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ORIGINAL RESEARCH

Association Between Age at Diagnosis of Atrial Fibrillation and Subsequent Risk of Ischemic Stroke

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BACKGROUND: Atrial fibrillation (AF) significantly increases the ischemic stroke risk. However, the relationship between age at diagnosis of AF and subsequent stroke risk remains poorly understood.

METHODS AND RESULTS: We analyzed data from 5 prospective cohorts: ARIC (Atherosclerosis Risk in Communities) study, CHS (Cardiovascular Health Study), CARDIA (Coronary Artery Risk Development in Young Adults), MESA (Multi-Ethnic Study of Atherosclerosis), and Framingham Heart Study (including Offspring cohort and the Third-Generation cohorts). Cox regression models and competing risk survival analyses were used to assess incidence rates and hazard ratios (HRs) for ischemic stroke stratified by age groups. Among 47 239 participants (median follow-up: 21.1 years), 6689 (14.2%) developed AF, and 536 (8.0%) subsequently experienced ischemic stroke. Younger age at AF diagnosis was significantly associated with a higher ischemic stroke risk. Fully adjusted HRs for ischemic stroke were 5.35 (95% CI, 3.56–8.03), 2.99 (95% CI, 2.32–3.86), 2.13 (95% CI, 1.75–2.58), and 1.93 (95% CI, 1.59–2.34) for AF diagnosed at ages 55, 65, 75, and 85, respectively. Compared with participants without AF at age 55, HRs for ischemic stroke were 7.30 (95% CI, 3.27–16.31) for AF diagnosed >10 years earlier, 4.98 (95% CI, 2.99–8.29) for 6 to 10 years earlier, and 4.60 (95% CI, 1.48–14.34) for ≤5 years earlier (*P*-trend <0.001). The presence of AF yielded a 13.9 years earlier occurrence of ischemic stroke among those with AF diagnosis at 55 years compared with 1.5 years earlier at age 85.

CONCLUSIONS: Younger age at AF diagnosis was associated with a higher risk of subsequent ischemic stroke.

Key Words: age at diagnosis ■ atrial fibrillation ■ ischemic stroke

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia globally, with a rising incidence and prevalence.[1,2] Patients with AF face a 5-fold higher risk of stroke.[3] The prevalence of AF escalates with age, starting at 0.1% in individuals <55 years and reaching 9.0% in those aged 80 years or older.[4] Age has been well recognized as a major risk factor of ischemic stroke in patients with AF and is included in all stroke risk stratification schemes.[5] The annual incidence of stroke over a 1-year (5-year) follow-up period among patients with AF increases with age, with rates of 1.2% (0.6%), 3.5% (1.6%), and 5.6% (2.8%) in the age groups of 30 to 50, 50 to 65, and 65 to 75, respectively.[6] Therefore, more attention has been paid in an older population

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CLINICAL PERSPECTIVE

What Is New?

- Younger age at atrial fibrillation diagnosis is associated with a significantly higher risk of ischemic stroke, with the highest risk observed among individuals diagnosed with atrial fibrillation at age 55, highlighting the importance of early risk stratification and management.

What Are the Clinical Implications?

- This study underscores the need for early diagnosis and aggressive stroke prevention strategies, and proactive stroke prevention strategies, including anticoagulation and risk factor management, particularly in younger patients with atrial fibrillation, as their long-term stroke risk is disproportionately higher compared with those diagnosed at older ages.

whereas the impact of early-onset AF on later-life stroke risk was often overlooked.

Recent years have seen an increasing AF incidence at young age[7] especially in those with concomitant congenital heart diseases.[8] Historically early-onset AF was often categorized as "lone" AF, implying an absence of comorbidities and AF risk factors.[9] Yet a recent study elucidated that 44% of early-onset AF had hypertension and 9% had concomitant HF, whereas only 11% occurs without identifiable comorbidities or risk factors.[10] In addition, patients with early-onset AF may also have higher stroke risks compared with later-onset AF. Among patients with AF and a CHA_2DS_2-VASc score of 1 point, the hazard ratio (HR) of stroke decreased with age: 2.81 (95% CI, 1.81–4.35) for the 30 to 50 years group, 1.25 (95% CI, 1.09–1.45) for the 50 to 65 years group, and 1.14 (95% CI, 1.03–1.27) for the 65 to 75 years group.[6] A similar trend was also observed among patients with a CHA_2DS_2-VASc of 2 or 3 points,[6] indicating a higher incident stroke risk in younger age groups compared with groups with advanced age. However, studies on the association between age at diagnosis of AF and subsequent ischemic stroke risks remain sparse, and no current guideline considers age at diagnosis as an important stroke risk stratifier. Therefore, this study aims to investigate the associations between age at diagnosis of AF and the risks of ischemic stroke in 5 large-scale cohorts.

METHODS

Study Population

To investigate the relationship between AF and ischemic stroke, we conducted a prospective cohort study. Five prospective cohorts were included in our analysis: ARIC (Atherosclerosis Risk in Communities),[11] CHS (Cardiovascular Health Study),[12] CARDIA (Coronary Artery Risk Development in Young Adults),[13] MESA (Multi-Ethnic Study of Atherosclerosis, 2000–2012),[14] and FHS (Framingham Heart Study)[15] (including 2 subcohorts: the Offspring cohort[16] and the Third-Generation cohorts[17]). The sample selection flow chart is shown in Figure S1, and detailed introductions to each cohort are presented in Data S1. Participants were excluded if they had a history of ischemic stroke at baseline or if history of stroke was unknown. The final sample size comprised 47 239 individuals.

All study protocols were approved by the institutional review boards at participating institutions and all participants provided written informed consent. Ancillary study approvals and data use agreements were also obtained from each parent study. As the current study used only deidentified data with no additional patient contact, no additional ethical approval or patient consent was required. The data sets used and analyzed in this study are available from the corresponding author upon reasonable request.

AF Exposure Definition

The date of AF at diagnosis was defined as the date when AF was first identified through ECG, or the first hospital discharge coded as AF.[11] The *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code for hospital discharge includes 427.31 (AF) or 427.32 (atrial flutter).[11] AF associated with cardiothoracic surgery was excluded.

Ischemic Stroke Outcome Definition

All stroke cases were confirmed by trained physicians during follow-up using surveillance, hospital *ICD-9* codes 430 to 438 until 1997, and *ICD-9* codes 430 to 436 afterwards or by death certificates.[18,19] Ischemic stroke was distinguished from hemorrhagic stroke among confirmed strokes when assessment of computed tomography or magnetic resonance imaging brain scans indicated no sign of cerebral hemorrhage. Only ischemic stroke was included in our analysis.

Statistical Analysis

Descriptive statistics for continuous variables included mean±SD or median (interquartile range), and categorical variables were presented as counts and percentages. Chi-square tests were used for the categorical variables and 2-sided Student's *t* test or nonparametric Wilcoxon *U* tests for the continuous variables.

Data on exposure at age 55, 65, 75, and 85 years were extracted from the 5 cohorts. For example, AF

diagnosis at age 55 includes participants diagnosed with AF on or before age 55. Follow-up began at ages 55, 65, 75, and 85, respectively, regardless of AF status. Participants reached the study end point at the first occurrence of either ischemic stroke or death. The incidence rates of ischemic stroke were calculated as the ratio of events to the accumulated person-time of follow-up for participants and reported as rates per 1000 person-years.

The analysis was consistent with previous methodologies.[20] Specifically, Cox regression analysis was performed to investigate the association between the presence of AF at different ages (at age 55, 65, 75, and 85 years) with the reference group at each age being participant free of AF at that specific age. For instance, in the age 55 group, participants with a diagnosis of AF at that age were considered as AF cases, whereas those without AF or who developed AF after 55 years old as non-AF cases. Proportional hazards assumption was examined via Schoenfeld residuals test. The HRs and 95% CIs of developing ischemic stroke were calculated. Three models were fit: in model 1, only the study cohort was adjusted; in model 2, sociodemographic variables (age, sex, race, and education) and study cohort were adjusted; model 3 additionally adjusted for health behaviors (alcohol consumption, current smoking status), health-related variables (systolic blood pressure, diastolic blood pressure, body mass index, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), history of cardiovascular diseases (hypertension, diabetes, coronary heart disease, and chronic heart failure), and use of cardiovascular medication (digitalis, antiarrhythmics, and oral anticoagulants).

Besides AF status at ages 55, 65, 75, and 85 years, we also examined AF and covariates as a time-varying measure. In addition, we performed analyses by using 5-year age bands for the diagnosis of AF. For example, at age 65 years the group defined as non-AF at age 65 was compared with a group diagnosed with AF at less than 5 years earlier, 6 to 10 years earlier, and more than 10 years earlier. Additionally, the association between every 5-year younger age at AF diagnosis and incident ischemic stroke was also evaluated.

To further explore the effects of younger age at diagnosis on the incidence of ischemic stroke across different age group, the years since AF diagnosis index date were calculated and divided into 0 to 2.5, 2.5 to 5, 5 to 7.5, 7.5 to 10, and >10 years. The expected ischemic stroke was derived from a separate Cox regression model fitted to individuals with AF versus controls as the only independent variable within each age group. Age was used as the timescale, with death counted for censoring. The conditional median expected ischemic stroke was estimated from the upper limit of each age interval. We fitted second-order fractional polynomial models using years since index date for each participant and each age group. Robust variance estimates were used to account for clustering of observations by participant. Models were fitted using the mfp command in Stata.

For sensitivity analysis, participants who died over the follow-up were censored at date of death to account for competing risk of death by using the Fine–Gray subdistribution hazard model.[21] The association between AF and ischemic stroke was further investigated, stratified by sex (female, male) and race (White, Black) for analysis.

All analyses were performed with Stata version 15.0 (Stata Corp). $P<0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics

A total of 47 239 participants were included in this study, and their characteristics at the end of the follow-up period are presented in Table 1. During a median follow-up period of 21.1 years (interquartile range, 13.8–28.7), 3460 (7.3%) participants were diagnosed with ischemic stroke. These individuals tended to be older, have lower education attainment, and exhibit a poorer cardiovascular risk profile.

Incidence Rate of Ischemic Stroke

During the follow-up period, 6689 participants (14.2%) developed AF, among whom 536 (8.0%) were subsequently diagnosed with ischemic stroke (Table 2).

Participants with AF have higher incidence rate of ischemic stroke compared with those without AF across all age categories (at ages 55, 65, 75, and 85 years). Furthermore, the incidence rate of ischemic stroke increased with age. Older participants exhibited higher incidence rate of ischemic stroke compared with younger participants regardless of AF status. Specifically, the incidence rate of ischemic stroke among the participants with AF diagnosed at ages 55, 65, 75, and 85 years were 12.16, 12.03, 15.39, and 28.96 per 1000 person-years, respectively.

Given that the majority of AF cases (5502 of 6689, 82.3%) occurred after the age of 65, all AF cases were analyzed by considering AF and covariates as time-varying measures. The ischemic stroke rates were 7.01 per 1000 person-years for individuals with AF compared with 2.61 per 1000 person-years for those without AF.

Risk of Ischemic Stroke Across Different Ages at AF Diagnosis

The risks of ischemic stroke across different ages at AF diagnosis are shown in Table 2 and Figure 1. Although the incidence of ischemic stroke is lower in younger age

Table 1. Characteristics of Participants According to Status of Ischemic Stroke at the End of the Follow-Up

Participant characteristics at the end of follow-up	Status of ischemic stroke		*P* value
	Ischemic stroke (n=3460)	No ischemic stroke (n=43779)	
Age, y	74.8 (11.0)	71.9 (13.5)	<0.001
Male sex, %	1605 (46.4)	20023 (45.7)	0.46
Race, White, %	2692 (77.8)	32945 (75.3)	0.81
Education, %			
<High school	990 (29.3)	7263 (17.5)	<0.001
High school/vocational school	1505 (44.5)	15399 (37.1)	
College, graduate, or professional school	890 (26.3)	18853 (45.4)	
Alcohol drinking, %	1993 (57.6)	26087 (59.6)	0.02
Current smoking, %	839 (24.3)	10738 (24.5)	0.71
Hypertension, %	1168 (33.8)	8790 (20.1)	<0.001
Diabetes, %	536 (15.5)	3292 (7.5)	<0.001
Atrial fibrillation, %	1132 (33.2)	5557 (12.8)	<0.001
Body mass index, kg/m^2	27.4 (5.0)	26.7 (5.1)	<0.001
Blood pressure, mm Hg			
Systolic	135.5 (23.4)	123.5 (20.0)	<0.001
Diastolic	77.9 (13.9)	74.2 (11.6)	<0.001
Laboratory findings, mg/dL			
Total cholesterol	214.6 (42.1)	202.3 (41.5)	<0.001
Low-density lipoprotein-cholesterol	135.4 (38.0)	125.0 (37.1)	<0.001
High-density lipoprotein-cholesterol	50.0 (15.8)	52.3 (15.9)	<0.001
Triglycerides	142.1 (96.0)	120.2 (86.3)	<0.001
Fasting blood glucose	110.4 (47.5)	99.6 (31.6)	<0.001
Use of cardiac medications, %			
Digitalis	488 (14.1)	2065 (4.7)	<0.001
Antiarrhythmics	246 (7.1)	1185 (2.7)	<0.001
Anticoagulants	510 (14.7)	2176 (5.0)	<0.001

Data are presented as mean±SD or No. (percentage) of participants.

groups, the highest risk is observed among individuals with AF diagnosed at age 55. The risk of ischemic stroke decreases as the age at diagnosis increases, with the fully adjusted HRs of 5.35 (95% CI, 3.56–8.03) for diagnoses at age 55, 2.99 (95% CI, 2.32–3.86) at age 65, 2.13 (95% CI, 1.75–2.58) at age 75, and 1.93 (95% CI, 1.59–2.34) at age 85, respectively. The findings remained consistent when considering death as a competing risk (Table S1). We observed a declining trend in the risk of ischemic stroke as the age at AF diagnosis increased, with HRs decreasing from 2.98 (95% CI, 1.77–5.02) at age 55 to 2.06 (95% CI, 1.51–2.82) at age 65. However, there was a slight increase in the risk at age 85 (HR, 1.55 [95% CI, 1.25–1.93]), compared with age 75 (HR, 1.29 [95% CI, 1.01–1.64]).

In addition, an earlier age at AF diagnosis was strongly associated with incident ischemic stroke, as shown by the test for linear trend (all *P*<0.001 in Table 3). For instance, in fully adjusted analyses compared with individuals without AF at age 55, AF diagnosed from 0 to 5 years earlier (HR, 4.60 [95% CI, 1.48–14.34]; incidence rate, 11.6/1000 person-years), 6 to 10 years earlier (HR, 4.98 [95% CI, 2.99–8.29]; incidence rate, 11.3/1000 person-years) and >10 years earlier (HR, 7.30 [95% CI, 3.27–16.31]; incidence rate, 15.4/1000 person-years), was significantly associated with subsequent ischemic stroke. When AF status was confirmed at age 85, the HR of ischemic stroke in participants with AF diagnosed more than 10 years earlier was 2.33 (95% CI, 1.66–3.28, ischemic stroke incidence rate, 34.04/1000 person-years), in participants with AF diagnosed 6 to 10 years earlier the HR was 1.76 (95% CI, 1.36–2.28; stroke rate, 26.98/1000 person-years), and in participants with AF diagnosed 0 to 5 years earlier the HR was 1.42 (95% CI, 0.78–2.59; stroke rate, 17.59/1000 person-years). Every 5-year younger age at AF diagnosis was significantly associated with an increased risk of ischemic stroke, with the highest HR observed at age 55 (2.10 [95% CI, 1.76–2.51]), followed by age 65 (HR, 1.70 [95% CI, 1.51–1.93]) and age 75

Table 2. Association of AF Status at 55, 65, 75, and 85 Years and Over the Total Follow-Up With the Risk of Ischemic Stroke

	No AF	AF
At age 55 y (median [IQR] follow-up: 21.4 [12.4–28.8] y)		
Ischemic stroke cases/total	3411/46 869	49/370
IR (per 1000 person-years)	3.81	12.16
Model 1, HR (95% CI)	1.00 (Ref.)	6.23 (4.16–9.33)
Model 2, HR (95% CI)	1.00 (Ref.)	5.55 (3.70–8.32)
Model 3, HR (95% CI)	1.00 (Ref.)	5.35 (3.56–8.03)
At age 65 y (median [IQR] follow-up: 14.3 [8.6, 20.5] y)		
Ischemic stroke cases/total	3287/46 052	173/1187
IR (per 1000 person-years)	5.63	12.03
Model 1, HR (95% CI)	1.00 (Ref.)	3.32 (2.58–4.28)
Model 2, HR (95% CI)	1.00 (Ref.)	3.16 (2.45–4.07)
Model 3, HR (95% CI)	1.00 (Ref.)	2.99 (2.32–3.86)
At age 75 y (median [IQR] follow-up: 8.0 [3.9, 12.8] y)		
Ischemic stroke cases/total	2962/44 127	498/3112
IR (per 1000 person-years)	9.23	15.39
Model 1, HR (95% CI)*	1.00 (Ref.)	2.25 (1.85–2.73)
Model 2, HR (95% CI)†	1.00 (Ref.)	2.23 (1.83–2.70)
Model 3, HR (95% CI)‡	1.00 (Ref.)	2.13 (1.75–2.58)
At age 85 y (median [IQR] follow-up: 4.0 [1.9, 6.7] y)		
Ischemic stroke cases/total	2523/41 678	937/5561
IR (per 1000 person-years)	16.80	28.96
Model 1, HR (95% CI)	1.00 (Ref.)	1.81 (1.49–2.19)
Model 2, HR (95% CI)	1.00 (Ref.)	2.02 (1.66–2.45)
Model 3, HR (95% CI)	1.00 (Ref.)	1.93 (1.59–2.34)
Overall (AF and covariates as time varying measures) (median [IQR] follow-up: 21.1 [13.8, 28.7] y)		
Ischemic stroke cases/total	2280/40 059	1132/6689
IR (per 1000 person-years)	2.61 (2.50–2.72)	7.01 (6.61–7.43)
Model 1, HR (95% CI)	1.00 (Ref.)	2.70 (2.50–2.91)
Model 2, HR (95% CI)	1.00 (Ref.)	1.78 (1.65–1.91)
Model 3, HR (95% CI)	1.00 (Ref.)	1.58 (1.47–1.71)

AF indicates atrial fibrillation; HR, hazard ratio; IQR, interquartile range; and IR, incidence rate.

*Model 1: Adjusted for study cohort.

†Model 2: Adjusted for age, sex, race, and study cohort.

‡Model 3: Model 2+systolic blood pressure, diastolic blood pressure, education, alcohol drinking, smoking status, body mass index, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, history of hypertension, diabetes, coronary heart disease and chronic heart failure, use of digitalis, antiarrhythmics, anticoagulants, and study cohort.

(HR, 1.46 [95% CI, 1.31–1.63]). Notably, the lowest HR was observed at age 85 (HR, 1.33 [95% CI, 1.22–1.45]) in fully adjusted analyses.

Those with younger age at AF diagnosis were younger at onset of ischemic stroke (Figure 2). At age ≤55, the absence of AF yielded a 13.9-year delay in the occurrence of ischemic stroke. However, the magnitude of this gap diminished in older age groups, with the absence of AF only causing a 1.5-year delay in ischemic stroke compared with those with AF diagnosed at age 85.

Risk of Ischemic Stroke Over Time Since AF Index Date

The risk of ischemic stroke in relation to years since AF diagnosis index date is presented in Figure 3. The risks of ischemic stroke were significantly higher in the individuals that with a diagnosis of AF at younger age, with those who diagnosed at age 55 exhibiting the highest risk. Within 2.5 years of follow-up, the HRs of ischemic stroke for AF diagnosed at ages 55, 65, 75, and 85 were 11.34 (95% CI, 4.94–26.01), 3.98 (95% CI, 2.31–6.88), 2.81 (95% CI, 1.96–4.05), and 2.18 (95% CI, 1.57–3.02), respectively. Notably, the risk estimates gradually decreased with every additional 2.5 years past the index date of AF diagnosis across all age groups, indicating a diminishing risk over time.

Stratified Analyses by Sex and Race

The consistent nature of these findings was preserved across stratified analyses based on sex and race. When treating AF and covariates as time-varying measures, no notable disparities in the risk of ischemic stroke were observed between men and women (P=0.09, Table S2). However, it is worth noting that the presence of AF was associated with a heightened risk of ischemic stroke in White people compared with Black people (HR, 1.63 [95% CI, 1.51–1.77] versus 1.37 [95% CI, 1.13–1.68]; P=0.002, as presented in Table S3).

DISCUSSION

In this large-scale study involving 47 239 participants, we found that younger age at diagnosis of AF was significantly associated with a higher risk of ischemic stroke. Each 5-year earlier diagnosis of AF corresponded to an increased risk of ischemic stroke, a trend that remained robust across sex-stratified analyses. In addition, participants with younger age at AF diagnosis were younger at onset of ischemic stroke. At age ≤55, the absence of AF yielded a 13.9-year delay in the occurrence of ischemic stroke, compared with only a 1.5-year delay in ischemic stroke with AF diagnosed at age 85. Notably, the ischemic stroke risk declined with each 2.5-year increase since AF onset, indicating a diminishing risk over time. Altogether, our study underscores the pivotal role of age at AF diagnosis in influencing subsequent ischemic stroke risk.

Our study aligns with previous research indicating that younger age at AF diagnosis is associated with a higher risk of ischemic stroke. A recent Danish study found the highest stroke risk in patients diagnosed with AF at age 50 or younger and observed a U-shaped risk pattern across age groups.[22] In contrast, our findings

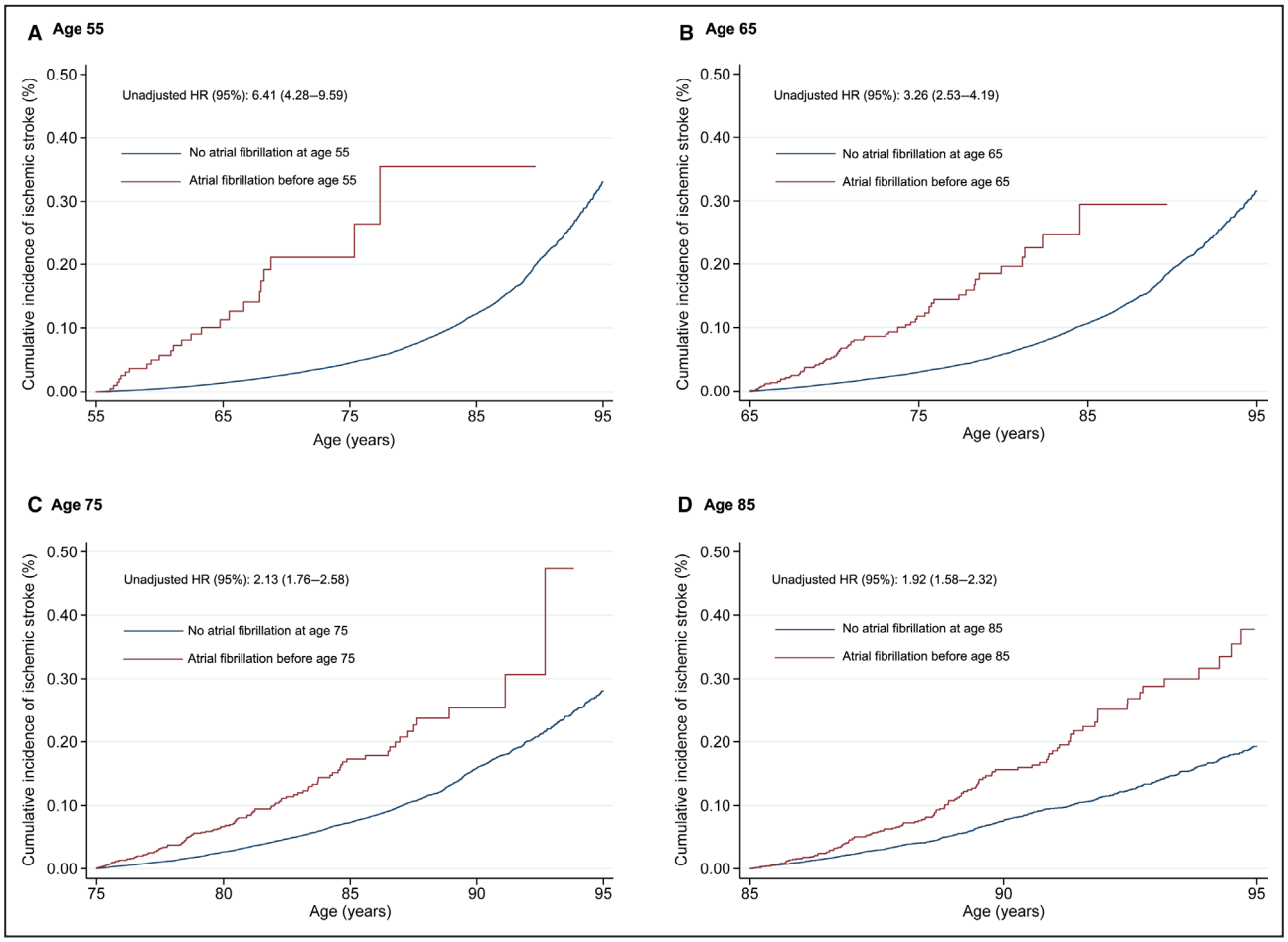


Figure 1. Cumulative hazards (nonadjusted Nelson–Aalen) of ischemic stroke in relation to age at diagnosis of atrial fibrillation.
A, At age 55, individuals diagnosed with AF before this age have the highest risk of ischemic stroke (HR, 6.41 [95% CI, 4.28–9.59]); **B**, at age 65, stroke risk remains elevated (HR, 3.26 [95% CI, 2.53–4.19]); **C**, at age 75, the risk decreases further (HR, 2.13 [95% CI, 1.76–2.58]); and (**D**) at age 85, individuals diagnosed with AF still exhibit an elevated cumulative risk (HR, 1.92 [95% CI, 1.58–2.32]). For adjusted HR, please see Table 2. AF indicates atrial fibrillation; and HR, hazard ratio.

revealed a linear increase in stroke risk with younger age at diagnosis, possibly due to our longer follow-up period of 21.1 years compared with 7.98 years in the Danish study, which allowed us to capture more long-term outcomes. Furthermore, whereas the Danish study focused on a European population, our research was based on US cohorts, potentially reflecting demographic or health care differences. Our study also used different age cutoffs (55, 65, 75, and 85 years versus 50, 60, 70, and 80 years), which could contribute to variations in stroke risk patterns. Other studies, such as that by Vinter et al,[23] have shown that the lifetime risk of AF and its complications, including stroke, is considerable even in younger individuals, underscoring the importance of early AF detection and management. Although these studies were primarily conducted in European populations, our research extends these findings to a broader population, reinforcing the evidence of age-related disparities in AF-associated stroke risk and highlighting potential differences in genetic predispositions, comorbid conditions, and AF management strategies.

Age plays a crucial role in the management of AF and ischemic stroke. Consistent with previous studies,[4] our study also observed an increasing incidence rate of ischemic stroke as individuals aged, from 12.16 per 1000 person-years at age 55 to 28.96 per 1000 person-years at age 85. However, when comparing individuals with and without AF, the relative risk of ischemic stroke decreased with age: the adjusted HRs dropped from 5.35 at age 55 to 1.93 at age 85. This suggests that although AF poses a greater relative risk of stroke at a younger age, this difference diminishes in older age groups, likely due to the prevalence of other risk factors such as hypertension, diabetes, and vascular diseases, as well as the impact of various therapies.[24] These findings underscore the need for early prevention and detection of AF to mitigate stroke risk, particularly in younger patients.

Table 3. Association Between AF and Incidence of Ischemic Stroke and According to Age at AF Diagnosis

	No AF	AF diagnosis 0–5 y earlier	AF diagnosis 6–10 y earlier	AF diagnosis >10 y earlier	*P* value for linear trend	5-y younger age at diagnosis
At age 55 y						
Ischemic stroke cases/total, No.*	3411/46 869	23/179	12/95	14/96		
IR (per 1000 person-years)	3.81	11.6	11.3	15.4		
Model 1, HR (95% CI)†	1.00 (Ref.)	5.71 (1.84–17.74)	5.68 (3.41–9.44)	8.81 (3.95–8.81)	<0.001	2.25 (1.88–2.68)
Model 2, HR (95% CI)‡	1.00 (Ref.)	4.84 (1.56–15.06)	5.15 (3.09–8.58)	7.59 (3.40–16.96)	<0.001	2.13 (1.79–2.55)
Model 3, HR (95% CI)§	1.00 (Ref.)	4.60 (1.48–14.34)	4.98 (2.99–8.29)	7.30 (3.27–16.31)	<0.001	2.10 (1.76–2.51)
At age 65 y						
Ischemic stroke cases/total, No.*	3287/46 052	83/534	49/371	41/282		
IR (per 1000 person-years)	5.63	9.25	12.50	14.78		
Model 1, HR (95% CI)	1.00 (Ref.)	2.79 (1.50–5.21)	3.34 (2.48–4.50)	4.33 (2.16–8.69)	<0.001	1.79 (1.58–2.01)
Model 2, HR (95% CI)	1.00 (Ref.)	2.67 (1.43–4.97)	3.18 (2.36–4.28)	4.08 (2.03–8.19)	<0.001	1.74 (1.54–1.97)
Model 3, HR (95% CI)	1.00 (Ref.)	2.61 (1.40–4.87)	2.96 (2.20–3.99)	4.11 (2.05–8.26)	<0.001	1.70 (1.51–1.93)
At age 75 y						
Ischemic stroke cases/total, No.*	2962/44 127	173/1186	175/1070	150/856		
IR (per 1000 person-years)	9.23	14.54	14.79	15.16		
Model 1, HR (95% CI)	1.00 (Ref.)	2.20 (1.71–2.83)	2.16 (1.48–3.17)	2.60 (1.56–4.34)	<0.001	1.51 (1.36–1.69)
Model 2, HR (95% CI)	1.00 (Ref.)	2.19 (1.70–2.81)	2.11 (1.44–3.09)	2.38 (1.43–3.97)	<0.001	1.48 (1.33–1.65)
Model 3, HR (95% CI)	1.00 (Ref.)	2.05 (1.59–2.63)	2.06 (1.41–3.02)	2.34 (1.40–3.90)	<0.001	1.46 (1.31–1.63)
At age 85 y						
Ischemic stroke cases/total, No.*	2523/41 678	490/3075	222/1232	225/1254		
IR (per 1000 person-years)	16.80	17.59	26.98	34.04		
Model 1, HR (95% CI)	1.00 (Ref.)	1.47 (0.81–2.67)	1.65 (1.27–2.13)	2.30 (1.64–3.22)	<0.001	1.31 (1.20–1.43)
Model 2, HR (95% CI)	1.00 (Ref.)	1.47 (0.81–2.68)	1.84 (1.42–2.38)	2.50 (1.78–3.50)	<0.001	1.36 (1.24–1.48)
Model 3, HR (95% CI)	1.00 (Ref.)	1.42 (0.78–2.59)	1.76 (1.36–2.28)	2.33 (1.66–3.28)	<0.001	1.33 (1.22–1.45)

AF indicates atrial fibrillation; HR, hazard ratio; and IR, incidence rate.

*Differences in the number of cases and noncases across age groups are due to death, onset of ischemic stroke, or lost to follow-up.

†Model 1: Adjusted for study cohort.

‡Model 2: Adjusted for age, sex, race, and study cohort.

§Model 3: Model 2+systolic blood pressure, diastolic blood pressure, education, alcohol drinking, smoking status, body mass index, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, history of hypertension, diabetes, coronary heart disease and chronic heart failure, use of digitalis, antiarrhythmics, anticoagulants, and study cohort.

The mechanisms underlying thrombogenesis in AF are not yet fully elucidated but can be best explained through Virchow's triad, which comprises endothelial injury, abnormal blood flow, and hypercoagulability.[25] The factors contributing to an elevated risk of stroke in patients with early-onset AF are multifaceted. First, recent study revealed that 10.1% of patients with early-onset AF possessed disease-associated variants, and this percentage elevates to 16.8% when AF is identified before age 30.[26] These variants were more common in genes correlated to inherited cardiomyopathies than channelopathies, and the most affected genes include *TTN, MYH7, MYH6, LMNA*, and *KCNQ1*.[26] Some of the genes (eg, *TTN, ANKRD1, CASQ2*) were also linked to abnormal left atrial volume and function[27] which in turn contribute to an increased risk of ischemic stroke. Second, nearly 90% of patients with young-onset AF (<60 years) had risk factors and comorbidities.[10] Individuals with early-onset AF were more prone to reduced left ventricular ejection fraction and increased atrial fibrosis irrespective of genetic variants carrier status,[28] which will also aggravate atrial remodeling.[29] Third, although the CHA_2DS_2-VASc score serves as a straightforward stroke risk stratification tool for identifying patients at high risk for stroke or thromboembolic events, it fails to consider the complex interplay among common modifiable risk factors, the hypercoagulability[30] duration, burden, and progression of AF in relation to stroke risk.[31] It was reported that the probability of progression from paroxysmal AF to chronic AF was 8.6% by 1 year and increased to 24.7% by 5 years, whereas the probability of documented recurrence

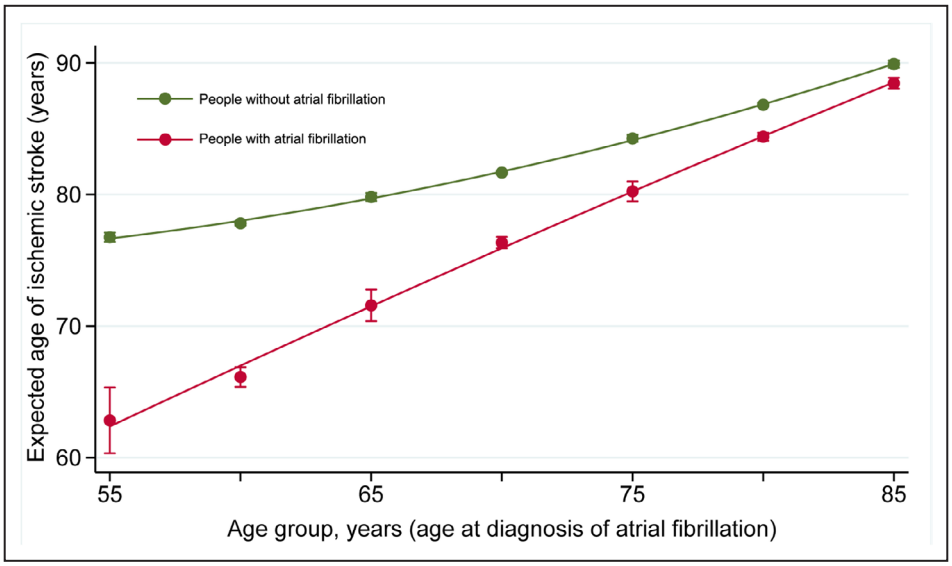
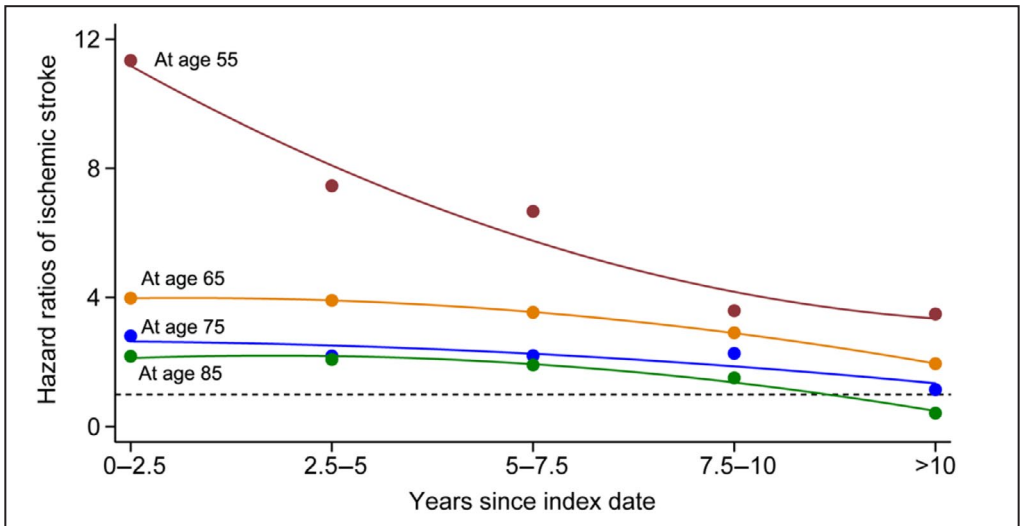


Figure 2. Expected age of ischemic stroke in relation to age at diagnosis of atrial fibrillation.
The differences of expected ischemic stroke age between individuals with and without AF at ages 55, 60, 65, 70, 75, 80, and 85 years were 13.9, 11.7, 8.2, 5.3, 4.0, 2.4, and 1.5 years, respectively. AF indicates atrial fibrillation.

of any AF by 5 years approached 63.2%.[32] Both the presence and persistency of AF were correlated with structural abnormalities in the atrium.[33] Consequently, individuals experiencing early-onset AF may exhibit a heightened risk of both AF progression and recurrence, which might in turn translate to an elevated risk



Follow-up since AF index date	0–2.5 years	2.5–5 years	5–7.5 years	7.5–10 years	>10 years
At age 55 years	11.34 (4.94–26.01)	7.46 (2.74–20.28)	6.67 (2.46–18.04)	3.59 (1.79–7.20)	3.49 (0.87–7.20)
age 65 years	3.98 (2.31–6.88)	3.91 (2.27–6.72)	3.54 (1.98–6.34)	2.91 (1.44–5.89)	1.95 (1.17–3.24)
age 75 years	2.81 (1.96–4.05)	2.19 (1.47–3.26)	2.20 (1.42–3.41)	2.27 (1.39–3.71)	1.15 (0.65–2.03)
age 85 years	2.18 (1.57–3.02)	2.08 (1.29–3.35)	1.91 (1.41–2.58)	1.51 (0.70–3.27)	0.42 (0.06–3.05)

Figure 3. The relative risk of ischemic stroke in relation to elapsed time since AF index date in patients with AF compared with age-matched individuals without AF among different age categories.
AF indicates atrial fibrillation.

of stroke. Further studies are warranted to evaluate the prognostic significance of age at onset and to incorporate this into future risk scores.

Lifelong AF management incorporates the A-B-C pathway: anticoagulation or stroke prevention, better rhythm management, and concomitant cardiovascular risk factors management.[34] According to current guidelines, younger patients with AF (≤65 years) without comorbidities have a very low annual risk of thromboembolic events and do not require anticoagulation.[35] However, the stroke rate remains substantially high among patients with AF aged 30 to 55 without comorbidities (CHA_2DS_2-VASc score of 0 in men and 1 in women) compared with individuals without AF (1.00 versus 0.25 per 100 person-years), with a sex-adjusted HR of 4.09.[36] Therefore, better stroke risk stratification tools are necessary to identify younger patients with AF and high stroke risk who require thromboprophylactic therapy. Furthermore, a growing body of evidence has showed that early rhythm control was associated with improved adverse effectiveness outcomes in patients diagnosed with AF within 1 year, resulting in a notable 22% reduction in the risk of stroke or systemic embolism.[37] Nevertheless, the patients included in the meta-analysis were predominantly aged 65 years or older.[37] Considering a 2.0% annual progression rate to permanent AF in patients with young-onset AF[10] and generally healthy atrial substrate in early stage, it is reasonable to consider early rhythm control for better maintenance of sinus rhythm.[38] Further clinical studies are warranted to assess effectiveness and safety.

Strengths and Limitations

The large sample size and long-term follow-up and comprehensive adjustments for confounding factors made the results convincing. However, our study has several limitations worth mentioning. First, the observational design prevents us from definitively establishing causal relationships. Second, some participants may progress from paroxysmal at diagnosis to permanent later in its course, which might also influence the outcomes. Third, due to the lack of data on peripheral artery disease and adherence to oral anticoagulants, we were unable to adjust for all relevant covariates. Finally, advances in the diagnosis stroke diagnosis since data collection may have affected the incidence of our primary outcome. Nevertheless, our study lays a solid foundation for future studies to explore the association between age at diagnosis and ischemic stroke. Future studies are needed to establish who might benefit from regular clinical evaluation and early initiation of therapy.

CONCLUSIONS

Younger age at AF diagnosis was associated with a higher risk of subsequent ischemic stroke.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S3
Figure S1
References [11–17,39–41]

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