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Atrial Fibrillation and the Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS)

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Abstract

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Background—It is unknown whether atrial fibrillation (AF) is associated with an increased risk of sudden cardiac death (SCD) in the general population. This association was examined in 2 population-based cohorts.

Methods—In the Atherosclerosis Risk in Communities (ARIC) Study, we analyzed data from 15439 participants (baseline 45–64 years, 55% women, and 27% black) from baseline (1987–1989) through December 31, 2001. In the Cardiovascular Health Study (CHS), we analyzed data from 5479 participants (baseline ≥65 years, 58% women, and 15% black) from baseline (first cohort, 1989–1990; second cohort, 1992–1993) through December 31, 2006. The main outcome was physician-adjudicated SCD, defined as death from a sudden, pulseless condition presumed due to a ventricular tachyarrhythmia. The secondary outcome was non-SCD (NSCD): coronary heart disease death not meeting SCD criteria. We used Cox proportional hazards models to assess the association between AF and SCD/NSCD, adjusting for baseline demographic and cardiovascular risk factors.

Results—In ARIC, 894 AF, 269 SCD, and 233 NSCD events occurred during follow-up (median, 13.1 years). The crude incidence rates of SCD were 2.89/1000 person-years (with AF) and 1.30/1000 person-years (without AF). The multivariable hazard ratios (HRs) (95% CI) of AF for SCD and NSCD were 3.26 (2.17–4.91) and 2.43 (1.60–3.71), respectively. In CHS, 1458 AF, 292 SCD, and 581 NSCD events occurred during follow-up (median, 13.1 years). The crude incidence rates of SCD were 12.00/1000 person-years (with AF) and 3.82/1000 person-years (without AF). The multivariable HRs (95% CI) of AF for SCD and NSCD were 2.14 (1.60–2.87) and 3.10 (2.58–3.72), respectively. The meta-analyzed HRs (95% CI) of AF for SCD and NSCD were 2.47 (1.95–3.13) and 2.98 (2.52–3.53), respectively.

Conclusions—Incident AF is associated with an increased risk of SCD and NSCD in the general population. Additional research to identify predictors of SCD in AF patients is warranted.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.[1, 2] AF is associated with an increased risk of stroke,[3] heart failure,[4] and death.[5–7] The Framingham Heart Study reported that AF increases the risk of death by 1.5-fold in men and 1.9-fold in women.[5] Similarly, a study from Olmsted County, Minnesota showed that new-onset AF doubles the risk of mortality.[6] More recently, the Women's Health Study showed that the risk of all-cause death was doubled and cardiovascular death quadrupled by new-onset AF in initially healthy women.[7]

The common causes of death in individuals with AF in these studies were coronary heart disease (CHD) and stroke.[5, 6] Sudden cardiac death (SCD) was not specifically reported.[5–7] However, there is evidence from post-myocardial infarction (MI) or heart failure patients that AF is associated with an increased risk of SCD.[8–10] It is unknown, however, whether AF increases the risk of SCD in the general population. Moreover, since AF and SCD share many common risk factors such as heart failure[11, 12]and CHD,[13, 14] it is unknown whether AF is independently associated with an increased risk of SCD in the general population.

We hypothesized that incident AF is associated with an increased risk of SCD in the general population. We tested our hypothesis in the Atherosclerosis Risk in Communities (ARIC) Study, and Cardiovascular Health Study (CHS), 2 large community-based cohort studies of cardiovascular disease in the USA.

METHODS

Study Populations

ARIC—The ARIC cohort is a biracial sample, consisting of 15792 men and women, 45–64 years of age at baseline (1987–1989), from 4 communities in North Carolina, Mississippi,

Minnesota, and Maryland.[15] After the baseline examination, participants had 3 additional exams, the last in 1996–1998. In addition to study exams, ARIC participants have received annual follow-up calls since the first visit (>90% response rate) collecting information on general health and hospitalizations. The present study is based on data obtained from baseline (1987–1989) through December 31, 2001. We excluded participants with missing or uninterpretable ECG at baseline (n=243), with missing covariates (n=73), or with prevalent AF (n=37). The final analysis cohort consisted of 15439 ARIC participants.

CHS—The CHS is a cohort study of risk factors for CHD and stroke in older people.[16] Between 1989–1990, 4 field centers (North Carolina, California, Maryland, Pennsylvania) recruited a total of 5201 participants aged ≥65 years from Medicare eligibility lists. To enhance minority representation, during 1992–1993, 687 African-American participants were recruited. The present study is based on data obtained from baseline (1989–1990 for first cohort and 1992–1993 for second cohort) through December 31, 2006. We excluded participants with missing covariates (n=260) or with prevalent AF (n=149). The final analysis cohort consisted of 5479 CHS participants.

The CHS and ARIC study protocols were approved by the institutional review board of each participating center, and informed consent was obtained from each study participant.

Ascertainment of Atrial Fibrillation

In ARIC and CHS, AF was ascertained from study ECGs and hospital discharge records.[14, 17] Details can be found in eMethods.

Outcomes Ascertainment

In ARIC and CHS, comprehensive data were gathered on cardiovascular events and deaths from hospital records, interviews with physicians, next of kin and/or witnesses, death certificates, and autopsy reports, where available. Causes of death were adjudicated by respective ARIC and CHS events committees. An independent review of CHD deaths[18] was conducted by each cohort study to identify SCD events. The primary outcome, SCD was similarly defined in both ARIC and CHS: a sudden pulseless condition presumed due to a ventricular tachyarrhythmia in a previously stable individual without evidence of a non-cardiac cause of cardiac arrest. All SCD cases occurred out of the hospital or in the emergency room and could not have a life-threatening noncardiac comorbidity or be under hospice care. For unwitnessed deaths, the participant must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest.

In ARIC, all CHD deaths that occurred by December 31, 2001 were reviewed by a panel of 5 physicians to identify SCD events. Each event was independently adjudicated by 2 physicians. If there was a disagreement, a third investigator reviewed the event to provide final classification. After review of available data, CHD deaths were classified as definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable.[19–21] For the present analysis, SCD was defined as definite or possible sudden arrhythmic deaths in ARIC.

In CHS, all CHD deaths through December 31, 2006 were reviewed by a cardiologist (NS) in order to classify SCD cases. A blinded second physician review of a random sample of 70 of these death records showed an 88% inter-reviewer agreement and κ=0.74 for SCD. Both of these physicians also participated on the ARIC SCD review panel. After review of available data in CHS, CHD deaths were classified as definite, possible, or not SCD. For the present analysis, the CHS SCD definition included both definite and possible SCDs.

In both cohorts, the secondary outcome, non-SCD (NSCD) was defined as CHD death not meeting SCD criteria.

Covariates

For the main analysis, we used covariates measured at baseline. Definitions of covariates are detailed in eMethods.

Statistical Analysis

We report means with standard deviations for continuous variables and counts with percentages for categorical variables. Person-years at risk were calculated from the date of baseline until the date of SCD/NSCD, other death, loss to follow-up, or end of follow-up, whichever occurred first.

To estimate the association of AF with risks of SCD and NSCD, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards model with AF as a time-dependent exposure variable. We ran 2 models: In Model 1, we adjusted for age, sex, race, and field center. In Model 2, we additionally adjusted for baseline covariates: heart rate, smoking status, body mass index, hypertension, diabetes mellitus, CHD, heart failure, ECG-based left ventricular hypertrophy, use of β-blockers, use of digoxin, and use of anti-arrhythmic drugs. We adjusted for anti-arrhythmic drugs because the latter may be a risk factor for SCD. We conducted 2 additional analyses using time-dependent covariates in ARIC. First, to account for confounding by covariates changing over time, we updated covariates to the time point just before ascertainment of AF, censoring, or SCD incidence, whichever occurred earlier. Second, to assess whether the association between AF and SCD is mediated by shared cardiovascular risk factors, we updated covariates to the end of follow-up.

In addition, we conducted 2 sensitivity analyses. First, we restricted the definition of SCD to include only cases that were classified as definite sudden arrhythmic death (n=252 in ARIC and n=194 in CHS). Second, to control for possible confounding by left ventricular systolic dysfunction, we adjusted for left ventricular fractional shortening on 2D-echocardiogram in ARIC participants at the Mississippi field center (n=2028, all black participants). In CHS, we adjusted for left ventricular ejection fraction (LVEF) (<45%, 45–54%, ≥55%) on 2D-echocardiogram (n=4816). The proportional hazards assumption was assessed with scaled Schoenfeld residuals for both graphical and numerical tests, time interaction terms, and inspection of log negative log survival curves. Modeling assumptions were not violated in any model.

ARIC and CHS results were meta-analyzed using fixed effect analysis. The meta-analysis results were considered the primary results. To determine whether the HR of AF for SCD differed from HR of AF for NSCD, we performed a proportional hazards competing risk analysis.[22]

Statistical analysis of ARIC data was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Statistical analysis of CHS data was performed using R (R Foundation for Statistical Computing, Vienna, Austria) and STATA version 11.2 (StataCorp, College Station, TX). All *P* values reported were 2-sided, and statistical significance threshold was chosen as 5%.

RESULTS

The cohort at risk for SCD in ARIC consisted of 8524 women and 6915 men aged 45–64 years at baseline, and in CHS, 3189 women and 2290 men aged ≥65 years at baseline (Table

1). Of the 5479 participants in CHS, 4857 (88.6%) were from the first cohort and 622 (11.4%) were from the second cohort. During follow-up in ARIC (median, 13.1; interquartile range [IQR], 12.4–13.9 years), 894 AF, 269 SCD, and 233 NSCD events occurred through 2001. During follow-up in CHS (median, 13.1 years; IQR, 8.0–16.3 years), 1458 AF, 292 SCD, and 581 NSCD events occurred through 2006.

Atrial Fibrillation, Sudden Cardiac Death, and Nonsudden Cardiac Death

ARIC—Compared with participants without AF, those with incident AF had higher incidence rates of SCD and NSCD (Table 2). After adjustment for age, sex, race, and ARIC field center, AF was significantly associated with an increased risk of SCD and NSCD (Table 2, Model 1). Although additional adjustment for cardiovascular risk factors attenuated these risk estimates (Table 2, Model 2), the associations remained statistically significant. Overall, the presence of incident AF was associated with a tripling of the risk of SCD and doubling of the risk of NSCD.

To account for confounding by change of covariates over time, we adjusted the main analysis for time-dependent covariates by updating the covariates to the time point just before ascertainment of AF, censoring, or SCD incidence, whichever occurred earlier. We found that AF remained significantly associated with SCD (HR, 2.87; 95% CI, 1.88–4.40; $P<.001$) (Table 3). AF also remained significantly associated with NSCD (HR, 2.16; 95% CI, 1.39–3.35; $P<.001$) (Table 3). To investigate whether shared risk factors could mediate the association between AF and SCD, we conducted another time-dependent regression analysis by updating the covariates to the time point before end of follow-up. We found that even after adjusting for risk factors that are potentially on the causal pathway, AF was significantly associated with an increased risk of SCD (HR, 2.03; 95% CI, 1.30–3.17; $P=.002$) (Table 3). By contrast, AF was no longer significantly associated with NSCD (HR, 1.48; 95% CI, 0.94–2.34; $P=.09$). The non-significant association between AF and NSCD, however, could be due to inadequate power. Moreover, the 2 HRs (2.03 versus 1.48) did not differ significantly ($P=.33$).

From sex-stratified analysis (Table 4), we found that the risk of SCD associated with AF in women (HR, 4.12; 95% CI, 1.91–8.90; $P<.001$) to be comparable with men (HR, 3.12; 95% CI, 1.93–5.04; $P<.001$) (P for interaction by sex=.60). However, race-stratified analysis showed that the risk of SCD associated with AF was higher in black (HR, 5.77; 95% CI, 2.96–11.24; $P<.001$) than non-black participants (HR, 2.49; 95% CI, 1.49–4.17; $P<.001$) (P for interaction by race=.02) (Table 4).

We performed 2 sensitivity analyses. First, we restricted the analysis to only definite cases of SCD. The presence of AF was associated with a doubling of the risk of definite SCD (HR, 2.00; 95% CI, 1.22–3.28; $P=.006$) (eTable 1). Second, to control for possible confounding by left ventricular systolic dysfunction, we restricted the analysis to participants at the ARIC Mississippi field center with fractional shortening measured by 2D-echocardiogram. Of 2028 participants in this sample, there were 53 AF and 30 SCD events through 2001. After adjustment for left ventricular fractional shortening, the HRs (95% CI) of AF for SCD and NSCD were 13.59 (4.20–43.93), $P<.001$, and 10.74 (2.87–40.24), $P<.001$, respectively (eTable 2).

CHS—Incident AF was associated with a doubling of the risk of SCD (HR, 2.14; 95% CI, [1.60–2.87], $P<.001$) and a tripling of the risk of NSCD (HR, 3.10; 95% CI, [2.58–3.72], $P<.001$) in CHS (Table 2). Similar to ARIC, the risk of SCD associated with AF in women (HR, 2.49; 95% CI, 1.57–.95; $P<.001$) was comparable with that in men (HR, 1.99; 95% CI, 1.37–2.91; $P<.001$) (P for interaction by sex=.33) (Table 4). In contrast to ARIC, we did not find an interaction of race with AF risk (P for interaction by race=.46) (Table 4).

From sensitivity analysis, we found that AF was associated with a doubling of the risk of definite SCD in CHS (HR, 2.25; 95% CI, 1.56–3.23; $P<.001$) (eTable 1). After adjustment for LVEF (<45%, 45–54%, ≥55%) on 2D-echocardiogram, AF was still associated with a significantly increased risk of SCD (HR, 2.07; 95% CI, 1.52–2.82; $P<.001$) and NSCD (HR, 2.92; 95% CI, (2.42–3.54); $P<.001$) (eTable 3).

Meta-Analysis—The meta-analyzed HR (95% CI) of AF for SCD in ARIC and CHS was 2.47 (1.95–3.13), $P<.001$. The meta-analyzed HR (95% CI) of AF for NSCD was 2.98 (2.52–3.53), $P<.001$ (Table 2). These 2 HRs did not differ significantly ($P=.21$).

COMMENT

In 2 large population-based cohort studies in the USA including middle-aged and elderly individuals, we found that participants who developed incident AF had an increased risk of SCD compared with participants who did not develop AF. Incident AF was also associated with an increased risk of NSCD. The strength of the association between AF and SCD was comparable to that between AF and NSCD. From meta-analysis results of ARIC and CHS, compared with participants without AF, the risks of SCD and NSCD were more than doubled in participants with AF

Although prospective cohort studies have compellingly demonstrated an association between AF and increased risk of total and cardiovascular mortality,[5–7] none has shown that AF increases the risk of SCD. However, AF may increase the risk of SCD in specific patient subgroups such as post-MI or heart failure patients.[8–10] In the Trandolapril Cardiac Evaluation registry,[8] development of AF during hospitalization for MI was found to be associated with a 1.3-fold higher risk of SCD during subsequent follow-up. In another study of patients who were discharged after hospitalization for MI, AF development during hospitalization increased the risk of SCD by 2.7-fold during follow-up.[10] In patients with severe heart failure, AF was found to be associated with a higher risk of SCD compared with patients without AF–the 1-year SCD-free survival in patients with AF was 69% as compared with 82% in patients without AF.[9].

To the best of our knowledge, the present study is the first to show that incident AF is associated with an increased risk of SCD in 2 independent population-based cohorts. This association was observed in men and women, blacks and non-blacks.

Several mechanisms might explain our observation. First, AF may facilitate the induction of ventricular tachyarrhythmias. A rapid ventricular rate during an atrial tachyarrhythmia will directly reduce ventricular refractoriness,[23] promoting ventricular tachyarrhythmias. In addition, the irregular rhythm of AF leads to short-long-short sequences that may be intrinsically proarrhythmic.[24] Evidence for AF facilitating induction of ventricular tachyarrhythmias comes from several sources. Somberg *et al.* reported from canine experiments that ventricular tachycardia (VT) was induced in 25 of 26 dogs by programmed electrical stimulation only in AF, and not in sinus rhythm.[25] Gronefeld *et al.* reported that AF is an independent predictor of implantable cardioverter-defibrillator therapy for VT or ventricular fibrillation (VF).[26] Analysis of device-stored electrograms revealed a higher incidence of short-long-short cycles preceding ventricular arrhythmias in AF compared with patients in sinus rhythm (50% versus 16%, $P=.002$).[26] Collectively, these observations suggest that atrial tachyarrhythmias may increase susceptibility to ventricular tachyarrhythmias.

Second, since AF is also associated with an increased risk of NSCD, it is possible that the association between AF and SCD is mediated by shared risk factors such as CHD or heart

failure. To assess this possibility, we conducted a secondary analysis in ARIC by updating covariates to the end of follow-up. Although the association between AF and SCD was attenuated in this analysis, AF remained significantly associated with SCD after adjustment for factors potentially in the causal pathway. This observation suggests that the association between AF and SCD is only partially, and not completely, explained by the measured shared risk factors.

The principal strength of this study is the reproducible finding of a strong association between AF and SCD in 2 independent large population-based cohorts. Other strengths include the long follow-up, inclusion of non-white participants, extensive measurement of covariates, large number of AF cases, and physician-adjudication of all SCD cases. However, several limitations should be noted. First, incident AF was identified mostly from hospitalization discharges in ARIC and CHS and we could not include asymptomatic AF or AF managed exclusively in an outpatient setting. However, we have previously shown that the validity of AF ascertainment using hospitalizations in ARIC and CHS is acceptable,[14, 17] that incidence rates of AF in ARIC and CHS are consistent with other population-based studies,[2, 11, 14, 17] and that the associations between genetic variants in the chromosome 4q25 locus and AF–extremely specific for AF risk–in ARIC and CHS are similar to other studies with a more rigorous ascertainment of AF.[27] Second, we could adjust for left ventricular systolic function in only a subgroup of the ARIC cohort. The small sample size for this subgroup analysis was reflected in the wide confidence intervals. However, even after this adjustment, the association between AF and SCD remained statistically significant. Moreover, after adjustment for LVEF in CHS, AF remained a significant risk factor for SCD. Third, although we adjusted for multiple potential confounders in our analyses, we cannot exclude residual confounding by imperfectly measured and unmeasured factors. Finally, we have limited power to detect a significant difference comparing the strengths of association between AF and SCD versus AF and NSCD.

In conclusion, in 2 large, population based-cohorts of middle-aged and elderly individuals, incident AF independently increases the risk of SCD. This finding should be confirmed in additional studies, and if so, it adds to our evolving understanding that AF is not a benign condition–not only does it predispose to stroke, heart failure, and death, but AF *per se* may increase risk of death from ventricular tachyarrhythmias. The latter is potentially preventable, and to this end, additional research to identify predictors of SCD in patients with AF is much needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics According to Atrial Fibrillation Status, Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS)[a]

	ARIC	Incident AF through 2001, ARIC		CHS	Incident AF through 2006, CHS[b]	
	Total sample (n=15439)	No (n=14545)	Yes (n= 894)	Total sample (n= 5479)	No (n= 4021)	Yes (n= 1458)
Age, mean (SD), y	54.2 (5.8)	54.0 (5.7)	57.5 (5.3)	72.7 (5.5)	72.5 (5.5)	73.4 (5.6)
Female	8524 (55.2)	8147 (56.0)	377 (42.2)	3189 (58.2)	2396 (59.6)	793 (54.4)
Black race	4107 (26.6)	3945 (27.1)	162 (18.1)	845 (15.4)	689 (17.1)	156 (10.7)
Current cigarette smoking	4044 (26.2)	3752 (25.8)	284 (31.8)	658 (12.0)	502 (12.5)	156 (10.7)
Body mass index, mean (SD) (kg/m^2)	27.7 (5.4)	27.6 (5.3)	28.9 (6.1)	26.7 (4.7)	26.6 (4.7)	26.9 (4.8)
Heart rate, mean (SD), (bpm)[c]	66.3 (10.3)	66.2 (10.2)	66.7 (11.3)	65.0 (11.4)	65.3 (11.6)	64.1 (11.0)
ECG-based LVH	338 (2.2)	292 (2.0)	46 (5.2)	280 (5.1)	205 (5.1)	75 (5.1)
Diabetes	1816 (11.8)	1633 (11.2)	183 (20.5)	878 (16.1)	620 (15.5)	258 (17.7)
Hypertension	5353 (34.7)	4892 (33.6)	461 (51.6)	3207 (58.5)	2275 (56.6)	932 (63.9)
Coronary heart disease	737 (4.8)	626 (4.3)	111 (12.4)	1049 (19.1)	697 (17.3)	352 (24.1)
Heart failure	716 (4.6)	613 (4.2)	103 (11.5)	211 (3.1)	129 (3.2)	82 (5.6)
Use of beta-blockers	1611 (10.4)	1415 (9.7)	196 (21.9)	695 (12.7)	482 (12.0)	213 (14.6)
Use of anti-arrhythmics	115 (0.7)	80 (0.6)	35 (3.9)	172 (3.1)	91 (2.3)	81 (5.6)

Abbreviations: AF, atrial fibrillation; LVH, left ventricular hypertrophy based on Cornell criteria

[a] Data are presented as No. (%) of participants unless otherwise stated

[b] The second CHS cohort had by design 3 years shorter follow-up than the first CHS cohort

[c] Heart rate was determined based on 12-lead ECG at baseline

Table 2

Risk of Sudden Cardiac Death and Nonsudden Cardiac Death by Atrial Fibrillation Status, Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS)

		Incident AF through 2001, ARIC			Incident AF through 2006, CHS			Meta-analysis		
		No	Yes	*P* Value	No	Yes	*P* Value	HR (95% CI)	*P* Value	*P* Value for heterogeneity
Sudden Cardiac Death										
Number of events		238	31		225	67				
Person-years		183086	10719		58877	5582				
Crude incidence rate (95% CI)[a]		1.30 (1.14–1.47)	2.89 (2.00–4.05)		3.82 (3.35–4.35)	12.00 (9.45–15.25)				
Hazard ratio (95% CI)	Model 1[b]	1 [Referent]	5.40 (3.63–8.04)	<.001	1 [Referent]	2.51 (1.88–3.33)	<.001	3.26 (2.58–4.11)	<.001	.002
	Model 2[c]	1 [Referent]	3.26 (2.17–4.91)	<.001	1 [Referent]	2.14 (1.60–2.87)	<.001	2.47 (1.95–3.13)	<.001	.10
Nonsudden Cardiac Death										
Number of events		189	44		379	202				
Person-years		183086	10719		58877	5582				
Crude incidence rate (95% CI)[a]		1.03 (0.89–1.19)	4.10 (3.02–5.46)		6.44 (5.82–7.11)	36.19 (31.52–41.54)				
Hazard ratio (95% CI)	Model 1[b]	1 [Referent]	4.66 (3.12–6.95)	<.001	1 [Referent]	3.55 (2.97–4.25)	<.001	3.72 (3.15–4.38)	<.001	.22
	Model 2[c]	1 [Referent]	2.43 (1.60–3.71)	<.001	1 [Referent]	3.10 (2.58–3.72)	<.001	2.98 (2.52–3.53)	<.001	.30

Abbreviations: AF, atrial fibrillation; CI, confidence interval

[a] Per 1000 person-years of follow-up

[b] Cox proportional hazards model adjusted for age, sex, race, and field center

[c] Model 1 additionally adjusted for baseline covariates: heart rate, smoking status, body mass index, hypertension, diabetes, coronary heart disease, heart failure, ECG-based left ventricular hypertrophy, use of beta-blockers, use of digoxin, and use of anti-arrhythmic drugs. In CHS, Model 2 was not adjusted for use of digoxin

Table 3

Risk of Sudden Cardiac Death and Nonsudden Cardiac Death by Atrial Fibrillation Using Time-Dependent Covariates, Atherosclerosis Risk in Communities Study

		Incident AF through 2001		
		No	**Yes**	***P* Value**
Sudden Cardiac Death				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	2.87 (1.88–4.40)	<.001
	Model 2[b]	1 [Referent]	2.03 (1.30–3.17)	.002
Nonsudden Cardiac Death				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	2.16 (1.39–3.35)	<.001
	Model 2[b]	1 [Referent]	1.48 (0.94–2.34)	.09

Abbreviations: AF, atrial fibrillation; CI, confidence interval

[a]Cox proportional hazards model adjusted for age, sex, race, ARIC field center and time-dependent covariates: heart rate, smoking status, body mass index, hypertension, diabetes, coronary heart disease, heart failure, ECG-based left ventricular hypertrophy, use of beta-blockers, use of digoxin, and use of anti-arrhythmic drugs. Time-dependent covariates were updated to the time point just before ascertainment of AF, censoring, or SCD incidence, whichever occurred earlier.

[b]Cox proportional hazards model adjusted for the same covariates as in Model 1. However, time-dependent covariates were updated to end of follow-up.

Table 4

Sex- and Race-Stratified Risks of Sudden Cardiac Death by Atrial Fibrillation Status, Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS)

		Incident AF through 2001, ARIC			Incident AF through 2006, CHS			Meta-Analysis		
		No	Yes	*P* Value	No	Yes	*P* Value	HR (95% CI)	*P* Value	*P* Value for hetero-geneity
By sex										
Female										
Number of SCD events		83	9		93	26				
Person-years		103852	4561		36831	2973				
Incidence rate(95% CI)[c]		0.80 (0.64–0.99)	1.97 (0.97–3.60)		2.53 (2.06–3.09)	8.74 (5.95–12.84)				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	6.63 (3.13–14.00)	<.001	1 [Referent]	2.86 (1.82–4.48)	<.001	3.58 (2.43–5.26)	<.001	.06
	Model 2[b]	1 [Referent]	4.12 (1.91–8.90)	<.001	1 [Referent]	2.49 (1.57–3.95)	<.001	2.85 (1.92–4.23)	<.001	.27
Male										
Number of SCD events		155	22		132	41				
Person-years		79235	6158		22046	2609				
Incidence rate(95% CI)[c]		1.96 (1.67–2.28)	3.57 (2.30–5.31)		5.99 (5.05–7.10)	15.71 (11.57–21.34)				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	5.01 (3.13–8.00)	<.001	1 [Referent]	2.35 (1.62–3.40)	<.001	3.14 (2.35–4.21)	<.001	.02
	Model 2[b]	1 [Referent]	3.12 (1.93–5.04)	<.001	1 [Referent]	1.99 (1.37–2.91)	<.001	2.36 (1.76–3.18)	<.001	.15
By race										
Non-Black										
Number of SCD events		136	20		175	61				
Person-years		135086	8879		50528	5031				
Incidence rate(95% CI)[c]		1.01 (0.85–1.19)	2.25 (1.42–3.41)		3.46 (2.99–4.02)	12.12 (9.43–15.58)				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	4.38 (2.66–7.23)	<.001	1 [Referent]	2.61 (1.92–3.54)	<.001	3.01 (2.32–3.90)	<.001	.08
	Model 2[b]	1 [Referent]	2.49 (1.49–4.17)	<.001	1 [Referent]	2.16 (1.59–2.96)	<.001	2.24 (1.72–2.93)	<.001	.64
Black										

		Incident AF through 2001, ARIC			Incident AF through 2006, CHS			Meta-Analysis		
		No	**Yes**	***P* Value**	**No**	**Yes**	***P* Value**	**HR (95% CI)**	***P* Value**	***P* Value for hetero-geneity**
Number of SCD events		102	11		50	6				
Person-years		48000	1840		8349	551				
Incidence rate(95% CI)[c]		2.13 (1.74–2.57)	5.98 (3.17–10.35)		5.99 (4.53–7.90)	10.89 (4.89–24.24)				
Hazard ratio (95% CI)	Model 1[a]	1 [Referent]	8.39 (4.42–15.91)	<.001	1 [Referent]	1.83 (0.77–4.34)	.17	4.89 (2.92–8.18)	<.001	.006
	Model 2[b]	1 [Referent]	5.77 (2.96–11.24)	<.001	1 [Referent]	2.01 (0.81–4.97)	.14	3.98 (2.33–6.82)	<.001	.07

Abbreviations: AF, atrial fibrillation; CI, confidence interval; SCD, sudden cardiac death

[a]Cox proportional hazards model adjusted for age, sex, race, and field center

[b]Model 1 additionally adjusted for baseline covariates: heart rate, smoking status, body mass index, hypertension, diabetes, coronary heart disease, heart failure, ECG-based left ventricular hypertrophy, use of beta-blockers, use of digoxin, and use of anti-arrhythmic drugs. In CHS, Model 2 was not adjusted for use of digoxin

[c]Per 1000 person-years of follow-up