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ORIGINAL RESEARCH

Association of Atrial Fibrillation With Incidence of Extracranial Systemic Embolic Events: The ARIC Study

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BACKGROUND: Atrial fibrillation (AF) increases the risk of stroke and extracranial systemic embolic events (SEEs), but little is known about the magnitude of the association of AF with SEE.

METHODS AND RESULTS: This analysis included 14 941 participants of the ARIC (Atherosclerosis Risk in Communities) study (mean age, 54.2±5.8, 55% women, 74% White) without AF at baseline (1987–1989) followed through 2017. AF was identified from study ECGs, hospital discharges, and death certificates, while SEEs were ascertained from hospital discharges. CHA_2DS_2-VASc was calculated at the time of AF diagnosis. Cox regression was used to estimate associations of incident AF with SEE risk in the entire cohort, and between CHA_2DS_2-VASc score and SEE risk in those with AF. Among eligible participants, 3114 participants developed AF and 270 had an SEE (59 events in AF). Incident AF was associated with increased risk of SEE (hazard ratio [HR], 3.58; 95% CI, 2.57–5.00), after adjusting for covariates. The association of incident AF with SEE was stronger in women (HR, 5.26; 95% CI, 3.28–8.44) than in men (HR, 2.68; 95% CI, 1.66–4.32). In those with AF, higher CHA_2DS_2-VASc score was associated with increased SEE risk (HR per 1-point increase, 1.24; 95% CI, 1.05–1.47).

CONCLUSIONS: AF is associated with more than a tripling of the risk of SEE, with a stronger association in women than in men. CHA_2DS_2-VASc is associated with SEE risk in AF patients, highlighting the value of the score to predict adverse outcomes and guide treatment decisions in people with AF.

Key Words: atrial fibrillation ■ CHA_2DS_2-VASc score ■ extracranial systemic embolism

Atrial Fibrillation (AF) affects an estimated 33.5 million patients worldwide and is associated with increased risk of stroke, mortality, and morbidity, accompanied by higher healthcare burden.[1,2] Cardioembolic stroke is one of the most important complications of AF, leading to substantial disability and mortality in these patients.[3] Oral anticoagulation has demonstrated consistent effectiveness in the prevention of cardioembolic stroke among AF patients.[4] The same mechanisms that lead to elevated risk of ischemic stroke in AF are also likely to increase risk of extracranial systemic embolic events (SEEs).[5] A pooled analysis of recent clinical trials of anticoagulation in AF showed that 1 in 9 thromboembolic events in AF patients were SEEs.[6]

Although there is extensive epidemiologic evidence of increased risk of ischemic stroke among individuals with AF,[7–9] no prior studies have explored the association of incident AF with the risk of SEE. This information is needed to fully characterize the impact of AF on cardiovascular outcomes, and the potential benefits of AF prevention and treatment in the population. Thus, to address this existing gap, the aims of this study were, first, to evaluate the association of AF with incidence of SEEs in the ARIC (Atherosclerosis Risk in Communities) study, a large community-based cohort and, second, to assess the association of the CHA_2DS_2-VASc score with SEE risk among people with diagnosed AF in this cohort.

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CLINICAL PERSPECTIVE

What Is New?

- This study estimates for the first time in a community-based cohort the association of incident atrial fibrillation (AF) with the risk of extracranial systemic embolic events, with AF patients having a 3.6 times higher risk of systemic embolic events.
- The association between AF and systemic embolic events was stronger in women than men.
- A higher CHA_2DS_2-VASc score was associated with higher risk of systemic embolic events among patients with AF.

What Are the Clinical Implications?

- This study complements the existing knowledge about the adverse outcomes associated with AF and further supports the use of CHA_2DS_2-VASc as a predictive tool in patients with AF.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
HR	hazard ratio
ICD	*International Classification of Diseases*
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
SEE	systemic embolic event

METHODS

The data, analysis, and study materials are not available to other researchers for purposes of reproducing the results or replicating the analysis because of human subject restrictions. Interested investigators may contact the ARIC Study Coordinating Center at the University of North Carolina to request access to ARIC study data.

Study Population and Design

The ARIC Study, conducted in 4 US communities (Forsyth County, NC; Jackson, MS; selected Minneapolis suburbs, MN; and Washington County, MD), is a prospective cohort study started in 1987 to understand in more detail the development of cardiovascular diseases and their risk factors in the general population.[10] All participants provided written informed consent at the time of each visit and trained interviewers collected information on demographic characteristics, health behaviors, medical history, and medication use. The ARIC Study initially recruited 15 792 men and women, aged 45 to 64 years, at visit 1 (1987–1989), and participants were invited to subsequent visits in 1990 to 1992 (visit 2, n=14 348), 1993 to 1995 (visit 3, n=12 887), 1996 to 1998 (visit 4, n=11 656), 2011 to 2013 (visit 5, n=6538), and 2016 to 2017 (visit 6, n = 4003). Institutional Review Boards at all participating institutions approved the study. A flowchart of study exclusions is depicted in Figure 1.

For the first aim, to evaluate the association of incident AF with SEE risk, we excluded participants with missing ECGs at baseline, missing covariates, race other than White and Black because of small numbers (n=48, <4%), Black adults from the Minnesota and Washington county centers because of the same reason (n=55, <4%), and prevalent AF, leaving 14 941 eligible participants.

For the second aim, to assess the association of the CHA_2DS_2-VASc score with SEE risk in participants with incident AF, we included all those who were diagnosed with AF during follow-up before developing SEE among the initial eligible sample. These criteria identified 3114 participants with incident AF.

Atrial Fibrillation

The methods used to define incident AF have been discussed in detail in previous publications.[11,12] Briefly, AF ascertainment was based on ECGs at study visits 1 to 5, hospital discharge records, and death certificates. All ECG records derived from MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI) were automatically coded. Those labeled as having AF were re-checked by a trained cardiologist to confirm the diagnosis. Participants with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 427.3x or *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* codes I48.x in the hospital discharge codes without codes for open cardiac surgery or participants with AF listed as a cause of death were defined as AF.

Extracranial Systemic Embolic Events

The main outcome of our study is incident SEE, which was defined as the presence of the following *International Classification of Diseases* (*ICD*) codes in any position as a discharge code in a hospitalization: *ICD-9-CM* 444.xx (arterial embolism and thrombosis) or *ICD-10-CM* I74.x (arterial embolism and thrombosis), with fourth and fifth digits indicating location (abdominal aorta, thoracic aorta, arteries in the extremities, iliac artery, other specified artery, unspecified artery). A previous study determined the validity of *ICD-10-CM* codes I74.x for the identification of

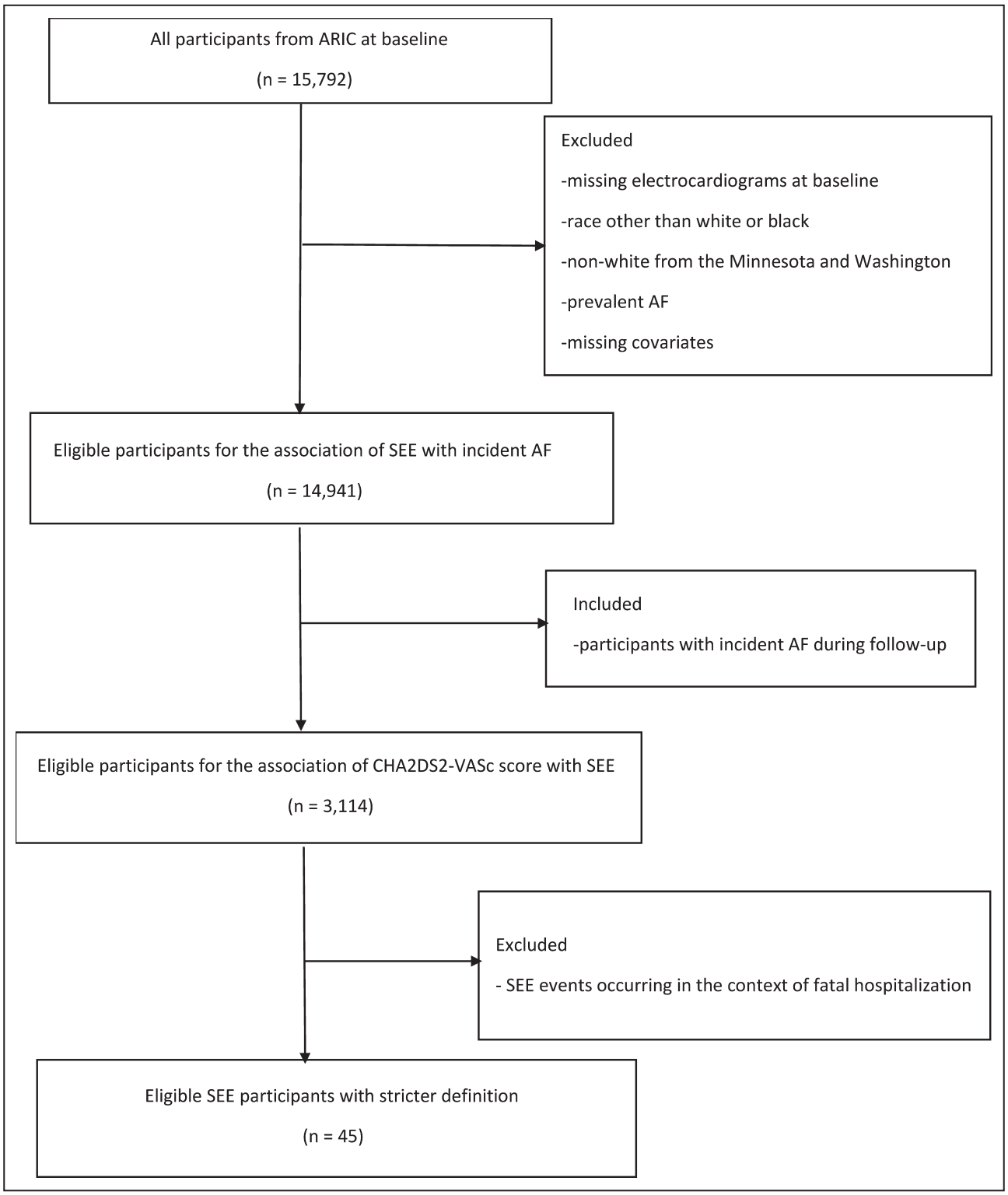

Figure 1. Flowchart of study participants, ARIC study, 1987 to 2017.
AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; and SEE: systemic embolic event.

arterial embolism and thrombosis, reporting a positive predictive value of 83%, 95% CI, 74% to 89%, demonstrating adequate validity of the code for identification of SEEs.[13]

Covariates

Covariates were obtained at the baseline visit and most were re-measured at each subsequent visits.

Covariates measures used only from the baseline visit, included sex (female, male), education level (grade school or 0 years education, high school but no degree, high school graduate, vocational school, college, graduate school or professional school), race (White, Black), and study center. Covariates measured at every visit (1–6) included age (years), height (cm), body mass index (kg/m^2), smoking status (current smoker, former smoker, never smoker), systolic and diastolic blood pressure (mm Hg), diabetes mellitus, history of myocardial infarction, heart failure, stroke, use of antihypertensive medication in the last 2 weeks before each visit, and use of aspirin and anticoagulants in the last 2 weeks before each visit. Questionnaires assessed self-reported sex, age, education level, race, center, and smoking status during study visits. Weight and height were measured with the participant wearing light clothes. Body mass index was defined as the ratio of weight in kilograms divided by height in meters squared. Medication use (antihypertension, aspirin, anticoagulants) was ascertained by checking medications brought to each visit by the participant. Hypertension was considered present if systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg and/or participants used antihypertension medications in the past 2 weeks. Diabetes mellitus was defined as meeting 1 of the following criteria: (1) self-reported physician's diagnosis of diabetes mellitus; (2) use of hypoglycemic medications; (3) non-fasting serum glucose levels ≥ 200 mg/dL; (4) fasting serum glucose level ≥ 126 mg/dL. Heart failure was measured by different methods at baseline and follow-up visits. At baseline, heart failure was defined as the reported use of heart failure medications in the previous 2 weeks or the presence of heart failure according to the Gothenburg criteria.[14] Incident heart failure was defined by the presence of *ICD-9-CM* code 428 in any hospitalization.[15] Baseline stroke and myocardial infarction were defined based on self-reported information of physician diagnoses or evidence of an old myocardial infarction on the baseline ECG.[16] Incident stroke and myocardial infarction was adjudicated by committee review, based on information from hospital records.

Statistical Analysis

Baseline characteristics of participants were presented stratified by incident AF status as means and SDs for continuous variables and as frequencies and percentages for categorical variables.

For ARIC participants without AF at the baseline visit, we calculated age-, sex-, race-specific incidence rate of SEE per 10 000 person-years, and incidence rate ratios and 95% CIs by incident AF status (referent category=no AF). Among participants with incident AF, person-years at risk were calculated from the date of incidence of AF until the date of incidence of SEE, death, censoring, or December 31, 2017, whichever occurred earlier. For the comparison group, follow-up time was defined as the time from the baseline visit to date of incidence of SEE, date of incidence AF, death, censoring, or December 31, 2017, whichever occurred earlier. SEEs diagnosed on the same day as AF were assumed to occur 1 day after the AF diagnosis. Age was categorized into 8 groups (45–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85 years) for the calculation of age-specific incidence rates.

We calculated the cumulative incidence of SEE by incident AF status accounting for the competing risk of death using the cumulative incidence function.[17] To determine the association of AF with SEE, we used Cox proportional hazards models with AF incidence as a time-dependent variable to compute hazard ratios (HR) and 95% CIs. Covariates were selected based on their availability and potential relationship with SEE risk, AF, and AF-related outcomes. Missing values in the covariates during follow-up visits were carried forward as the values obtained from the previous visit, and missing values in chronic diseases at baseline, such as diabetes mellitus, history of myocardial infarction, and history of stroke, were considered as disease-free status. In an initial model (model 1), we adjusted for age, sex, and race. A second model (model 2a) additionally adjusted for education level, race-center, height, and time-dependent body mass index, smoking status, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes mellitus, history of myocardial infarction, heart failure, stroke, and regular use of aspirin and anticoagulants. In a final model (model 3a), we excluded SEEs occurring in the context of fatal hospitalization as a sensitivity analysis to evaluate the impact of outcome definition in our results. Supplemental models (model 2b, model 3b) adjusted for the same covariates corresponding to model 2a and model 3a, respectively, however, excluding regular use of aspirin and anticoagulants. Covariates were updated at each visit throughout follow-up for people who did not develop AF and were updated at each visit until the visit in which the participant developed AF. We evaluated effect measure modification by sex and race by including a multiplicative interaction term, and then we conducted stratified analyses.

In subsequent analyses restricted to ARIC participants with incident AF during follow-up, we calculated CHA_2DS_2-VASc score-specific incidence rate and 95% CI of SEE per 10 000 person-years to evaluate the association of the CHA_2DS_2-VASc score and its components with SEE risk. The CHA_2DS_2-VASc

was calculated based on patient characteristics at the time of AF diagnosis (age, sex, heart failure, stroke, vascular disease) or from the prior visit (hypertension, diabetes mellitus) using the standard criteria: 0 points for age < 65 years, 1 point for age 65 to 74 years, 2 points for age ≥75 years, 1 point for female sex, 1 point for history of heart failure, 1 point for hypertension history, 2 points for history of stroke, 1 point for history of diabetes mellitus, 1 point for history of vascular disease.[18] Follow-up time was defined as the time from the date of incidence of AF to the date of incidence of SEE, death, censoring, or December 31, 2017, whichever occurred earlier. Cox regression was used to calculate HRs and 95% CIs of SEE by CHA_2DS_2-VASc score. An initial analysis included CHA_2DS_2-VASc score as the main independent variable, age, sex, race-center, and anticoagulants as covariates, and considered SEEs defined using standard methods. A second analysis used the alternative definition of SEE (excluding events occurring in the context of fatal hospitalization) as a sensitivity analysis. CHA_2DS_2-VASc score was modeled both as a continuous (HR per 1-point increase) and as a categorical variable (0–1 [reference], 2, 3, 4, 5, 6–9). All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Carolina).

RESULTS

Baseline Characteristics

At baseline, a total of 14 941 ARIC participants met the inclusion criteria. Baseline characteristics, stratified by AF status during the follow-up, are shown in Table 1. The mean age ± SD was 55.9 ± 5.5 years for participants who developed AF and 53.7±5.7 years for those who did not. In addition, participants who developed AF were more likely to be White and men, be former smokers, have higher systolic blood pressure, lower education level, higher prevalence of stroke, prevalent heart failure, diabetes mellitus, history of myocardial infarction, and use of anticoagulants or aspirin-containing analgesics, compared with participants without AF (Table 1).

Table 1. Baseline Characteristics of Participants by Incident AF Status, ARIC Study, 1987 to 1989

Variables	No AF	Incident AF
No.	11 827	3114
Age (y), mean (SD)	53.7 (5.7)	55.9 (5.5)
Women, %	6728 (56.9)	1529 (49.1)
Race, %		
White	8493 (71.8)	2541 (81.6)
Black	3334 (28.2)	573 (18.4)
Education level, %		
Grade school or 0 y education	1084 (9.2)	327 (10.5)
High school, but no degree	1618 (13.7)	471 (15.1)
High school graduate	3816 (32.3)	1038 (33.3)
Vocational school	1028 (8.7)	248 (8.0)
College	3057 (25.8)	766 (24.6)
Graduate school or professional school	1224 (10.3)	264 (8.5)
Standing height (cm), mean (SD)	168.1 (9.2)	170.0 (9.5)
BMI (kg/m^2), mean (SD)	27.4 (5.2)	28.6 (5.7)
Systolic blood pressure (mm Hg), mean (SD)	120.4 (18.8)	124.1 (18.9)
Diastolic blood pressure (mm Hg), mean (SD)	73.6 (11.2)	73.8 (11.5)
Cigarette smoking status, %		
Current smoker	3091 (26.1)	804 (25.8)
Former smoker	3711 (31.4)	1127 (36.2)
Never smoker	5025 (42.5)	1183 (38.0)
Diabetes mellitus, %	1336 (11.3)	443 (14.2)
History of stroke, %	198 (1.7)	67 (2.2)
Prevalent heart failure, %	492 (4.2)	199 (6.4)
History of myocardial infarction, %	391 (3.3)	178 (5.7)
Baseline use of anticoagulants, %	43 (0.4)	25 (0.8)
Baseline use of aspirin-containing analgesics, %	5310 (45.7)	1531 (49.2)

[a]The table is based on baseline sample after excluding individuals with missing ECGs, race other than White or Black, non-Whites from the Minnesota and Washington country centers, prevalent AF, or missing covariates. AF indicates atrial fibrillation; and ARIC, Atherosclerosis Risk in Communities.

AF and SEE

During 345 138 person-years of follow-up, we identified 3114 incident AF and 270 SEEs (59 in those with AF). A majority of these events corresponded to events in the extremities (*ICD-9-CM* codes 444.21 and 444.22, *ICD-10-CM* codes I74.2 and I 74.3, n=180 or 67%), followed by events in the iliac artery (*ICD-9-CM* code 444.81 or *ICD-10-CM* code I74.5, n=34 or 13%) and abdominal aorta (*ICD-9-CM* codes 444.0x or *ICD-10-CM* codes I74.0x, n=23 or 9%), with the remaining 33 (12%) being unspecified or occurring in other locations. The cumulative risk of SEE by incident AF status and accounting for the competing risk of death is shown in Figure 2, demonstrating a higher risk of SEE in those who were diagnosed with AF. Crude incidence rates of SEE were 6.4 (95% CI, 5.6–7.3) per 10 000 person-years in those without AF and 34.9 (95% CI, 26.8–44.8) in those with AF. After standardizing by age, incident AF was remarkably associated with increased rates of SEE (age-standardized incidence rate ratios, 5.63; 95% CI, 4.11–7.73) (Table 2) compared with those without AF.

The association between incident AF and incident SEE is depicted in Table 3. After adjustment for age, sex, and race, incident AF was associated with a higher risk of SEE compared with no AF (model

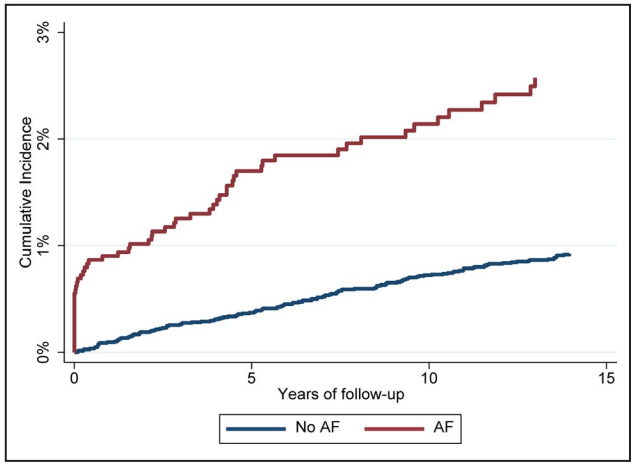

Figure 2. Cumulative incidence of extracranial systemic embolic events, unadjusted, by AF status, considering death as a competing risk, ARIC cohort, 1987 to 2017.
AF indicates atrial fibrillation; and ARIC, Atherosclerosis Risk in Communities.

1: HR, 5.39, 95% CI, 3.92–7.41). Further adjustment somewhat attenuated the association; however, AF was associated with 3.5 times the risk of SEE compared with those without AF (model 2a: HR, 3.58; 95% CI, 2.57–5.00). The association was similar after using a stricter definition of SEE (n=241 events; model 3a: HR, 2.85; 95% CI; 1.96–4.14). After excluding regular use of aspirin and anticoagulants from covariates, the association of AF with SEE was notably increased in both model 2b and model 3b (model 2b: HR, 3.86; 95% CI, 2.80–5.33; model 3b: HR, 3.21; 95% CI, 2.24–4.60).

The association of incident AF with SEE was stronger in women (HRs, 5.26; 95% CI, 3.28–8.44) than in men (HR, 2.68; 95% CI, 1.66–4.32) after adjustment for model 2 covariates (*P* for interaction=0.002). The association was similar in White and Black adults; HRs for SEE were 3.96 (95% CI, 2.70–5.80) and 3.35 (95% CI, 1.69–6.62) for White and Black adults, respectively (*P* for interaction=0.52) (Table 3).

Table 3. Hazard Ratios of Extracranial Systematic Embolic Events by AF Incidence Status, ARIC Study, 1987 to 2017

	No AF	AF		
No. of SEE	211	59		
Person-years	335 754	18 447		
Crude IR	6.28	31.98		
	HR		95%CI	
Model 1	1 (ref)	5.39	3.92	7.41
Model 2a	1 (ref)	3.58	2.57	5.00
Model 2b	1 (ref)	3.86	2.80	5.33
Model 3a	1 (ref)	2.85	1.96	4.14
Model 3b	1 (ref)	3.21	2.24	4.60
Women	1 (ref)	5.26	3.28	8.44
Men	1 (ref)	2.68	1.66	4.32
White	1 (ref)	3.96	2.70	5.80
Black	1 (ref)	3.35	1.69	6.62

Model 1 adjusts for age, sex and race. Model 2a adjusts for age, sex, education level, race-center, height, body mass index, smoking status, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes mellitus, history of myocardial infarction, heart failure, stroke, and regular use of aspirin and anticoagulants. Model 3a adjusts for the same variables as Model 2 but defines SEE as events not occurring in the context of fatal hospitalizations. Model 2b and 3b adjust for the same covariates as Model 2a and Model 3a respectively, except regular use of aspirin and anticoagulants. Sex and race stratified analyses adjust for variables in model 2a. Crude IR indicates crude incidence rate per 10 000 person; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; HR, hazard ratio; and SEE, systemic embolic event.

Table 2. Age-Specific Incidence Rates of Extracranial Systematic Embolic Events per 10 000 Person-Years by AF status, ARIC Study, 1987 to 2017

	No AF			AF		
Age Group	No. of SEE	Person-Years	IR	No. of SEE	Person-Years	IR
45–54 y	18	42 996	4.2	0	138	0
55–59 y	31	48 071	6.4	2	469	42.6
60–64 y	45	61 705	7.3	5	1259	39.7
65–69 y	48	62 465	7.7	12	2474	48.5
70–74 y	33	53 527	6.2	13	3841	33.9
75–79 y	25	35 500	7.0	12	4001	30.0
80–84 y	10	17 423	5.7	8	3129	25.6
≥85 y	1	6530	1.5	7	1575	44.4
TOTAL	211	328 217*	6.4	59	16 886*	34.9
Crude IRR (95% CI)	1(Ref.)			5.44 (4.07–7.25)		
Age-standardized IRR (95% CI)	1(Ref.)			5.63 (4.11–7.73)		

*AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; IR, incidence rate; IRR, incidence rate ratio; and SEE, systemic embolic event. Total person-time differs from numbers in Table 3 due to rounding in calculation of person-years by age group.

SEE and CHA_2DS_2-VASc scores

Among 3114 individuals with incident AF during follow-up, 2898 of them had at least 1 day of follow-up. Among these, 59 participants developed SEE. A higher CHA_2DS_2-VASc score was associated with higher incidence rates of SEE ranging from 8.8 events per 10 000 person-years for those with a score of 0 to 1 to 82.6 for those with score of 6 to 9 (Table 4).

Table 4 also reports HR (95% CI) of SEE by CHA_2DS_2-VASc score. In multivariable analyses, 1-point increase in the score was associated with a 1.24-fold risk of SEE (95% CI, 1.05–1.47), with a similar association using the more restrictive definition of SEE (n=45, HR, 1.28; 95% CI, 1.06–1.56), after adjusting for age, sex, race-center, and use of anticoagulants at the time of AF diagnosis. Categorization of the CHA_2DS_2-VASc similarly showed higher risk of SEE with higher score, but CIs were quite wide because of the limited number of events in each category.

DISCUSSION

In this analysis of a large community-based cohort, we found that individuals who developed AF had >3 times the risk of SEE compared with those without AF. This association was independent from sociodemographic variables and time-dependent confounders. AF was a stronger risk factor for SEE in women than in men. Similarly, higher CHA_2DS_2-VASc score, which is used for the prediction of stroke in AF patients, was also associated with SEE risk among those with AF.

Although the incidence and predictive factors of ischemic stroke in patients with AF have been well evaluated,[18] relatively little is known about the incidence and risk factors of SEE in people with AF. A previous study described that SEE constituted 11.5% of clinically recognized thromboembolic events in patients with AF and was associated with high morbidity and mortality.[19] However, no prior studies have specifically reported whether the relative risk of SEE was similar in magnitude to the relative increment in stroke risk among AF patients. Prior ARIC studies have evaluated increased risk of stroke in both individuals with AF[20] and individuals without AF.[21] Among ARIC participants, those with incident AF had approximately double the risk of stroke than those without AF (HR, 2.1; 95% CI, 1.4–3.0 in Black adults, and HR, 1.8; 95% CI, 1.4–2.3 in Whites),[22] which revealed a remarkable increment in stroke risk associated with AF. Furthermore, the association of AF and stroke has been revealed stronger in Black adults (rate difference: 21.4 per 1000 person-years, 95% CI, 10.2–32.6 per 1000 person-years) compared with Whites (rate difference: 10.2 per 1000 person-years, 95% CI, 6.6–13.9 per 1000 person-years) [22]. Another systematic review and meta-analysis also demonstrated AF was associated with an increased risk of a range of different outcomes, including 2.4-fold risk of stroke, almost 5-fold risk of heart failure, 1.3-fold risk of peripheral artery disease, and 1.6-fold risk of chronic kidney disease, which were consistent with results from the ARIC cohort study.[23] Overall, the association of incident AF with SEE seems to be slightly stronger than the association of incident AF with stroke.

Based on their beneficial effect, oral anticoagulants are recommended for prevention of stroke and systemic embolism in AF.[24–27] A study demonstrated anticoagulant medications significantly reduced both stroke risk (odds ratio, 0.60; 95% CI, 0.45–0.81) and death risk (odds ratio, 0.54; 95% CI, 0.38–0.75) among patients with CHA_2DS_2-VASc score ≥2.[24] Another prior study also reported that apixaban was associated with lower risk and costs of stroke and SEE compared with warfarin, although both were effective and safe in reducing stoke and SEEs.[26]

As has been observed previously for the association of AF with stroke,[28] we found a stronger association of

Table 4. Incidence Rates (per 10 000 Person-Years) and Hazard Ratios (95% CI) of Extracranial Systematic Embolic Events by CHA_2DS_2-VASc score in participants with incident AF, ARIC Study, 1987 to 2017

CHA_2DS_2-VASc score	No. of SEE	Person-Years	IR	95% CI		Model 1			Model 2		
						HR	95% CI		HR	95% CI	
Per 1-point increase						1.24	1.05	1.47	1.28	1.06	1.56
0–1	3	3,418	8.8	2.2	23.9	1 (Ref)			1 (Ref)		
2	9	3,979	22.6	11.0	41.5	2.37	0.64	8.77	2.00	0.39	10.3
3	16	4,341	36.9	21.8	58.6	3.32	0.96	11.5	4.40	0.99	19.6
4	17	2,952	57.6	34.7	90.3	4.66	1.34	16.2	5.91	1.31	26.6
5	8	1,475	54.2	25.2	103.0	3.90	1.00	15.2	2.99	0.53	16.9
6–9	6	726	82.6	33.5	171.9	5.54	1.32	23.2	8.48	1.62	44.3

Model 1 adjusts for age, sex, race-center, and use of anticoagulants. Model 2 defines SEE as the presence of codes *ICD-9-CM* 444.xx or *ICD-10-CM* 174.x in any position as a discharge code in a non-fatal hospitalization, adjusting for same covariates as Model 1. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; HR, hazard ratio; IR, incidence rate; and SEE, systemic embolic event.

incident AF with the risk of SEE in women compared with men. This observation is consistent with the previously described increased risk of stroke among women with AF compared with men with AF, as reflected by the inclusion of female sex in the CHA_2DS_2-VASc score. Sex differences related to risk of SEE could be explained by longer life expectancy since age is the strongest independent risk factor for stroke,[29] or by hormone-based mechanisms as sex-specific hormones vary largely between sexes.[30]

Another aim in our study was to determine the association of the CHA_2DS_2-VASc score with SEE risk in patients with AF, which has not been explored before. CHA_2DS_2-VASc score is recommended to guide decisions about anticoagulant treatment in AF[27] and can be used to guide the screening of AF.[31] Our findings demonstrate good discriminatory capacity and extend the value of the CHA_2DS_2-VASc score to the prediction of SEE in people with AF, underscoring its role in guiding prevention of thromboembolic complications in AF. The results from our study revealed increased incidence rates and hazard risks of SEE as CHA_2DS_2-VASc score increased among participants with AF.

Our study has several strengths. First, the large sample of White and Black adults from 4 different communities in the United States and extended follow-up allowed the identification of numerous participants with AF and SEE. Second, the extensive and rigorous measurement of variables in repeated visits allowed appropriate adjustment for multiple covariates, reducing the risk of confounding. There are some limitations of our study. First, the ascertainment of incident AF required routine ECGs or hospital discharge records, which would lead to missed asymptomatic or paroxysmal AF as well as some AF cases managed outside hospital settings. However, the validity of AF ascertainment is adequate,[11,32] and incidence rates in the ARIC cohort are quite similar to those from other studies with more intensive case ascertainment, such as the Mayo Clinic study and the Framingham Heart Study.[33,34] Second, we used hospital discharge codes to define SEE events, without adjudication by physicians in the ARIC study, which likely led to misclassification of the outcome. However, a prior validation study has demonstrated adequate positive predictive value of this approach.[13] Also, our sensitivity analysis using a more restrictive definition of SEE showed similar association between AF and SEE, or between CHA_2DS_2-VASc score and SEE. Third, some participants did not attend follow-up visits, leading to lack of updated information on time-dependent risk factors, potentially leading to uncontrolled confounding. Fourth, our study only included White and Black adults, questioning the generalizability of our results to individuals of other racial groups. Fifth, anticoagulation use was only ascertained at study visits and we lacked information on the quality of anticoagulation received, with long periods of time in which anticoagulant use would not be captured. Therefore, we were not able to fully evaluate the impact of anticoagulation on the association of AF with SEE risk, which may be different in patients properly anticoagulated. Also, our findings may not generalize to other AF patients experiencing different levels of anticoagulation or anticoagulation with modern direct oral anticoagulants. Finally, we did not perform separate analysis by location of the thromboembolic event because ofthe limited number of events for most locations.

CONCLUSIONS

Our analysis of a large community-based cohort followed for almost 30 years provided evidence that incident AF was associated with a higher risk of SEE compared with people without AF. In addition, people with AF and higher CHA_2DS_2-VASc score had a substantially increased risk of SEE, pointing to a potential pathway in identifying SEE events. This knowledge could help identify patients at high risk of SEE and, eventually, may lead to the development of therapeutic approaches specifically tailored to prevent AF-caused SEE in this patient population. Replication of results in independent studies is recommended.

ARTICLE INFORMATION

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Disclosures

None.

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