (Table 3, model B), only heavier weight was more strongly associated with the development of nonparoxysmal AF (*P*=0.001 for nonequal association). Taller height was equally associated with the development of paroxysmal and nonparoxysmal AF.

Interim development of CVE (n=2152) was equally associated with the subsequent development of AF subtypes (HR 1.75, 95% CI 1.29 to 2.37 [paroxysmal] vs HR 1.60, 95% CI 1.07 to 2.40 [nonparoxysmal]; *P*=0.74 for nonequal association). In multivariable models adjusting for interim CVE, the differential relationships persisted for age, BMI, and weight (Table 3, model 2). When women were censored at the time of the development of CVD, the differential relationships for age, BMI, and weight were similar (*P*<0.001, *P*=0.001, and *P*=0.001 for nonequal association, respectively).

We then examined the sensitivity of these results to the presence or absence of symptoms, rate control medications, or LA enlargement at the time of the AF diagnosis using case-only logistic regression models. Among 940 women who developed AF, age (OR 1.04, 95% CI 1.02 to 1.06) and BMI (OR 1.04, 95% CI 1.02 to 1.07) were significantly associated with nonparoxysmal AF after controlling for symptom status and rate control medications. The relationship between BMI and nonparoxysmal AF was attenuated and became nonsignificant (OR 1.02, 95% CI 0.99 to 1.05) in models additionally controlling for LA enlargement, whereas the association with age remained significant (OR 1.03, 95% CI 1.01 to 1.05).

## Biomarkers and AF Type

After adjustment for other baseline biomarkers and traditional risk factors, increasing quartiles of baseline HbA1c level were associated with increasing risks for the early development of nonparoxysmal AF and lower risks of paroxysmal AF (*P*=0.01 for nonequal association, Table 4, model 1). These differential relationships persisted after censoring women who developed incident CVE over the course of the study (Table 4, model 2) and after eliminating diabetic subjects and women with HbA1c >5.66 (n=1340) from the analysis (*P*=0.01 for nonequal association). None of the other biomarkers tested exhibited significant differential associations with paroxysmal versus nonparoxysmal AF. In these models controlling for biomarkers, relationships for traditional and lifestyle risk factors were similar to the updated models, except for age, which was no longer significantly associated with paroxysmal versus nonparoxysmal AF after controlling for Hba1c (*P*=0.10 for nonequal association). HbA1c remained significantly associated with nonparoxysmal AF (OR 1.32, 95% CI 1.10 to 1.58) after adjustment for symptom status, rate control medications, and LA enlargement in a case-only multivariable logistic regression model.

## Discussion

In this large, prospective cohort study, we found that increasing age, adiposity, and higher HbA1c levels were differentially associated with the development of nonparoxysmal AF compared

**Table 4.** Age- and Multivariable-Adjusted Hazard Ratios (95% CI) for Development of Paroxysmal Versus Nonparoxysmal AF According to Baseline Levels of Biomarkers Among 25 007 Women Who Donated Blood Samples

| Risk Factor | Paroxysmal AF (N=530) | *P* Value | Nonparoxysmal AF (N=277) | *P* Value | *P* Value* |
|---|---|---|---|---|---|
| *HbA1c*[*] | | | | | |
| Age-adjusted model | | | | | |
| 4.84% to <5.00% | 0.89 (0.69 to 1.15) | 0.38 | 1.29 (0.87 to 1.91) | 0.21 | |
| >5.00% to 5.19% | 1.02 (0.80 to 1.30) | 0.87 | 1.44 (0.98 to 2.10) | 0.06 | |
| >5.19% | 0.91 (0.71 to 1.16) | 0.44 | 1.74 (1.20 to 2.50) | 0.003 | |
| Multivariable-adjusted model 1[‡] | | | | | 0.01 |
| 4.84% to <5.00% | 0.88 (0.68 to 1.14) | 0.32 | 1.27 (0.84 to 1.90) | 0.26 | |
| >5.00% to 5.19% | 0.96 (0.75 to 1.23) | 0.73 | 1.39 (0.94 to 2.06) | 0.10 | |
| >5.19% | 0.78 (0.60 to 1.01) | 0.06 | 1.47 (1.00 to 2.18) | 0.05 | |
| Multivariable-adjusted model 2[§] | | | | | |
| 4.84% to <5.00% | 0.90 (0.69 to 1.17) | 0.42 | 1.30 (0.85 to 1.97) | 0.22 | 0.01 |
| >5.00% to 5.19% | 0.99 (0.77 to 1.27) | 0.93 | 1.43 (0.96 to 2.15) | 0.08 | |
| >5.19% | 0.76 (0.58 to 1.00) | 0.05 | 1.48 (0.98 to 2.22) | 0.06 | |
| GFR, <60 mL/min per 1.73 $m^2$ | | | | | |
| Age-adjusted model | 1.08 (0.74 to 1.57) | 0.69 | 1.57 (1.02 to 2.42) | 0.04 | |
| Multivariable-adjusted model 1[‡] | 1.21 (0.82 to 1.78) | 0.35 | 1.56 (0.99 to 2.47) | 0.06 | 0.40 |
| Multivariable-adjusted model 2[§] | 1.05 (0.68 to 1.60) | 0.84 | 1.31 (0.79 to 2.17) | 0.29 | 0.51 |
| *Inflammation score*[*] | | | | | |
| Age-adjusted model | | | | | |
| 1 | 1.26 (1.01 to 1.58) | 0.04 | 1.33 (0.97 to 1.83) | 0.07 | |
| 2 | 1.49 (1.17 to 1.89) | 0.001 | 1.61 (1.15 to 2.24) | 0.01 | |
| 3 | 1.87 (1.41 to 2.47) | <0.001 | 1.84 (1.24 to 2.74) | 0.003 | |
| Multivariable-adjusted model 1[‡] | | | | | 0.27 |
| 1 | 1.17 (0.93 to 1.47) | 0.18 | 1.15 (0.84 to 1.59) | 0.38 | |
| 2 | 1.31 (1.02 to 1.70) | 0.04 | 1.14 (0.80 to 1.63) | 0.47 | |
| 3 | 1.51 (1.11 to 2.07) | 0.009 | 1.14 (0.73 to 1.78) | 0.56 | |
| Multivariable-adjusted model 2[§] | | | | | 0.28 |
| 1 | 1.23 (0.97 to 1.55) | 0.09 | 1.16 (0.83 to 1.61) | 0.39 | |
| 2 | 1.31 (1.00 to 1.71) | 0.05 | 1.16 (0.80 to 1.68) | 0.42 | |
| 3 | 1.51 (1.09 to 2.10) | 0.01 | 1.10 (0.69 to 1.75) | 0.79 | |
| *Lipids* | | | | | |
| HDL, mg/dL | | | | | |
| Age-adjusted model | 0.84 (0.67 to 1.05) | 0.12 | 0.91 (0.67 to 1.24) | 0.57 | |
| Multivariable-adjusted model 1[‡] | 1.04 (0.81 to 1.35) | 0.74 | 1.15 (0.81 to 1.63) | 0.43 | 0.66 |
| Multivariable-adjusted model 2[§] | 1.07 (0.83 to 1.40) | 0.59 | 1.19 (0.83 to 1.71) | 0.34 | 0.65 |
| LDL, mg/dL | | | | | |
| Age-adjusted | 0.87 (0.79 to 0.96) | 0.01 | 1.01 (0.88 to 1.15) | 0.94 | |
| Multivariable-adjusted model 1[‡] | 0.83 (0.74 to 0.93) | 0.001 | 0.92 (0.79 to 1.06) | 0.25 | 0.29 |
| Multivariable-adjusted model 2[§] | 0.82 (0.74 to 0.92) | 0.001 | 0.94 (0.80 to 1.10) | 0.41 | 0.19 |
| Triglycerides, mg/dL | | | | | |
| Age-adjusted model | 1.06 (0.99 to 1.15) | 0.12 | 1.01 (0.90 to 1.13) | 0.89 | |

Continued

**Table 4.** Continued

| Risk Factor | Paroxysmal AF (N=530) | *P* Value | Nonparoxysmal AF (N=277) | *P* Value | *P* Value* |
|---|---|---|---|---|---|
| Multivariable-adjusted model 1‡ | 1.02 (0.93 to 1.11) | 0.74 | 0.90 (0.79 to 1.03) | 0.14 | 0.15 |
| Multivariable-adjusted model 2§ | 1.02 (0.93 to 1.12) | 0.68 | 0.91 (0.79 to 1.05) | 0.20 | 0.18 |

AF indicates atrial fibrillation; HbA1c, hemoglobin A1c; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**P* values from likelihood ratio tests of the null hypothesis that a risk factor has an equal effect on development of paroxysmal vs nonparoxysmal AF based on trend.
†Hazard ratios are for categories; however, likelihood ratio tests are based on comparison of models that use continuous trend values.
‡Model 1: additionally adjusted for aspirin, vitamin E, beta-carotene, body mass index, hypertension, cholesterol, alcohol consumption, smoking and exercise, inflammation score, HBA1c, GFR, and lipids assessed at baseline (n=24 392 women due to missing data in the blood cohort).
§Model 2: censored for interim myocardial infarction, stroke, revascularization, and heart failure (n=24 392 women due to missing data in the blood cohort).

with paroxysmal AF in women without established CVD or AF at baseline. There was a significant graded-risk relationship between these risk factors and the development of persistent or chronic AF within 2 years after initial AF diagnosis, which was significantly stronger than that observed for paroxysmal AF. In the case of hemoglobin A1c, the directionality of the association differed as well. These differential associations did not appear to be mediated by the subsequent development of CVD, which was equally associated with the development of nonparoxysmal and paroxysmal AF in this healthy cohort.

Rates of progression to sustained forms of AF among patients with paroxysmal AF appear to be greatest within the first year,[8] with estimates ranging from 8.6% to 15%.[7,8,30] Using definitions in accordance with current guidelines, one third of woman in our study either present with or develop nonparoxysmal AF within 2 years of their incident AF diagnosis, suggesting that for many patients efforts aimed at preventing sustained AF may need to begin early.

Increasing age and established CVD have been consistently associated with the development of sustained forms of AF among patients with established AF.[7,8,15] A longitudinal cohort study[9] and case-control study[18] also found a linear relationship between a single measure of BMI and progression and sustained forms of AF among patients with a higher burden of CVD. Our study suggests both increasing age and adiposity are preferentially associated with the early development of nonparoxysmal AF even among relatively healthy populations without established AF, and these differential relationships are not mediated through the development of CVE. The strong association between updated measures of BMI and nonparoxysmal AF also raises the possibility that dynamic changes in BMI might be expected to influence risk for the development of sustained forms of AF.[31]

Experimental[32,33] and clinical studies[9,34,35] have provided several possible mechanisms for the underlying relationship between adiposity and AF susceptibility. Obesity has been associated with the development of diastolic dysfunction leading to an increased LA pressure and enlargement,[9,35] which in turn leads to neurohormonal activation, atrial stretch, and fibrosis, all of which can result in an atrial substrate facilitating the maintenance of AF.[9,34,35]Weight gain also results in myocardial lipid deposition and inflammatory infiltrates in atrial tissue in experimental models, which contribute to further electrostructural remodeling and increased AF burden.[32] The results of our case-only analysis are consistent with the hypothesis that LA enlargement and/or 1 of these processes that accompany LA enlargement mediate at least part of the association between obesity and nonparoxysmal AF.

The differential association between HbA1c and AF subtypes in our population of healthy women is a novel finding. Our data suggest that a strong positive relationship exists between HbA1c and the development of nonparoxysmal AF, whereas an inverse relationship exists for paroxysmal AF. These relationships persisted even among women without overt clinical or undiagnosed prediabetes. The positive association for nonparoxysmal AF and the inverse association for paroxysmal AF suggest that hyperglycemia, concomitant insulin resistance, or other associated unmeasured metabolic abnormalities may influence AF risk primarily through mechanisms involved in maintenance rather than initiation of AF. The observed differential association between HbA1c and AF subtypes might also provide an explanation for the apparently discrepant findings regarding the association among diabetes, glycemic control, and incident AF risk in previous studies.[16,22,23,36,37] Associations may vary depending on the degree of glycemic control among diabetic patients and may relate to the proportion of incident AF cases that are paroxysmal and nonparoxysmal in each cohort.

In contrast to earlier work among patients with established AF, we did not find a differential association between hypertension and AF types in our female subjects without established AF. This may be partly explained by the different study populations. The female health professionals in our study may have had been more aggressively treated for hypertension than the general population of patients with AF enrolled in the Euro Heart Survey.[7] Consistent with this possibility, a case-control study[17] performed among hypertensive patients found the average systolic blood pressure

achieved on treatment was more strongly associated with sustained rather than nonsustained forms of AF.

## Strengths and Limitations

This study has several strengths, including the prospective design, large number of participants with long follow-up, updated measures of traditional variables, and medical record confirmation of AF pattern according to current guidelines. There are also several limitations of the present study, which warrant discussion. First, the study included relatively healthy, middle-aged, white female health professionals and results may not be generalizable to other populations. Second, traditional risk factor assessments were based on self-report, which may lead to nondifferential misclassification and could have biased results toward the null. However, high correlations have been demonstrated between self-reported and directly measured variables such as weight ($r$=0.96) and BMI in comparable cohorts.[38,39] Third, AF detection and classification of AF pattern over time can be challenging without continuous ECG monitoring, which is impractical in free living cohort studies. Thus, some degree of misclassification of AF pattern resulting from underdetection likely exists due to asymptomatic episodes of AF in this cohort. However, the differential associations with AF subtypes persisted for age, BMI, and HbA1c in case-only analyses controlling for symptom status at the time of AF diagnosis. Fourth, because we limited our evaluation of AF pattern to the time period within 2 years of AF diagnosis, these data may not be able to be extrapolated to later time points. Fifth, standardized echocardiograms were not systematically collected in this cohort, and therefore, we were unable to perform a formal mediation analysis. Sixth, biomarker measurements were available only at baseline, and therefore, we could not evaluate whether dynamic changes in HbA1c or other biomarkers over time were differentially associated with the development of paroxysmal and nonparoxysmal AF. Last, due to the observational nature of the study, we cannot exclude the possibility that residual or unmeasured confounding may have accounted for part of the associations observed.

These prospective data suggest increasing age, adiposity, and higher HbA1c levels are preferentially associated with the early development of nonparoxysmal AF among a cohort of middle-aged women without previous cardiovascular disease. These data raise the hypothesis that early efforts aimed at weight reduction or glycemic control in the general population, before the development of AF, might have a significant impact on the proportion of individuals who develop sustained forms of AF. Given the considerable health care costs,[40] adverse outcomes,[7,12,13] and limited long-term success rates[14] associated with the treatment of persistent AF once established, the potential to reduce the proportion of individuals who develop sustained forms of AF through early preventive efforts is appealing and warrants further study.

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## Disclosures

Dr Ridker is listed as a co-inventor on patents held by Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. No conflicts of interest exist for the other authors.

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