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Risk of Death and Cardiovascular Events in Initially Healthy Women with New-Onset Atrial Fibrillation

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Abstract

Context—The risks associated with new-onset AF among middle-aged women and populations with a low co-morbidity burden are poorly defined.

Objective—To examine the association between incident AF and mortality in initially healthy women, and to evaluate the influence of associated cardiovascular co-morbidities on risk.

Design, Setting and Participants—Between 1993 and March 16, 2010, 34722 women participating in the Women's Health Study underwent prospective follow-up. Participants (95% white) were >45 years (median (interquartile range) 53 (49–59) years) and free of AF and cardiovascular disease at baseline. Cox proportional-hazards models with time-varying covariates were utilized to determine the risk of events among women with incident AF. Secondary analyses were performed among women with paroxysmal AF.

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Authors' contributions David 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
Administrative support: Everett
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Main outcome measure—Primary outcomes included total, cardiovascular, and non-cardiovascular mortality. Secondary outcomes included stroke, congestive heart failure and myocardial infarction.

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

Conclusion—Among a group of healthy women, new-onset AF was independently associated with cardiovascular, non-cardiovascular and all-cause mortality, with some of the risk potentially explained by non-fatal cardiovascular events.

Keywords

Atrial fibrillation; lone atrial fibrillation; women; cardiovascular disease; death; epidemiology; stroke

Introduction

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

In comparison, small numbers of younger individuals with “lone” AF, not associated with co-morbidities such as hypertension or structural heart disease, have been found to have similar longevity as age- and sex-matched controls over 25 years of follow-up[12]. 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 aim of this study was 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 co-morbidities on risk.

Methods

Study participants

Study subjects were participants of the Women's Health Study (WHS), 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[13, 14]. Beginning in 1993, 39876 female health professionals in the United States who were ≥45 years old and free of cardiovascular disease and cancer were randomly assigned to receive 100 mg aspirin every other day, 600 IU 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 34722 women (87.1%). AF investigations were not pre-specified as part of the original WHS, but were pre-specified 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.

Ascertainment of baseline characteristics and incident AF

Questionnaires asking participants about cardiovascular risk factors, study outcomes and other information were sent every six 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 $CHADS_2$ score (1 point each for CHF, Hypertension, Age>75 years, Diabetes; 2 points for Stroke/transient ischemic attack) as a measure of baseline risk of embolic complications[15].

Confirmation of AF has been described in detail previously[16]. We systematically collected permission to review medical records of women who indicated an AF event on at least one yearly questionnaire. For all deceased participants who reported AF during follow-up, family members were contacted to obtain consent and additional information. An endpoint 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.

AF patterns were defined as suggested by current guidelines[17] and classified according to the most severe pattern within two years of AF onset. Paroxysmal AF was defined as self-terminating AF lasting <7 days that did not require cardioversion. Persistent AF was sustained beyond seven days and/or required cardioversion. Permanent/chronic AF was defined as AF where cardioversion has failed or not been attempted[17]. 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 endpoints 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 endpoint committee of physicians[14]. 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. Non-fatal stroke was confirmed if the participant had a new focal-neurological deficit of sudden or rapid onset that persisted for >24 hours and was attributed to a cerebrovascular event. CHF was confirmed if either the Framingham Heart Study[18] and Cardiovascular Health Study[19] criteria for CHF were met, and both definite and probable cases were included in the analysis. Deaths were confirmed to be from 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-square tests for categorical variables. To compare the risk of death and cardiovascular events among women with and without incident AF we calculated 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 endpoint, 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 (kg/m^2), diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment and race/ethnicity. We estimated the population-attributable risk proportion for new-onset AF defined as *pd**(HR-1/HR) where *pd* is the prevalence of AF among decedents and HR is the adjusted HR[20]. In order to evaluate the degree of confounding and mediation by cardiovascular events, we performed a third set of multivariable models additionally adjusting for the occurrence of non-fatal 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 pre-specified series of Cox models where our exposure of interest was limited to paroxysmal AF[17]. These analyses were also performed to further limit confounding by associated co-morbidities[21]. 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 the age of 60 years and without evidence of hypertension or CHF at the time of AF diagnosis[17]. Finally, we examined the impact of AF on other cardiovascular events using time to first stroke, CHF, MI or a composite of these endpoints as the outcome of interest.

We used a complete-case analysis in multivariable models without imputation for missing data. The sample size analyzed in each multivariable model is presented in Tables 2–4, and no model excluded more than 882 participants (2.5%) due to 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 endpoint, CHF and MI in overall AF models, and for the composite cardiovascular endpoint and MI in paroxysmal AF models. For these endpoints, we performed separate analyses on early events (women with an event after 5 years of 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 analyzes were carried out using SAS version 9 (SAS Institute Inc, Cary, NC). A two-tailed p value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

During a median (interquartile range) follow-up of 15.4 (14.7–15.8) years, 1011 women (2.9%) developed new-onset AF, of whom 656 (64.9%) were classified as having paroxysmal 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 thrombo-embolic events, with 706 (69.8%) having a $CHADS_2$ score ≤1. Available echocardiographic information suggested a low prevalence of significant structural heart disease among women with new-onset AF (eTable). Around the time of AF diagnosis, warfarin was prescribed in 53% of women. Other prescribed AF medications included beta-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%.

As compared with women who developed persistent or chronic AF, women with paroxysmal AF were significantly younger, had a lower body mass index and a lower prevalence of hypertension (Table 1). These women also had a significantly lower $CHADS_2$ score ($CHADS_2$ ≤1; 72.9% versus 64.2%; p=0.004). Among women with paroxysmal AF, 45% were prescribed warfarin around the time of AF diagnosis, as compared with 68% with non-paroxysmal AF (p<0.001).

AF and mortality

Death rates stratified by the presence or absence of incident AF are shown in Table 2. As compared to women without AF, those diagnosed with interim AF had a higher crude total, cardiovascular and non-cardiovascular mortality rate during follow-up (Table 2). Of the 63 deaths in women with an incident AF diagnosis, four (6.3%) occurred within 30 days of AF development, all of these being cardiovascular.

The age-adjusted relative risk of all-cause, cardiovascular and non-cardiovascular mortality was significantly higher among women with new-onset AF (Table 2). Adjustment for established cardiovascular risk factors (Table 2, 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 2.2% of all deaths could be attributed to incident AF. Additional adjustment for non-fatal cardiovascular events attenuated these risk estimates, but incident AF remained a significant risk factor for all mortality endpoints after adjustment for non-fatal events. Excluding the four women who died within 30 days after new-onset AF provided similar results (HR (95%

CI) for multivariable model 1 1.98 (1.51–2.59), 3.47 (2.15–5.60) and 1.64 (1.18–2.28), respectively).

Relationships between incident paroxysmal AF and subsequent mortality are presented in Table 3. Women with paroxysmal AF did not have a significantly increased risk of all-cause death (HR (95% CI) 1.44 (0.98–2.11), p=0.06) and death from non-cardiovascular causes (HR (95% CI) 1.11 (0.69–1.81), p=0.66), but remained at an increased risk of cardiovascular death (2.94 (1.55–5.59), p=0.001) after adjustment for cardiovascular risk factors. After additional adjustment for the development of non-fatal cardiovascular events, none of relationships between paroxysmal AF and mortality remained statistically significant (Table 3).

Lone AF occurred in 74 women (7.3%). The median age (interquartile range) at AF diagnosis of these women was 56 (54–58) years, and median follow-up after the first AF episode was 7.4 (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 endpoint of stroke, CHF or MI and for each of the individual components (Table 4). 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 endpoint, CHF and MI in women with new-onset AF, as shown in Table 4. 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 (95% CI) 1.03 (0.51–2.08)). Similar results were obtained among women with paroxysmal AF (Table 4). Among the 74 women with lone AF, there were no strokes or MIs, but two CHF events. Low numbers 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 non-fatal 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 co-morbidities present at the time of 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 co-morbidities and a low short-term mortality rate. However, the absolute excess in mortality was fairly low, with only 2.2% of the deaths in this population attributable to AF.

This study further adds to the prior literature by showing that adjustment for non-fatal cardiovascular events substantially attenuates the risk of death associated with AF, suggesting that this increased risk is partly mediated through the occurrence of non-fatal 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 confounding by non-cardiovascular co-morbidities is likely lower among women with paroxysmal AF[21, 31, 32], and these women had a lower burden of cardiovascular risk factors in our population. Total and non-cardiovascular 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. Due to the lower number of events among these women, confidence intervals 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 endpoints 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 >7 years, and only two 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[5, 12]. 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[12] in Olmsted County, Minnesota was similar to the general population, with the exception of a late increase in stroke risk after 30 years of follow-up[12]. However, by the time of a stroke, all lone AF patients had developed at least one established stroke risk factor. More data are needed on the prognosis associated with lone AF.

Strengths and limitations

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 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 professionals, who are medically sophisticated and have access to health care, under-detection is less likely. In support of this contention, we found a similar number of asymptomatic AF cases in this cohort (n=103, 10.2%) as compared to AF cases detected by screening electrocardiograms in other cohorts[33, 34]. 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, as 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 women'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, as 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. Finally, information on echocardiography, medical therapy and side effects was not systematically collected during follow-up in the WHS. We were therefore unable to evaluate the effect 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 non-fatal 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.

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Table 1

Baseline characteristics at study entry

Characteristic (N=34722)	No incident AF (n=33711)	Incident AF (n=1011)	P value*	Incident paroxysmal AF (n=656)	Incident other AF (n=355)	P value†
Age, years	53 (49–59)	59 (53–65)	<0.001	58 (52–64)	61 (54–66)	<0.001
Body mass index, kg/m^2‡	24.9 (22.5–28.3)	26.2 (23.2–30.5)	<0.001	25.8 (23.1–29.8)	26.6 (23.5–31.9)	0.007
Hypertension, %			<0.001			0.03
Yes	8723 (25.9)	443 (43.8)		271 (41.3)	172 (48.5)	
No	24988 (74.1)	568 (56.2)		385 (58.7)	183 (51.6)	
Diabetes, %			<0.001			0.92
Yes	886 (2.6)	56 (5.5)		36 (5.5)	20 (5.6)	
No	32825 (97.4)	955 (94.5)		620 (94.5)	335 (94.4)	
Hypercholesterolemia, %			0.001			0.09
Yes	10122 (30.0)	355 (35.1)		218 (33.2)	137 (38.6)	
No	23589 (70.0)	656 (64.9)		438 (66.8)	218 (61.4)	
Smoking, %			<0.001			0.18
Current	4213 (12.5)	92 (9.1)		53 (8.1)	39 (11.0)	
Past/never	29474 (87.5)	917 (90.9)		601 (91.9)	316 (89.0)	
Alcohol consumption, %			0.27			0.28
Rarely/never	14889 (44.2)	472 (46.7)		319 (48.6)	153 (43.1)	
1–3 drinks per month	4458 (13.2)	129 (12.8)		84 (12.8)	45 (12.7)	
1–6 drinks per week	10876 (32.3)	300 (29.7)		182 (27.7)	118 (33.2)	
≥1 drink per day	3478 (10.3)	110 (10.9)		71 (10.8)	39 (11.0)	
Highest education level, %			0.002			0.77
< bachelor's degree	18429 (55.6)	610 (61.4)		397 (61.6)	213 (61.0)	
Bachelor's degree	7882 (23.8)	207 (20.8)		137 (21.2)	70 (20.1)	
Master's degree or doctorate	6827 (20.6)	177 (17.8)		111 (17.2)	66 (18.9)	
Race/ethnicity, %			<0.001			0.62
White	31761 (95.0)	984 (98.0)		636 (97.9)	348 (98.3)	
Other	1659 (5.0)	20 (2.0)		14 (2.2)	6 (1.7)	
$CHADS_2$ score§			-			0.01
0	-	229 (22.7)		165 (25.2)	64 (18.0)	

Characteristic (N=34722)	No incident AF (n=33711)	Incident AF (n=1011)	P value*	Incident paroxysmal AF (n=656)	Incident other AF (n=355)	P value†
1	-	477 (47.2)		313 (47.7)	164 (46.2)	
2	-	237 (23.4)		140 (21.3)	97 (27.3)	
3	-	42 (4.2)		20 (3.1)	22 (6.2)	
4	-	25 (2.5)		17 (2.6)	8 (2.3)	
5	-	1 (0.1)		1 (0.2)	0	

Data are median (interquartile range) or counts (percentages). Numbers across categories may not sum to the given numbers because of missing data

*P values comparing women with and without incident AF are based on Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables

†P values comparing women with paroxysmal AF to those with other AF patterns are based on Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables

‡N=34275

§1 point each for Congestive Heart Failure, Hypertension, Age>75 years, Diabetes; 2 points for Stroke/transient ischemic attack

Table 2

Risk of death among women with new-onset AF

Outcome	No incident AF (n=33711)	Incident AF (n=1011)
All-cause mortality (n=1602)		
Events / Incidence rate*	1539 / 3.1 (2.9–3.2)	63 / 10.8 (8.1–13.5)
Age-adjusted model (n=34722)	1.0 (Reference)	2.19 (1.69–2.83)
Multivariable adjusted model 1† (n=33840)	1.0 (Reference)	2.14 (1.64–2.77)
Multivariable adjusted model 2‡ (n=33840)	1.0 (Reference)	1.70 (1.30–2.22)
Cardiovascular mortality (n=309)		
Events / Incidence rate*	284 / 0.57 (0.5–0.6)	25 / 4.3 (2.6–6.0)
Age-adjusted model (n=34722)	1.0 (Reference)	4.67 (3.06–7.14)
Multivariable adjusted model 1† (n=33840)	1.0 (Reference)	4.18 (2.69–6.51)
Multivariable adjusted model 2‡ (n=33840)	1.0 (Reference)	2.57 (1.63–4.07)
Non-cardiovascular mortality (n=1293)		
Events / Incidence rate*	1255 / 2.5 (2.4–2.6)	38 / 6.5 (4.4–8.6)
Age-adjusted model (n=34722)	1.0 (Reference)	1.63 (1.18–2.26)
Multivariable adjusted model 1† (n=33840)	1.0 (Reference)	1.66 (1.19–2.30)
Multivariable adjusted model 2‡ (n=33840)	1.0 (Reference)	1.42 (1.02–1.98)

Data are incidence rates (95% confidence intervals) or hazard ratios (95% confidence intervals)

*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 1526 deaths (290 of them cardiovascular) among 33840 women because of missing data.

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

Table 3

Risk of death among women with new-onset paroxysmal AF

Outcome	No paroxysmal AF (n=34066)[§]	Incident paroxysmal AF (n=656)
All-cause mortality (n=1567)		
Events / Incidence rate[*]	1539 / 3.0 (2.9–3.2)	28 / 7.2 (4.5–9.8)
Age-adjusted model (n=34722)	1.0 (Reference)	1.52 (1.04–2.22)
Multivariable adjusted model 1[†] (n=33840)	1.0 (Reference)	1.44 (0.98–2.11)
Multivariable adjusted model 2[‡] (n=33840)	1.0 (Reference)	1.18 (0.80–1.73)
Cardiovascular mortality (n=295)		
Events / Incidence rate[*]	284 / 0.56 (0.5–0.6)	11 / 2.8 (1.2–4.5)
Age-adjusted model (n=34722)	1.0 (Reference)	3.27 (1.78–6.04)
Multivariable adjusted model 1[†] (n=33840)	1.0 (Reference)	2.94 (1.55–5.59)
Multivariable adjusted model 2[‡] (n=33840)	1.0 (Reference)	1.86 (0.97–3.59)
Non-cardiovascular mortality (n=1272)		
Events / Incidence rate[*]	1255 / 2.5 (2.3–2.6)	17 / 4.4 (2.3–6.4)
Age-adjusted model (n=34722)	1.0 (Reference)	1.14 (0.70–1.84)
Multivariable adjusted model 1[†] (n=33840)	1.0 (Reference)	1.11 (0.69–1.81)
Multivariable adjusted model 2[‡] (n=33840)	1.0 (Reference)	0.97 (0.60–1.58)

Data are incidence rates (95% confidence intervals) or hazard ratios (95% confidence intervals)

[*] 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 33840 women because of missing data.

[‡] Additionally adjusted for intercurrent myocardial infarction, stroke and congestive heart failure

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

Table 4

Risk of cardiovascular events among women with new-onset AF

Endpoint	All AF events		Paroxysmal AF events only[§]	
	No incident AF	Incident AF	No paroxysmal AF	Incident Paroxysmal AF
Composite endpoint [*], N events	1186	135	1209	53
Entire follow-up (n=33840)	1.0 (Reference)	6.94 (5.75–8.38)	1.0 (Reference)	3.82 (2.87–5.08)
Early follow-up only (n=33840)[‡]	1.0 (Reference)	5.08 (3.17–8.13)	1.0 (Reference)	2.36 (1.06–5.29)
Late follow-up only (n=33840) [‡]	1.0 (Reference)	2.46 (1.73–3.49)	1.0 (Reference)	1.92 (1.35–2.73)
Stroke, N events	560	47	572	23
Entire follow-up (n=33840)	1.0 (Reference)	4.17 (3.04–5.71)	1.0 (Reference)	3.09 (2.00–4.76)
Congestive heart failure, N events	252	83	258	29
Entire follow-up (n=33840)	1.0 (Reference)	14.67 (11.18–19.24)	1.0 (Reference)	4.52 (3.11–6.57)
Early follow-up only (n=33840)[†]	1.0 (Reference)	13.52 (7.46–24.50)	1.0 (Reference)	7.47 (3.05–18.26)
Late follow-up only (n=33840) [‡]	1.0 (Reference)	3.97 (2.34–6.73)	1.0 (Reference)	1.44 (0.46–4.51)
Myocardial infarction, N events	472	24	479	15
Entire follow-up (n=33840)	1.0 (Reference)	3.14 (2.06–4.78)	1.0 (Reference)	2.81 (1.64–4.82)
Early follow-up only (n=33840)[†]	1.0 (Reference)	3.87 (1.43–10.44)	1.0 (Reference)	2.06 (0.51–8.28)
Late follow-up only (n=33840) [‡]	1.0 (Reference)	1.37 (0.65–2.90)	1.0 (Reference)	0.87 (0.28–2.72)

Data are hazard ratios (95% confidence intervals) adjusted for age, height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol consumption, education, randomized treatment assignment and race/ethnicity.

[*] Time to first stroke, congestive heart failure or myocardial infarction

[†] Women with a cardiovascular event occurring after 5 years of AF diagnosis were censored at the time of AF onset.

[‡] Women with a cardiovascular event occurring within 5 years of AF diagnosis were censored at the time of AF onset.

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