Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence is markedly increasing over time.\textsuperscript{1-3} Substantial evidence exists that the risk of stroke, congestive heart failure (CHF), and cognitive dysfunction is higher in patients with AF, underscoring the importance of AF as a public health problem.\textsuperscript{4-7} In addition, several studies involving mainly older individuals with and without cardiovascular disease found an increased risk of death in patients with AF.\textsuperscript{5,8-11} For example, among participants with new-onset AF in the Framingham Heart Study, the relative risk for mortality was 1.5 (95% confidence interval [CI], 1.2-1.8) in men and 1.9 (95% CI, 1.5-2.2) in women.\textsuperscript{8} Most of this increased risk could be ascribed to individuals who died within 30 days after a first AF episode, suggesting that comorbidities with an elevated case-fatality rate explained a substantial part of the excess mortality in AF patients.\textsuperscript{8,11}

**Context** The risks associated with new-onset atrial fibrillation (AF) among middle-aged women and populations with a low comorbidity burden are poorly defined.

**Objectives** To examine the association between incident AF and mortality in initially healthy women and to evaluate the influence of associated cardiovascular comorbidities on risk.

**Design, Setting, and Participants** Between 1993 and March 16, 2010, 34,722 women participating in the Women’s Health Study underwent prospective follow-up. Participants were 95% white, older than 45 years (median, 53 [interquartile range (IQR), 49-59] years), and free of AF and cardiovascular disease at baseline. Cox proportional hazards models with time-varying covariates were used to determine the risk of events among women with incident AF. Secondary analyses were performed among women with paroxysmal AF.

**Main Outcome Measures** Primary outcomes included all-cause, cardiovascular, and noncardiovascular mortality. Secondary outcomes included stroke, congestive heart failure, and myocardial infarction.

**Results** During a median follow-up of 15.4 (IQR, 14.7-15.8) years, 1011 women developed AF. Incidence rates per 1000 person-years among women with and without AF were 10.8 (95% confidence interval [CI], 8.1-13.5) and 3.1 (95% CI, 2.9-3.2) for all-cause mortality, 4.3 (95% CI, 2.6-6.0) and 0.57 (95% CI, 0.5-0.6) for cardiovascular mortality, and 6.5 (95% CI, 4.4-8.6) and 2.5 (95% CI, 2.4-2.6) for noncardiovascular mortality, respectively. In multivariable models, hazard ratios (HRs) of new-onset AF for all-cause, cardiovascular, and noncardiovascular mortality were 2.14 (95% CI, 1.64-2.77), 4.18 (95% CI, 2.69-6.51), and 1.66 (95% CI, 1.19-2.30), respectively. Adjustment for nonfatal cardiovascular events potentially on the causal pathway to death attenuated these risks, but incident AF remained associated with all mortality components (all-cause: HR, 1.70 [95% CI, 1.30-2.22]; cardiovascular: HR, 2.57 [95% CI, 1.63-4.07]; and noncardiovascular: HR, 1.42 [95% CI, 1.02-1.98]). Among women with paroxysmal AF (n=656), the increase in mortality risk was limited to cardiovascular causes (HR, 2.94; 95% CI, 1.55-5.59).

**Conclusion** Among a group of healthy women, new-onset AF was independently associated with all-cause, cardiovascular, and noncardiovascular mortality, with some of the risk potentially explained by nonfatal cardiovascular events.
In comparison, small numbers of younger individuals with “lone” AF, not associated with comorbidities such as hypertension or structural heart disease, have been found to have longevity similar to age- and sex-matched controls during 25 years of follow-up. These data raise the possibility that AF itself may not inevitably be associated with an increased mortality risk and that a substantial part of this risk may be due to these coexisting conditions.

In this context, few data are available on the risk of adverse events associated with new-onset AF among large populations of healthy individuals with low overall cardiovascular risk factor burden, particularly among middle-aged women. Therefore, the primary aims of this study were to assess the risk of death and cardiovascular events among initially healthy middle-aged women with new-onset AF and to evaluate the influence of associated cardiovascular comorbidities on risk.

METHODS

Study Participants

Study participants were members of the Women’s Health Study (WHS) cohort, a completed randomized trial examining the effects of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been described previously. Beginning in 1993, 39,876 female health care professionals in the United States who were aged 45 years or older and free of cardiovascular disease and cancer were randomly assigned to receive 100 mg of aspirin every other day, 600 IU of vitamin E every other day, both agents, or placebo. After the end of the randomized treatment on March 31, 2004, all women were invited to participate in continued observational follow-up, which, for this analysis, was censored on March 16, 2010.

We excluded from this analysis 888 women (2.2%) with a history of AF at study entry and 60 women (0.2%) who had a cardiovascular event (stroke, myocardial infarction [MI], or CHF) prior to randomization. Women of the original cohort who were lost to follow-up (n = 1246 [3.1%]) or opted out of the observational follow-up (n = 2960 [7.4%]) were also excluded from this analysis because incident AF and subsequent cardiovascular events could not be reliably confirmed. The final study population consisted of 34,722 women (87.1%). Atrial fibrillation investigations were not prespecified as part of the original WHS but were prespecified in 2006 before AF confirmation began. Written informed consent was obtained from all participants. The study was approved by the institutional review board of Brigham and Women’s Hospital, Boston, Massachusetts.

Ascertainment of Baseline Characteristics and Incident AF

Questionnaires asking participants about cardiovascular risk factors, study outcomes, and other information were sent every 6 months during the first year and every 12 months thereafter. Covariates of interest that were assessed at study entry and at various points of follow-up included age, height, weight, diabetes, hypertension, blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, and race/ethnicity, self-reported as white, black, Hispanic American, Asian American, or other. Women also reported the occurrence of transient ischemic attacks, and these data were combined to calculate the CHADS2 score (1 point each for CHF, hypertension, age >75 years, and diabetes; 2 points for stroke/transient ischemic attack) as a measure of baseline risk of embolic complications.

Confirmation of AF has been described in detail previously. We systematically collected permission to review medical records of women who indicated an AF event on at least 1 yearly questionnaire. For all deceased participants who had reported AF during follow-up, family members were contacted to obtain consent and additional information. An end-point committee of cardiologists reviewed all medical records for reported events according to predefined criteria and collected available information on cardiac structure and function. We considered an incident AF event confirmed if there was electrocardiographic evidence of AF or if a medical report clearly indicated a personal history of AF. The date of onset of AF was set as the earliest date in the medical records when AF documentation was believed to have occurred. Only confirmed AF events were included in this study.

Atrial fibrillation patterns were defined as suggested by current guidelines and classified according to the most severe pattern within 2 years of AF onset. Paroxysmal AF was defined as self-terminating AF lasting fewer than 7 days that did not require cardioversion. Persistent AF was sustained beyond 7 days and/or required cardioversion. Permanent/chronic AF was defined as AF for which cardioversion had failed or not been attempted. During the validation process, we also assessed whether warfarin and/or antiarrhythmic drugs were prescribed around the time of AF diagnosis.

Ascertainment of Incident Cardiovascular Events and Death

Women reported the occurrence of cardiovascular end points via annual follow-up questionnaires, letters, or telephone calls. Information on MI and stroke was collected from the beginning of the study. For CHF, women were first asked to report prior physician diagnoses on the 48-month questionnaire. Deaths were usually reported by family members or postal authorities or ascertained through the National Death Index. After obtaining written consent, medical records were acquired for all cardiovascular end points and deaths.

All events were adjudicated according to predefined criteria in a blinded fashion by an end-point committee of physicians. The occurrence of MI was confirmed if symptoms met World Health Organization criteria and if the
event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. Nonfatal stroke was confirmed if the participant had a new focal neurological deficit of sudden or rapid onset that persisted for more than 24 hours and was attributed to a cerebrovascular event. Congestive heart failure was confirmed if either the Framingham Heart Study\(^1\) or Cardiovascular Health Study\(^2\) criteria for CHF were met, and both definite and probable cases were included in the analysis. Deaths were confirmed to be due to cardiovascular causes on the basis of autopsy reports, death certificates, medical records, and information obtained from family members.

**Statistical Analysis**

Baseline characteristics were compared using Wilcoxon rank sum tests for continuous variables and \(\chi^2\) tests for categorical variables. To compare the risks of death and cardiovascular events among women with and without incident AF, we calculated hazard ratios (HRs) and 95% CIs using Cox proportional hazards models. Person-years of follow-up were calculated from the date of return of the run-in questionnaire to the occurrence of first end point, death, loss to follow-up, or March 16, 2010, whichever came first.

For the primary mortality analyses, new-onset AF and other model covariates were entered in the Cox models as time-dependent covariates whenever appropriate. Age-adjusted models were further adjusted for height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment, and race/ethnicity. We estimated

### Table 1. Baseline Characteristics at Study Entry\(^a\)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Incident AF (N = 33 711)</th>
<th>Incident AF (N = 1011)</th>
<th>(P) Value</th>
<th>Incident Paroxysmal AF (N = 656)</th>
<th>Incident Other AF (N = 355)</th>
<th>(P) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>53 (49-59)</td>
<td>59 (53-65)</td>
<td>&lt;.001</td>
<td>58 (52-64)</td>
<td>61 (54-66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, median (IQR)(^d)</td>
<td>24.9 (22.5-28.3)</td>
<td>26.2 (23.2-30.5)</td>
<td>&lt;.001</td>
<td>25.8 (23.1-29.8)</td>
<td>26.6 (23.5-31.9)</td>
<td>.007</td>
</tr>
</tbody>
</table>

**Hypertension**

- Yes | 8723 (25.9) | 443 (43.8) | <.001 | 271 (41.3) | 172 (48.5) | .03 |
- No | 24 988 (74.1) | 668 (56.2) |            | 385 (58.7) | 183 (51.6) | .92 |

**Diabetes**

- Yes | 886 (2.6) | 56 (5.5) | <.001 | 36 (5.5) | 20 (5.6) | .92 |
- No | 32 825 (97.4) | 955 (94.5) |            | 620 (94.5) | 335 (94.4) | .09 |

**Hypercholesterolemia**

- Yes | 10 122 (30.0) | 355 (35.1) | <.001 | 218 (33.2) | 137 (38.6) | .09 |
- No | 23 589 (70.0) | 656 (64.9) |            | 438 (66.8) | 218 (61.4) | .18 |

**Smoking**

- Current | 4213 (12.5) | 99 (9.1) | <.001 | 53 (8.1) | 39 (11.0) | .28 |
- Past/never | 29 474 (87.5) | 937 (90.9) |            | 601 (91.9) | 316 (89.0) | .77 |

**Alcohol consumption**

- Rarely/never | 14 899 (44.2) | 472 (46.7) | .27 | 319 (48.6) | 153 (43.1) | .01 |
- 1-3 Drinks/mo | 4458 (13.2) | 129 (12.8) |            | 84 (12.8) | 45 (12.7) | .09 |
- 1-6 Drinks/wk | 10 876 (32.3) | 300 (29.7) |            | 182 (27.7) | 118 (33.2) | .04 |
- ≥1 Drinks/d | 3478 (10.3) | 110 (10.9) |            | 71 (10.8) | 39 (11.0) | .77 |

**Highest education level**

- < Bachelor’s degree | 18 429 (55.6) | 610 (61.4) | .002 | 397 (61.6) | 213 (61.0) | .01 |
- Bachelor’s degree | 7882 (23.8) | 207 (20.8) |            | 137 (21.2) | 70 (20.1) | .01 |
- Master’s degree or doctorate | 6827 (20.6) | 177 (17.8) |            | 111 (17.2) | 66 (18.9) | .01 |

**Race/ethnicity**

- White | 31 761 (95.0) | 984 (98.0) | <.001 | 636 (97.9) | 348 (98.3) | .01 |
- Other | 1659 (5.0) | 20 (2.0) |            | 14 (2.2) | 6 (1.7) | .01 |

**CHADS\(^2\) score\(^c\)**

<table>
<thead>
<tr>
<th>Score</th>
<th>No Incident AF (N = 34 275)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>229 (22.7)</td>
<td>165 (25.2)</td>
</tr>
<tr>
<td>1</td>
<td>477 (47.2)</td>
<td>313 (47.7)</td>
</tr>
<tr>
<td>2</td>
<td>237 (23.4)</td>
<td>140 (21.3)</td>
</tr>
<tr>
<td>3</td>
<td>42 (4.2)</td>
<td>20 (3.1)</td>
</tr>
<tr>
<td>4</td>
<td>25 (2.5)</td>
<td>17 (2.6)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; IQR, interquartile range.

\(^a\)Data are expressed as number (percentage) of participants unless otherwise indicated. Numbers across categories may not sum to the given totals because of missing data.

\(^b\)P values comparing women with and without incident AF are based on Wilcoxon rank sum tests for continuous variables and \(\chi^2\) tests for categorical variables.

\(^c\)P values comparing women with paroxysmal AF with those with other AF patterns are based on Wilcoxon rank sum tests for continuous variables and \(\chi^2\) tests for categorical variables.

\(^d\)N=34 275. Body mass index is calculated as weight in kilograms divided by height in meters squared.

\(^e\)One point each for congestive heart failure, hypertension, age greater than 75 years, and diabetes; 2 points for stroke/transient ischemic attack.
the population-attributable risk proportion for new-onset AF, defined as \(pd \times (HR - 1)/HR\), where \(pd\) is the prevalence of AF among decedents and HR is the adjusted HR.\(^{20}\) To evaluate the degree of confounding and mediation by cardiovascular events, we performed a third set of multivariable analyses additionally adjusting for the occurrence of nonfatal MI, stroke, and CHF. We also repeated the main analyses after exclusion of women who died within 30 days of AF onset, to further minimize the influence of end-stage disease.\(^{8,11}\)

To explore whether mortality risk differs depending on the pattern of AF, we constructed another prespecified series of Cox models in which our exposure of interest was limited to paroxysmal AF.\(^{17}\) These analyses were also performed to further limit confounding by associated comorbidities.\(^{11}\) In these models, women who presented with persistent or permanent AF were censored at the time of AF diagnosis and not considered for events thereafter. We also assessed the risk of death among women with lone AF, defined as AF onset before age 60 years without evidence of hypertension or CHF at the time of AF diagnosis.\(^{17}\) Finally, we examined the effect of AF on other cardiovascular events using time to first stroke, CHF, MI, or a composite of these end points as the outcome of interest.

We used a complete-case analysis in multivariable models without imputation for missing data. No model excluded more than 882 participants (2.5%) because of missing data. The proportional hazards assumption was examined for all models using AF by logarithm of follow-up time interaction terms. We found a violation of this assumption for the composite cardiovascular end point, CHF, and MI in overall AF models and for the composite cardiovascular end point and MI in paroxysmal AF models. For these end points, we performed separate analyses on early events (women with an event more than 5 years after AF diagnosis were censored at the time of AF onset) and late events (women with an event within 5 years of AF diagnosis were censored at the time of AF onset). Statistical analyses were carried out using SAS software, version 9 (SAS Institute Inc, Cary, North Carolina). A 2-tailed \(P < .05\) was considered to indicate statistical significance.

### RESULTS

#### Baseline Characteristics

During a median follow-up of 15.4 interquartile range [IQR], 14.7-15.8 years, 1011 women (2.9%) developed new-onset AF, of whom 656 (64.9%) were classified as having paroxysmal AF.

### Table 2. Cardiac Structure and Function in Women With New-Onset AF at the Time of AF Diagnosis

<table>
<thead>
<tr>
<th>Characteristics(^a)</th>
<th>All</th>
<th>Minimal/Mild</th>
<th>Moderate to Severe</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal left ventricular function</td>
<td>61/871 (7)</td>
<td>36/871 (4)</td>
<td>25/871 (3)</td>
<td>810/871 (93)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>235/728 (32)</td>
<td>184/728 (25)(^b)</td>
<td>37/728 (5)(^b)</td>
<td>493/728 (68)</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>310/748 (41)</td>
<td>204/748 (27)(^c)</td>
<td>66/748 (13)(^c)</td>
<td>438/748 (59)</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>5/809 (1)</td>
<td>804/809 (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>117/813 (14)</td>
<td>696/813 (86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other valve disease</td>
<td>106/807 (13)</td>
<td>701/807 (87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Abnormal left ventricular function was defined as an ejection fraction of less than 50% or a qualitative description of reduced left ventricular function. Left ventricular hypertrophy was defined as a maximal wall thickness of at least 12 mm or qualitative description of left ventricular hypertrophy. Left atrial enlargement was defined as a left atrial diameter larger than 40 mm or qualitative description of left atrial enlargement. Significant valve disease was defined as at least moderate (\(\geq 2\)) valve disease. 
\(^b\) In 14 women with left ventricular hypertrophy, the severity of hypertrophy was not available. 
\(^c\) In 10 women with left atrial enlargement, the severity of enlargement was not available.

### Table 3. Risk of Death Among Women With New-Onset AF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incident AF (n = 1011)</th>
<th>Non Incident AF (n = 33,711)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (n = 1602)</td>
<td>1539</td>
<td>63</td>
</tr>
<tr>
<td>Incidence rate (95% CI)(^a)</td>
<td>3.1 (2.9-3.2)</td>
<td>10.8 (8.1-13.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>Age-adjusted model (n = 34,722)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>2.14 (1.64-2.77)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>1.70 (1.30-2.22)</td>
</tr>
<tr>
<td>Cardiovascular mortality (n = 309)</td>
<td>284</td>
<td>25</td>
</tr>
<tr>
<td>Incidence rate (95% CI)(^a)</td>
<td>0.57 (0.5-0.6)</td>
<td>4.3 (2.6-6.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>Age-adjusted model (n = 34,722)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>4.18 (2.69-6.51)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>2.57 (1.63-4.07)</td>
</tr>
<tr>
<td>Noncardiovascular mortality (n = 1293)</td>
<td>155</td>
<td>38</td>
</tr>
<tr>
<td>Incidence rate (95% CI)(^a)</td>
<td>2.5 (2.4-2.6)</td>
<td>6.5 (4.4-8.6)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>Age-adjusted model (n = 34,722)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>1.66 (1.19-2.30)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33,840)</td>
<td>1 [Reference]</td>
<td>1.42 (1.02-1.98)</td>
</tr>
</tbody>
</table>

\(^a\) Per 1000 person-years of follow-up.
\(^b\) Additionally adjusted for height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment, and race/ethnicity. These multivariable models were based on 1526 deaths (290 of them cardiovascular) among 33,840 women because of missing data.

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AF. Baseline characteristics of women with and without incident AF are shown in Table 1. Although 72.4% of women with new-onset AF had prevalent hypertension, they were at a predicted low risk of thromboembolic events, with 706 (69.8%) having a CHADS2 score of 1 or lower. Available information on cardiac structure and function suggested a low prevalence of significant structural heart disease among women with new-onset AF (Table 2). At about the time of AF diagnosis, warfarin was prescribed in 53% of women. Other prescribed AF medications included β-blockers in 50%, calcium channel blockers in 23%, digoxin in 22%, flecainide or propafenone in 11%, amiodarone in 11%, sotalol in 8%, and other drugs in 2%.

Compared with women who developed persistent or chronic AF, women with paroxysmal AF were significantly younger and had a lower body mass index and a lower prevalence of hypertension (Table 1). Women with paroxysmal AF also had a significantly lower CHADS2 score (72.9% had a score ≤1 vs 64.2% among those with persistent or chronic AF; \( P = .004 \)). Among women with paroxysmal AF, 45% were prescribed warfarin at about the time of AF diagnosis, compared with 68% with nonparoxysmal AF (\( P < .001 \)).

**AF and Mortality**

Death rates stratified by the presence or absence of incident AF are shown in Table 3. Compared with women without AF, those diagnosed as having interm AF had higher crude all-cause, cardiovascular, and noncardiovascular mortality rates during follow-up (Table 3). Of the 63 deaths in women with an incident AF diagnosis, 4 (6.3%) occurred within 30 days of AF development, all related to cardiovascular causes.

The age-adjusted relative risk of all-cause, cardiovascular, and noncardiovascular mortality was significantly higher among women with new-onset AF (Table 3). Adjustment for established cardiovascular risk factors (Table 3; multivariable model 1) had a small effect on these risk estimates, such that AF remained a significant predictor of all mortality components. We estimated that after taking into account these risk factors, approximately 2.1% of all deaths could be attributed to incident AF. Additional adjustment for nonfatal cardiovascular events attenuated these risk estimates, but incident AF remained a significant risk factor for all mortality end points after adjustment for nonfatal events. Excluding the 4 women who died within 30 days after new-onset AF provided similar results (HRs for multivariable model 1, 1.98 [95% CI, 1.51-2.59] for all-cause, 3.47 [95% CI, 2.15-5.60] for cardiovascular, and 1.64 [95% CI, 1.18-2.28] for noncardiovascular deaths).

Relationships between incident paroxysmal AF and subsequent mortality are presented in Table 4. Women with paroxysmal AF did not have a significantly increased risk of all-cause death (HR, 1.44; 95% CI, 0.98-2.11; \( P = .06 \)) or death from noncardiovascular causes (HR, 1.11; 95% CI, 0.69-1.81; \( P = .66 \)) but remained at an increased risk of cardiovascular death (HR, 2.94; 95% CI, 1.55-5.59; \( P = .001 \)) after adjustment for cardiovascular risk factors. After additional adjustment for the development of nonfatal cardiovascular events, none of the relationships between paroxysmal AF and mortality remained statistically significant (Table 4).

### Table 4. Risk of Death Among Women With New-Onset Paroxysmal AF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Paroxysmal AF (n = 34 066)</th>
<th>Incident Paroxysmal AF (n = 656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (n = 1567)</td>
<td>1539</td>
<td>28</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>3.0 (2.9-3.2)</td>
<td>7.2 (4.5-9.8)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1 [Reference]</td>
<td>1.52 (1.04-2.22)</td>
</tr>
<tr>
<td>Age-adjusted model (n = 34 722)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>1.44 (0.98-2.11)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>1.18 (0.80-1.73)</td>
</tr>
<tr>
<td>Cardiovascular mortality (n = 295)</td>
<td>284</td>
<td>11</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.56 (0.5-0.6)</td>
<td>2.8 (1.2-4.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1 [Reference]</td>
<td>3.27 (1.78-6.04)</td>
</tr>
<tr>
<td>Age-adjusted model (n = 34 722)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>2.94 (1.55-5.59)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>1.86 (0.97-3.59)</td>
</tr>
<tr>
<td>Noncardiovascular mortality (n = 1272)</td>
<td>1255</td>
<td>17</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>2.5 (2.3-2.6)</td>
<td>4.4 (2.3-6.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1 [Reference]</td>
<td>1.14 (0.70-1.84)</td>
</tr>
<tr>
<td>Age-adjusted model (n = 34 722)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model 1 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>1.11 (0.69-1.81)</td>
</tr>
<tr>
<td>Multivariable-adjusted model 2 (n = 33 840)</td>
<td>1 [Reference]</td>
<td>0.97 (0.60-1.58)</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CI, confidence interval.

*Women with a confirmed first event of persistent or chronic AF were censored at the time of AF diagnosis.

*Per 1000 person-years of follow-up.

*Additionally adjusted for height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment, and race/ethnicity. These multivariable models were based on 1492 deaths (277 of them cardiovascular) among 33 840 women because of missing data.

*Additionally adjusted for intercurrent myocardial infarction, stroke, and congestive heart failure.

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Lone AF occurred in 74 women (7.3%). The median age at AF diagnosis in these women was 56 (IQR, 54-58) years, and median follow-up after the first AF episode was 7.4 (IQR, 3.9-8.8) years, during which no deaths occurred.

**AF and Risk of Cardiovascular Events**

In multivariable models, both new-onset AF and new-onset paroxysmal AF were strong risk factors for the composite cardiovascular end point of stroke, CHF, or MI and for each of the individual components (TABLE 5). In agreement with the violation of the proportional hazards assumption, we found a higher relative hazard during early follow-up and attenuation over time for the composite end point, CHF, and MI in women with new-onset AF, as shown in Table 5. The risk of MI was not elevated during late follow-up or when events occurring within 30 days of the initial AF event were excluded (HR, 1.03; 95% CI, 0.51-2.08). Similar results were obtained among women with paroxysmal AF (Table 5). Among the 74 women with lone AF, there were no strokes or MIs, but 2 CHF events occurred. The low number of events precluded further analyses in this subgroup.

**COMMENT**

In this large, prospective cohort of initially healthy women, we found that even in a population with a low burden of cardiovascular disease at baseline, participants with new-onset AF had an increased risk of death during subsequent follow-up. Adjustment for nonfatal cardiovascular events potentially on the causal pathway to death attenuated these relationships, but new-onset AF remained significantly associated with all mortality components.

Most prior studies found relative risk estimates for fatal events after new-onset AF similar to the current study.8,11,22 All of these studies found that the risk was substantially higher shortly after AF diagnosis, raising the possibility that associated comorbidities present at the time of AF diagnosis may be responsible for at least a portion of the excess risk of death in these individuals. Our study suggests that the risk of death is increased even in AF populations with a low burden of comorbidities and a low short-term mortality rate. However, the absolute excess in mortality was fairly low, with only 2.1% of the deaths in this population attributable to AF.

This study adds to the prior literature by showing that adjustment for nonfatal cardiovascular events substantially attenuates the risk of death associated with AF, suggesting that this increased risk is partly mediated through the occurrence of nonfatal cardiovascular disease, particularly the development of CHF and stroke. As in prior studies, individuals with new-onset AF had an increased risk of these events.6,7,23 The observed association with MI is relatively novel; however, the finding was driven primarily by events occurring within 30 days of the AF diagnosis, suggesting that the relationship may be primarily due to concomitant disease processes. As both CHF and stroke are at least partly preventable through blood pressure control and anticoagulation,24-27 our data reinforce the importance of strict risk factor control in AF patients. However, not all of the mortality risk associated with AF could be accounted for by the development of cardiovascular disease, which underscores the need for more effective primary AF prevention strategies to lower mortality from this highly prevalent disease.28-30

In secondary analyses, we explored the possibility that mortality risks may vary according to AF subtype. We hypothesized that con-

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### Table 5. Risk of Cardiovascular Events Among Women With New-Onset AF (n = 33 840)

<table>
<thead>
<tr>
<th>End Point</th>
<th>All AF Events</th>
<th>Paroxysmal AF Events Onlya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Incident AF</td>
<td>Incident AF</td>
</tr>
<tr>
<td>Composite end pointb</td>
<td>1186</td>
<td>135</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire follow-up</td>
<td>6.94</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Early follow-up onlyd</td>
<td>5.08</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Late follow-up onlya</td>
<td>2.46</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>560</td>
<td>47</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire follow-up</td>
<td>4.17</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>252</td>
<td>83</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire follow-up</td>
<td>14.67</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Early follow-up onlyd</td>
<td>13.52</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Late follow-up onlya</td>
<td>3.97</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>472</td>
<td>24</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire follow-up</td>
<td>3.14</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Early follow-up onlyd</td>
<td>3.87</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Late follow-up onlya</td>
<td>1.37</td>
<td>1 (Reference)</td>
</tr>
</tbody>
</table>

aAbbreviations: AF, atrial fibrillation; CI, confidence interval.

bTime to first stroke, congestive heart failure, or myocardial infarction.

cData are adjusted for age, height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment, and race/ethnicity.

dWomen with a cardiovascular event occurring more than 5 years after AF diagnosis were censored at the time of AF onset.

eWomen with a cardiovascular event occurring within 5 years of AF diagnosis were censored at the time of AF onset.

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found by noncardiovascular comorbidities is likely lower among women with paroxysmal AF, and these women had a lower burden of cardiovascular risk factors in our population. Total and noncardiovascular mortality were not significantly increased in women with paroxysmal AF. However, an elevation in cardiovascular mortality primarily due to cardiovascular events persisted after multivariable adjustment. Because of the lower number of events among these women, CIs are wide and our power is limited, precluding definitive conclusions. Nevertheless, these data raise the possibility that individuals with paroxysmal AF may have a lower mortality risk than those with other AF patterns. Future studies with more end points are needed to confirm this important possibility.

Finally, none of the 74 women with lone AF in our study died or had a stroke during a median follow-up of more than 7 years, and only 2 developed CHF. Although this represents the largest prospective sample of women with lone AF reported so far, the number is still too small and follow-up is not long enough to draw definite conclusions about long-term outcomes. Nevertheless, these data are consistent with prior observations that lone AF may be a benign disease, at least in the short term. In the study with the longest follow-up to date, the risk of death, stroke, or CHF among 76 predominantly male patients with lone AF in Olmsted County, Minnesota, was similar to that in the general population, with the exception of a late increase in stroke risk after 30 years of follow-up. However, by the time of a late increase in stroke risk after 30 years of follow-up, all lone AF patients had developed at least 1 established stroke risk factor. More data are needed on the long-term prognosis associated with lone AF.

Important strengths of this study include its prospective design, large sample size, and confirmation of all incident events. Our study also has several potential limitations. First, the study included initially healthy, middle-aged female health care professionals, and generalizability of these results to other populations may be limited. Second, screening electrocardiograms are not systematically available in this cohort, and some asymptomatic cases of AF may have gone undetected. However, in this cohort of health care professionals, who are medically sophisticated and have access to health care, underdetection is less likely. In support of this contention, we found a similar number of asymptomatic AF cases in this cohort (n=103 [10.2%]) compared with AF cases detected by screening electrocardiograms in other cohorts. Third, defining the initial AF episode and AF patterns over time accurately may be challenging, especially when 10% of women are asymptomatic at the time of diagnosis. Fourth, because participants must survive to at least the next questionnaire to indicate an AF episode, we may have missed some AF events that occurred shortly before a woman’s death. Misclassification of these events may have somewhat underestimated the short-term mortality risk associated with new-onset AF. Fifth, the number of events among women with new-onset AF was low in some secondary analyses, such as those examining AF subtypes, leading to wide CIs. We did not perform formal power calculations because multiple assumptions are needed in time-updated models and because the lower bounds of the CIs for our primary analyses clearly exclude unity, providing good certainty for the significance of these results. Given the small number of events and wide CIs for some secondary analyses, these results need independent confirmation and should be interpreted with caution. Sixth, P values in secondary analyses were not adjusted for multiple testing. Seventh, information on echocardiography, medical therapy and adverse effects was not systematically collected during follow-up in the WHS. We were therefore unable to evaluate the effects of these factors on event development.

CONCLUSION

In this large cohort of initially healthy women at low risk of cardiovascular disease, women with new-onset AF had an increased risk of death and incident cardiovascular events. Because a significant proportion of the excess mortality risk appears attributable to the occurrence of nonfatal cardiovascular events prior to death, there is a potential opportunity to improve the outcome of individuals with new-onset AF through both prevention and optimal management of these associated comorbidities.

Author Contributions: Dr Conen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study Concept and Design: Conen, Albert.
Acquisition of data: Conen, Chae, Tedrow, Everett, Buring, Albert.
Analysis and interpretation of data: Conen, Chae, Glynn, Tedrow, Everett, Buring, Albert.
Drafting of the manuscript: Conen, Albert.

Critical revision of the manuscript for important intellectual content: Conen, Chae, Glynn, Tedrow, Everett, Buring, Albert.

Statistical analysis: Conen, Glynn.
Obtained funding: Buring, Albert.
Administrative, technical, or material support: Everett.
Study supervision: Albert.

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REFERENCES

RISK OF DEATH IN WOMEN WITH NEW-ONSET ATRIAL FIBRILLATION