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Title: Relation of the CHA₂DS₂-VASc Score to Risk of Thrombotic and Embolic Stroke in Community-Dwelling Individuals Without Atrial Fibrillation (From The Atherosclerosis Risk in Communities [ARIC] Study)

Short title: CHA₂DS₂-VASc Score Stroke Risk without AF

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Abstract

Recent hospital-based cohort studies found the CHA₂DS₂-VASc score to be associated with ischemic stroke in individuals without atrial fibrillation (AF). Our aim was to determine the distribution of embolic and thrombotic strokes and association with the CHA₂DS₂-VASc score, among community-dwelling individuals without AF. We included participants from the Atherosclerosis Risk in Communities (ARIC) Study who attended visit 4 (1996-98) and had no prior AF, stroke, or anticoagulant use (n=10,671). During follow-up through 2008, incident AF cases (n=760) and participants who started warfarin were censored. Incident AF was ascertained from study ECGs and hospital discharge diagnosis codes, and stroke was physician-adjudicated. After 10 years of follow-up, 280 ischemic strokes were identified, of which 146 were thrombotic and 57 embolic. The hazard ratios (95% confidence intervals [CI]) for thrombotic stroke were 1 (reference), 1.71 (1.13-2.59), 2.92 (1.91-4.45), 3.22 (1.70-6.11), and 1.25 (0.17-9.09), with CHA₂DS₂-VASc scores of 0-1, 2, 3, 4, and ≥5, respectively. The hazard ratios (95% CI) for embolic stroke were 1 (ref), 4.91 (2.10-11.5), 7.07 (2.93-17.0), 14.8 (5.50-39.6), and 15.2 (3.16-73.3), with CHA₂DS₂-VASc scores of 0-1, 2, 3, 4, and ≥5, respectively. A receiver-operating characteristic model had a C statistic of 0.65 for ischemic stroke, 0.61 for thrombotic stroke, and 0.71 for embolic stroke. In conclusion, in community-dwelling individuals without AF, the CHA₂DS₂-VASc score can assess ischemic stroke risk and has good discriminatory capacity for embolic stroke.

Key words: Ischemic stroke; CHA₂DS₂-VASc score; Epidemiology

Introduction

The CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease, age 65-74 years, female sex) is widely used to stratify the risk of ischemic stroke in nonvalvular atrial fibrillation (AF).¹ Recent evidence suggests that the CHA₂DS₂-VASc score may also predict ischemic stroke in individuals without AF.²⁻⁶ These studies, however, were comprised of highly-selected individuals, often lacked adjudication of stroke, and did not account for the competing risk of death. Furthermore, the proportion of thrombotic versus embolic strokes were not reported, which could clarify the role for anticoagulation in those without AF. We therefore aimed to evaluate the association of the CHA₂DS₂-VASc score with incident ischemic stroke—paying particular attention to the association with thrombotic and embolic subtypes—among community-dwelling individuals without AF from the Atherosclerosis Risk in Communities (ARIC) study.

Methods

The ARIC study is a prospective community-based cohort study that was designed to investigate the causes of atherosclerosis and its clinical outcomes as well as variation in cardiovascular risk factors, medical care, and disease by race and sex.⁷ From 1987 to 1989 (ARIC study baseline), 15,792 adults (55% women, 45-64 years of age) from 4 US communities (Washington County, MD; suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, NC) were enrolled and underwent a home interview and clinic visit. After the visit 1 examination, there were 4 additional exams: visit 2 (1990–1992), visit 3 (1993–1995), visit 4 (1996–1998) and visit 5 (2011-2013). Refer to **Supplemental Material** for further details.

We included all ARIC participants who attended visit 4 (n = 11,656) (1996-1998).

Visit 4 was used as the baseline because patients were now older and had more cardiovascular risk factors, yielding a wider spread of CHA₂DS₂-VASc scores which facilitated our analyses. Of the visit 4 attendees, we excluded those with prevalent AF or unreadable ECG (n= 524), prevalent stroke (n = 360), and prior anticoagulant use (n=101). After these exclusions, there were 10,671 participants for the main analysis. Participants were censored if they developed AF or began anticoagulant therapy during the follow-up period, regardless of the indication. Figure 1 illustrates the flow of study participants.

AF cases were identified from review of hospital discharge diagnoses.^{8,9} AF during follow-up was defined as International Classification of Disease 9th revision, Clinical Modification [ICD-9-CM] 427.31 or 427.32 diagnosis codes. Hospital diagnosis codes for AF ascertainment have been shown to have good positive predictive value of 98.6%.^{8,10}

Stroke at visit 1 was defined as a self-reported history of physician-diagnosed stroke, while stroke after visit 1 was adjudicated.¹¹ To identify subsequent stroke, cohort participants were followed over time through annual telephone interviews, field center examinations, surveillance of the ARIC community hospitals for all cohort members' hospitalizations, and the review of death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews. The **Supplemental Material** explains how hospitalizations for possible validation of stroke were identified. Once identified, pertinent medical records from hospitalizations were copied and sent to a single nurse abstractor at a central ARIC office who abstracted each record for pertinent information (see **Supplemental Material**). Next, using criteria adopted from the National Survey of Stroke,¹² strokes were classified by computer algorithm and categorized into 1 of 4 main types: SAH, intracerebral hemorrhage, thrombotic brain infarction, or embolic brain infarction (with carotid and non-carotid subtypes) (see **Supplemental Material** for computerized algorithm). In addition to a

computer-determined diagnosis, cases were independently reviewed by a physician, who was provided with all pertinent details from the medical records. Disagreement between the computer and physician classification were adjudicated by a second physician-reviewer. Aside from a classification algorithm (see **Supplemental Material**), physicians also used their own discretion when the clinical picture deviated from the algorithm. Only “definite” but not “probable” ischemic strokes were further classified into thrombotic or embolic subtypes.

For this analysis, covariates included all CHA₂DS₂-VASc score components. Covariates were taken from visit 4. Definitions of the covariates are detailed in the **Supplemental Material**.

In our analysis, the crude 10-year incidence of stroke was calculated for each predictor and CHA₂DS₂-VASc score category. Hazard ratios to assess the association between each variable and stroke were calculated using univariate Cox proportional hazards models. To account for competing risk of death, 1-, 5-, and 10-year absolute risks for ischemic stroke stratified by CHA₂DS₂-VASc categories in participants using the Aalen-Johansen estimator (see **Supplemental Material** for more information).

Results

Of the 10,671 participants (mean age 62.7 years; 57% women; 23% non-whites) included in this 10-year analysis, 280 (2.6%) developed ischemic stroke. The mean follow-up was 9.3±1.9 years. Baseline clinical characteristics of the study are shown in Table 1, stratified by ischemic stroke. Participants who developed ischemic stroke were older and more likely to be non-white, non-female, and on aspirin compared to those who did not

develop ischemic stroke. Additionally, participants who developed ischemic stroke had a higher prevalence of each variable of the CHA₂DS₂-VASc score (except female status).

Table 2 shows the crude 10-year incidence and hazards ratios for ischemic stroke, and thrombotic and embolic subtypes, for each CHA₂DS₂-VASc score category and individual component. With increasing CHA₂DS₂-VASc score, the 10-year incidence of ischemic stroke increased from 1.3 per 1000 person-years (score 0-1) to 8.9 per 1000 person-years (score \geq 5). Similarly, the incidence for both thrombotic (except for score \geq 5) and embolic subtypes increased with increasing CHA₂DS₂-VASc score. With increasing CHA₂DS₂-VASc score, the hazard ratios for ischemic stroke, thrombotic subtype (except for score \geq 5), and embolic subtype also increased, although in a more exponential manner for embolic subtype compared to thrombotic subtype (more linearly). Univariate predictors for ischemic stroke included age 65 to 74, male sex, heart failure, hypertension, diabetes, vascular disease, and aspirin use; univariate predictors of thrombotic stroke included age 65 to 74, male sex, hypertension, diabetes, and vascular disease. Univariate predictors for embolic stroke included age 65 to 74, heart failure, hypertension, and diabetes.

Figure 2 shows that the CHA₂DS₂-VASc score provided moderate discriminatory performance for ischemic and thrombotic stroke, but good discriminatory performance for embolic stroke. The C-statistic (95% CI) was 0.65 (0.62-0.68) for ischemic stroke, 0.61 (0.56-0.65) for thrombotic stroke, and 0.71 (0.65-0.77) for embolic stroke.

Table 3 combines the 1- and 5-year crude incidences of ischemic stroke with the 10-year results. Similar to the 10-year follow up, there was an increasing risk in 1- and 5-year ischemic stroke with increasing CHA₂DS₂-VASc scores. Thrombotic and embolic subtypes were not calculated at 1 or 5 years due to relatively low event rates.

Sensitivity analyses were performed to assess the impact of aspirin and anticoagulant use on these results. Not excluding participants on anticoagulation at baseline or during follow up had a miniscule effect on the results (**Supplemental Table I**) as was also the case after adjusting the main analysis for aspirin (**Supplemental Table II**).

Taking into account the competing risk of death, the 1-year absolute risk of ischemic stroke was 0.1%, 0.4%, 0.3%, and 1.2%, and 3.5% for CHA₂DS₂-VASc scores of 0-1, 2, 3, 4 and 5, respectively. Absolute stroke risks at 5 years were 0.6%, 1.8%, 2.1%, 3%, and 5.2% for CHA₂DS₂-VASc scores 0-1, 2, 3, 4, and ≥ 5 , respectively. Absolute stroke risks at 10 years were 1.2%, 3.1%, 4.6%, 5.8%, and 7%, for CHA₂DS₂-VASc scores 0-1, 2, 3, 4, and ≥ 5 , respectively (Figure 3).

Discussion

In this large cohort of middle-aged, community-dwelling individuals without AF, higher CHA₂DS₂-VASc scores were associated with higher risk of ischemic stroke, including both thrombotic and embolic subtypes. The embolic stroke risk, while low in participants with a CHA₂DS₂-VASc scores of 0-1, increased exponentially in the setting of cumulative risk factors, carrying a 5-fold greater risk at a score of 2 and a 15-fold greater risk at a score of 4. The risk of thrombotic stroke also increased with higher CHA₂DS₂-VASc score but more linearly than in embolic stroke. This suggests that, when combined, the risk factors of the CHA₂DS₂-VASc score have a potentiating effect that markedly increases embolic stroke risk. In addition, the CHA₂DS₂-VASc score demonstrated good discriminatory performance in the prediction of embolic stroke, and modest performances for ischemic and thrombotic stroke. The findings of this study suggest that the CHA₂DS₂-VASc score may be useful as a prediction tool for ischemic stroke, including embolic stroke, in people without AF.

For patients with AF, current guidelines recommend anticoagulation for a CHA₂DS₂-VASc of 2 (and higher), which confers a 2.2% per year stroke risk, although anticoagulation can be considered for a score of 1, which confers a 1.3% per year stroke risk.¹³ In our present study of non-AF individuals, after accounting for the competing risk of death, the 1-year absolute risks of ischemic stroke were 1.2% and 3.5% for CHA₂DS₂-VASc scores of 4 and \geq 5, respectively. Further, we have demonstrated that embolic stroke risk—in which anticoagulation would be particularly useful—increases exponentially in non-AF participants with increasing CHA₂DS₂-VASc scores. Collectively, these findings suggest that antithrombotic therapy may be useful at a CHA₂DS₂-VASc score of \geq 5 in non-AF patients, although further studies evaluating their effect would be needed.

The mechanisms by which CHA₂DS₂-VASc risk factors contribute to the pathogenesis of thromboembolism in AF are not well understood. Conventional wisdom holds that in the absence of the dysrhythmia of AF, these vascular risk factors *per se* do not increase the risk of thromboembolism; AF is often presumed to be a necessary instigating factor for thromboembolism. In our study, however, the association between increasing CHA₂DS₂-VASc score and increasing risk of embolic stroke was observed in the absence of AF. This observation suggests that these risk factors, in and of themselves, may be intrinsically pro-thrombotic. This is supported by studies showing that maintenance of sinus rhythm versus a rate-control strategy does not reduce the risk of stroke.¹⁴ Also, studies assessing subclinical AF in patients with implanted cardiac devices (e.g. pacemakers and defibrillators) have shown an increased risk of stroke with higher AF burden, but have failed to show a temporal relationship between the timing of AF events and stroke.^{15,16} Studies have also shown paroxysmal supraventricular tachycardias to be associated with stroke, although the mechanism and causality of this relationship remains unclear.¹⁷ Finally, ECG-defined left

atrial abnormalities and left atrial enlargement have been shown to be associated with ischemic stroke, independent of AF.^{11,18,19}

The principal strengths of our study include a prospective community-based investigation with meticulous physician-adjudication of ischemic stroke, including classification of thrombotic and embolic stroke. Other strengths include inclusion of community non-white participants, extensive measurement of covariates, and large number of participants. Several limitations need to be considered. First, the higher CHA₂DS₂-VASc categories had a small number of events, and thus were combined. Second, it is possible that non-hospitalized stroke events that were not validated in the study could influence the results, although underestimation of the rate of stroke is estimated to be small (<5%).²⁰ Third, we recognize that the criteria for classifying embolic stroke were not as rigorous compared to those currently recommended, and the classification for cryptogenic stroke was not used in the study.²¹ Fourth, adjustment for aspirin did not affect our results, which was unexpected in that it should have been associated with fewer thrombotic strokes. Finally, AF was identified mostly from hospitalization discharges in ARIC and we could not include asymptomatic AF or AF managed exclusively in an outpatient setting. However, prior analysis within the ARIC cohort to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in AF ascertainment,⁹ and that incidence rates of AF in ARIC are consistent with other population-based studies.²²⁻²⁴

In conclusion, the CHA₂DS₂-VASc score may be used to assess the risk of ischemic stroke, including both thrombotic and embolic subtypes, in community-dwelling people without AF. Our findings will need to be replicated in other cohorts. If replicated, further research would be needed to determine whether anticoagulant use in certain individuals

without AF but with high CHA₂DS₂-VASc risk scores would reduce the risk of ischemic stroke.

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Figure Legends

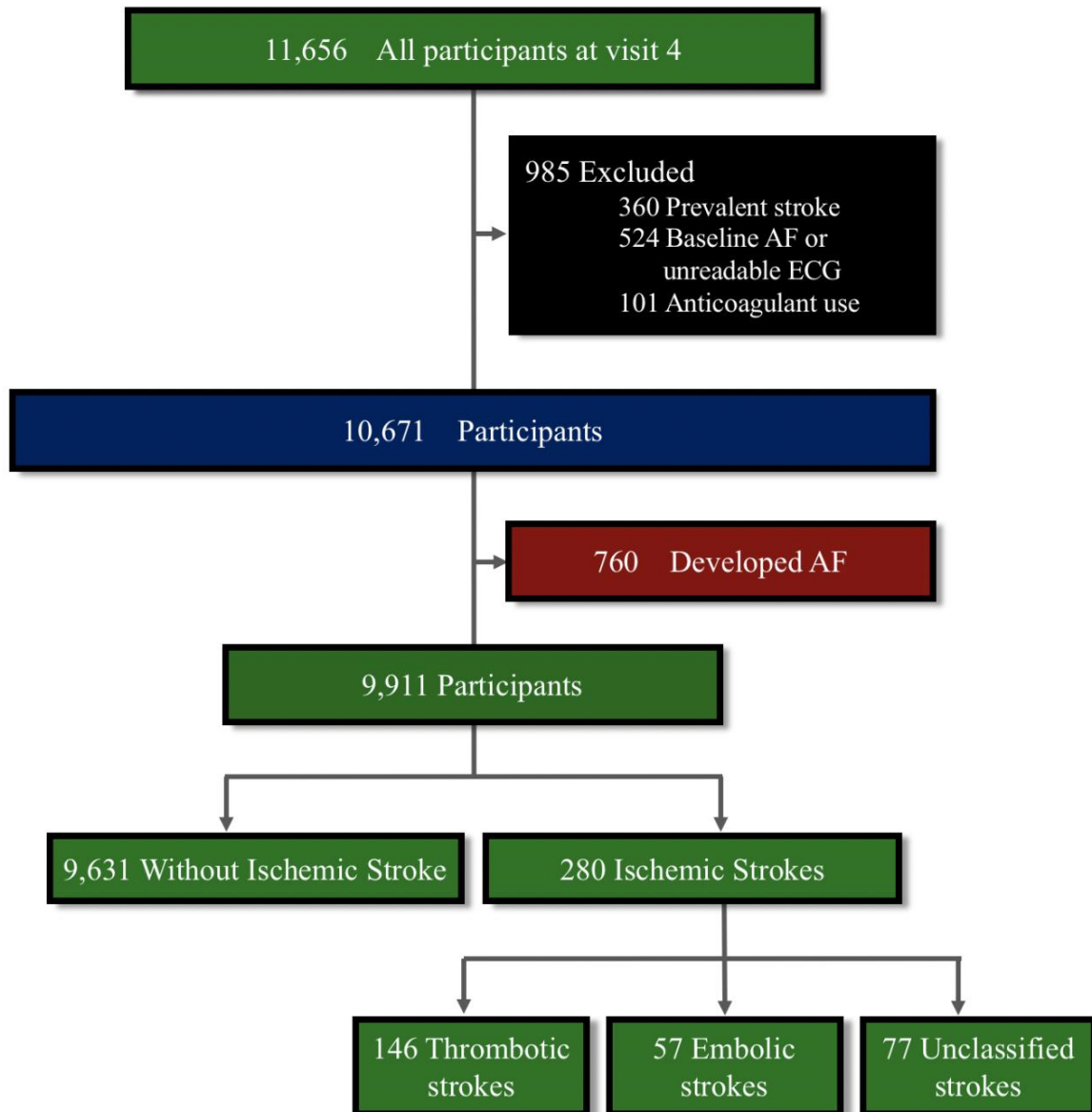


Figure 1. Participant selection flowchart.

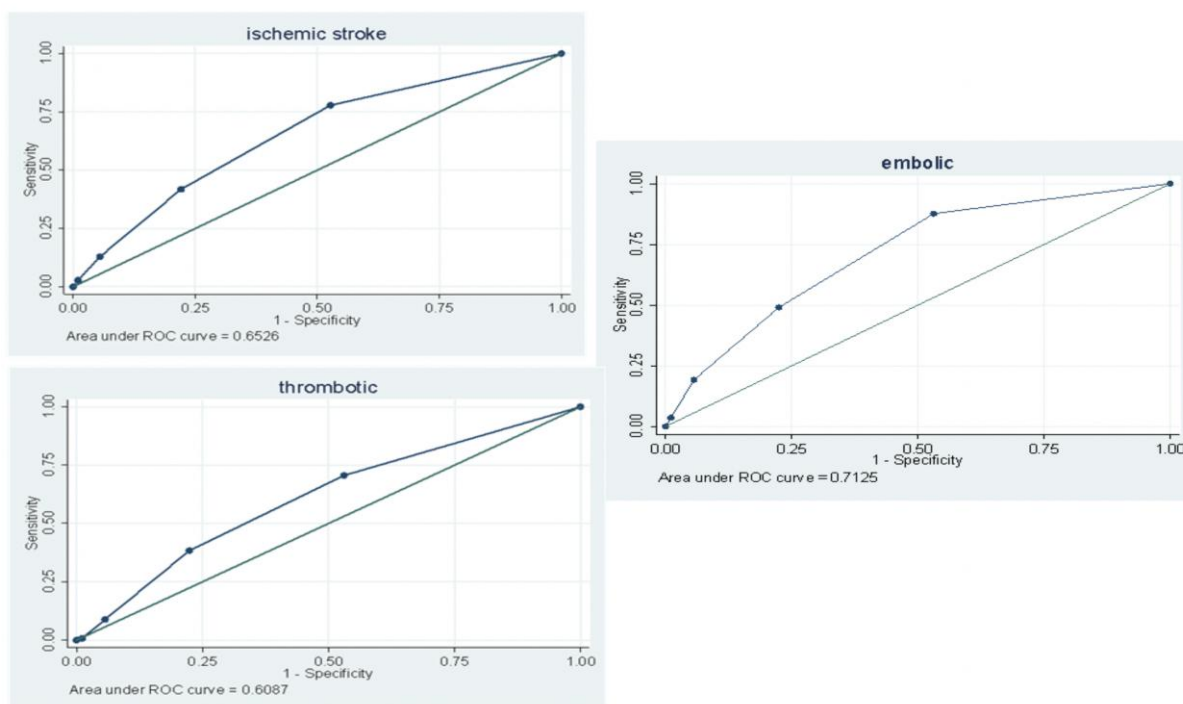


Figure 2. Receiver operating characteristic curves for the CHA₂DS₂-VASc scores for prediction of ischemic stroke, thrombotic stroke, and embolic stroke in participants without atrial fibrillation.

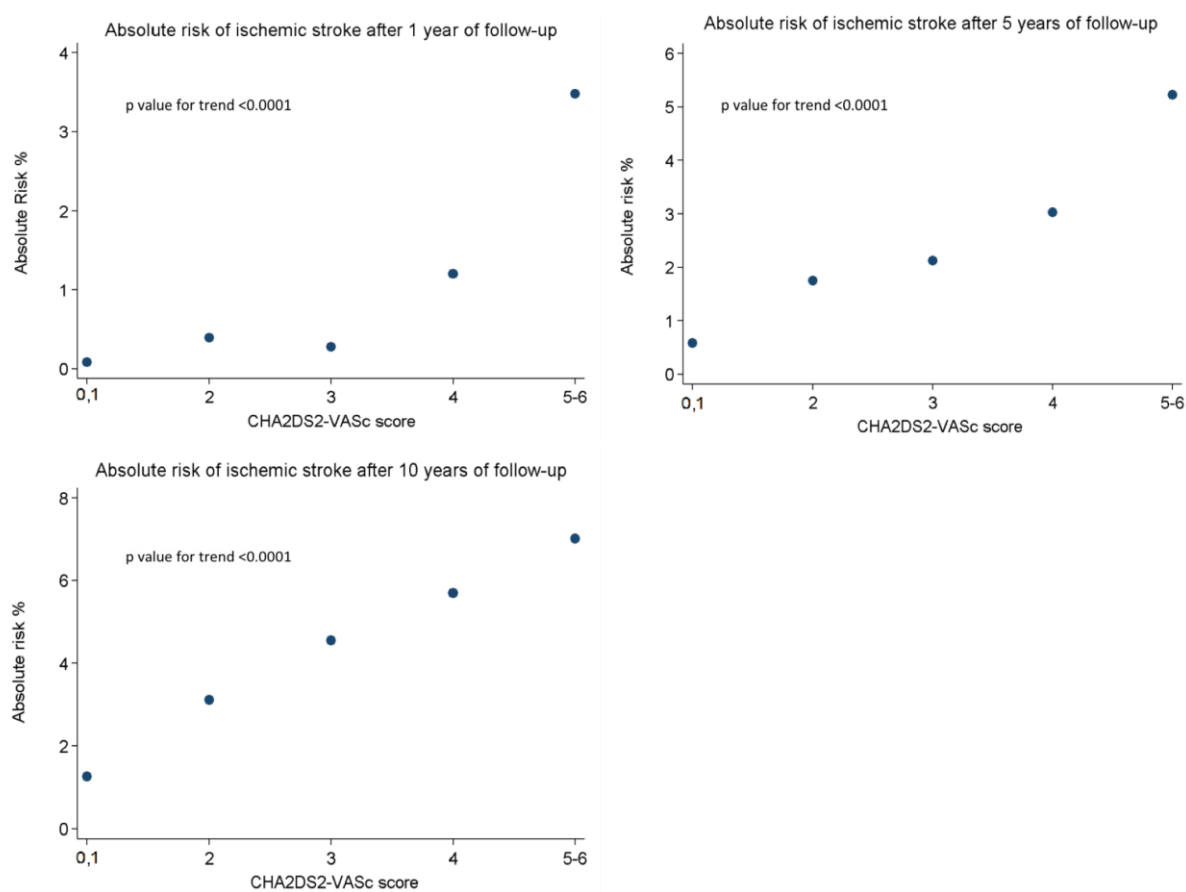


Figure 3. Absolute ischemic stroke risks by CHA2DS2-VASc risk score during 1-, 5-, and 10- years of follow-up, accounting for competing risk of death.

Table 1. Baseline Characteristics of Participants without Atrial Fibrillation† in the Atherosclerosis Risk in Communities (ARIC) Study at Visit 4 (1996-98), stratified by future ischemic stroke

	No AF (n= 10,671)	Ischemic stroke (within 10 years) (n=280)	No stroke (within 10 years) (n=10,391)
Mean age (SD), years	62.7 (5.6)	65.1 (5.6)	62.6 (5.6)
Non-white race	2435 (23%)	99 (35%)	2336 (22%)
Female	6039 (57%)	134 (48%)	5905 (57%)
Hypertension	4936 (46%)	187 (67%)	4749 (46%)
Hyperlipidemia	5897 (55%)	158 (56%)	57339 (55%)
Diabetes mellitus	1699 (16%)	89 (32%)	1610 (15%)
Heart failure	470 (4%)	24 (9%)	446 (4%)
Peripheral arterial disease / MI	861 (8%)	49 (18%)	812 (8%)
Coronary heart disease	788 (7%)	26 (16%)	742 (7%)
CHA ₂ DS ₂ VASc score	1.7 (1.1)	2.3 (1.1)	1.7 (1.1)
Aspirin use	5968 (56%)	184 (66%)	5784 (56%)
Statin use	1168 (11%)	35 (13%)	1133 (11%)

AF is for atrial fibrillation; MI, myocardial infarction

† Also excluding anticoagulant use at baseline (n=101)

Medication history was obtained by self-report of medication intake during the prior 2 weeks before Visit 4 and by reviewing medications brought by the participants to the Visit

Table 2. Univariate analysis and incidence rates per 1,000 person-years for ischemic stroke, thrombotic stroke, and embolic stroke in participants without atrial fibrillation,† Atherosclerosis Risk in Communities Study, (1996-2005)

	Ischemic stroke		Thrombotic stroke‡		Embolic stroke‡	
Events within 10 yrs	280		146		57	
Incidence rates	2.8		1.5		0.58	
Individual predictors	Incidence	HR (95% CI)	Incidence	HR (95% CI)	Incidence	HR (95% CI)
Age ≥75§	--	--	--	--	--	--
Age 65-74 vs. <65	4.3	2.22 (1.75-2.81)	2.1	1.89 (1.37-2.62)	1.0	3.13 (1.82-5.39)
Male vs. female sex	3.5	1.48 (1.17-1.87)	1.8	1.52 (1.10-2.11)	0.55	0.92 (0.54-1.56)
Heart failure	6.2	2.29 (1.51-3.48)	1.8	1.24 (0.58-2.65)	2.3	4.59 (2.25-9.36)
Hypertension	4.2	2.42 (1.89-3.11)	1.9	1.78 (1.28-2.48)	0.91	3.09 (1.73-5.51)
Hyperlipidemia	2.9	1.04 (0.82-1.32)	1.6	1.15 (0.83-1.60)	0.44	0.61 (0.37-1.03)
Diabetes mellitus	6.0	2.64 (2.05-3.40)	3.2	2.71 (1.91-3.83)	1.2	2.62 (1.50-4.59)
Vascular disease	6.7	2.68 (1.97-3.65)	2.7	2.02 (1.26-3.24)	1.1	2.07 (0.98-4.37)
Aspirin	3.3	1.54 (1.20-1.97)	1.6	1.29 (0.93-1.80)	0.63	1.28 (0.75-2.18)
Statin use	3.3	1.18 (0.83-1.69)	1.7	1.17 (0.71-1.91)	0.37	0.61 (0.22-1.69)
CHA2DS2-VASc						
0-1 reference	1.3	1 (ref)	0.91	1 (ref)	0.15	1 (ref)
2	3.3	2.54 (1.85-3.49)	1.6	1.71 (1.13-2.59)	0.72	4.91 (2.10-11.5)
3	5.0	3.80 (2.73-5.28)	2.6	2.92 (1.91-4.45)	1.0	7.07 (2.93-17.0)
4	6.8	5.16 (3.30-8.06)	2.9	3.22 (1.70-6.11)	2.2	14.8 (5.50-39.6)
≥5	8.9	6.84 (3.27-14.3)	1.1	1.25 (0.17-9.09)	2.2	15.2 (3.16-73.3)

Abbreviations: HR, hazard ratios

† Excluding and censoring anticoagulant use at baseline and follow up

‡ Incidence rates for thrombotic and embolic stroke includes “definite” stroke only; ischemic stroke incidence includes “definite” as well as “probable” stroke.

§ Insufficient data (only 1 patient was aged ≥75 at baseline)

Table 3. Incidence rates per 1,000 person-years for ischemic stroke in participants without AF based on CHA₂DS₂-VASc risk score at 1 year, 5 years, and 10 years of follow-up.[†] Atherosclerosis Risk in Communities Study

	CHA ₂ DS ₂ -VASc score				
	0-1	2	3	4	≥5
No AF, Number of participants	4976	3282	1800	498	115
1 Year of follow-up					
# of Ischemic stroke events	4	13	5	6	4
Person-years	4959	3266	1790	489	114
Incidence rate (95% CI)	0.81 (0.27-1.92)	3.98 (2.23-6.61)	2.79 (1.06-6.12)	12.3 (5.10-25.3)	35.1 (11.7-83.4)
5 Years of follow-up					
# of Ischemic stroke events	29	57	38	15	6
Person-years	24407	15874	8660	2299	523
Incidence rate (95% CI)	1.19 (0.81-1.68)	3.59 (2.75-4.62)	4.39 (3.15-5.96)	6.52 (3.81-10.5)	11.5 (4.8-23.6)
10 Years of follow-up					
# of Ischemic stroke events	62	101	81	28	8
Person-years	47370	30351	16310	4151	897
Incidence rate (95% CI)[‡]	1.31 (1.01-1.67)	3.33 (2.73-4.03)	4.97 (3.97-6.14)	6.75 (4.58-9.61)	8.9 (4.20-16.8)

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

[†] Excluding and censoring anticoagulant use at baseline and follow up[‡] The data in this row was also reported in Table 2The p-value for trend of the CHA₂DS₂-VASc score for ischemic stroke was <0.0001 for the 1, 5, and 10 year follow-up years