ORIGINAL RESEARCH

Risk of Stroke in Patients With Atrial Fibrillation Is Associated With Stroke in Siblings: A Nationwide Study

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***Background*—**It remains unclear whether heritable factors can contribute to risk stratification for ischemic stroke in patients with atrial fibrillation (AF). We examined whether having a sibling with ischemic stroke was associated with increased risk of ischemic stroke and mortality in patients with AF.

***Methods and Results*—**In this nationwide study of the Swedish population, patients with AF and their siblings were identified from the Swedish patient registers and the Swedish MGR (Multi-Generation Register). Ischemic stroke events were retrieved from the Swedish patient registers and CDR (Cause of Death Register). Risk of ischemic stroke was compared between patients with AF with and without a sibling affected by ischemic stroke, AF, or both ischemic stroke and AF. The total study population comprised 113 988 subjects (mean age, 60±12 years) diagnosed with AF between 1989 and 2012. In total, 11 709 of them were diagnosed with a first ischemic stroke and 20 097 died during a mean follow-up time of 5.5 years for ischemic stroke and 5.9 years for mortality. After adjustment for covariates having a sibling with ischemic stroke, or both ischemic stroke and AF, was associated with increased risk of ischemic stroke (hazard ratio, 1.31; 95% CI, 1.23–1.40 or hazard ratio, 1.36; 95% CI, 1.24–1.49, respectively). Furthermore, ischemic stroke in a sibling was associated with all-cause mortality (hazard ratio, 1.09; 95% CI, 1.05–1.14). In contrast, the risk of stroke was only marginally increased for patients with AF with a spouse affected by ischemic stroke.

***Conclusions*—**Having a sibling affected by ischemic stroke confers an increased risk of ischemic stroke and death independently of traditional risk factors in patients with AF. **(*J Am Heart Assoc*. 2020;9:e014132. DOI: 10.1161/JAHA.119.014132.)**

Key Words: atrial fibrillation • family history • genetics • risk factors • stroke

Stroke is one of the leading causes of death and disability worldwide. Atrial fibrillation (AF) and its cardioembolic complications are important causes of ischemic stroke.[1] Several studies have indicated that family history is an important risk factor for AF.[2–7] The familial contribution is less well explored for stroke, although some reports have described familial aggregation.[8,9] Heritability for overall ischemic stroke has been estimated to be 38%, with higher estimates in certain subtypes, including 40% for large-vessel disease, 32% for cardioembolic stroke, but only 16% for small-vessel disease.[10]

The use of oral anticoagulants in subjects with AF reduces the risk for thromboembolic events by two thirds.[11,12] Current clinical practice guidelines recommend the use of risk assessment tools for stroke, such as the $CHADS_2$ and more recently CHA_2DS_2-VASc risk scores, to identify subjects with

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Clinical Perspective

What Is New?

- It is unclear whether a familial predisposition of stroke contributes to stroke risk in patients with atrial fibrillation (AF).
- This study investigates the ischemic stroke risk caused by familial factors in patients with AF.
- Having a sibling affected by ischemic stroke is associated with an increased risk of ischemic stroke in patients with AF.

What Are the Clinical Implications?

- The results of this study could identify patients with AF with an increased risk of ischemic stroke.
- The results of this study suggest that the genetic component for ischemic stroke in patients with AF could be important.
- Further studies are needed to explore whether a sibling history of stroke could contribute to risk prediction of ischemic stroke.

AF at high risk to guide use of anticoagulation, although the individual risk discrimination ability is modest.[13,14]

It remains unclear whether a familial predisposition of stroke influences stroke risk in subjects with AF. Such information could be particularly important for risk stratification in addition to CHA_2DS_2-VASc risk scores in AF cases. A recent study found no increased risk for stroke and coronary events in subjects with AF with a first-degree relative affected by AF.[15] However, the study did not investigate whether the relatives had a history of stroke or a combination of familial AF and familial stroke.

The aim of the present study was to assess the contribution of familial occurrence of ischemic stroke, AF, or both ischemic stroke and AF to the risk of ischemic stroke and mortality in subjects with AF.

Methods

Study Design

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Statistics Sweden at Ph: +46-10-479 50 00; e-mail: scb@scb.se. Several nationwide population and healthcare registers were linked to identify AF among individuals in Sweden.[16–18] Linkage of the registers was conducted on the basis of the individually unique Swedish 10-digit personal number assigned at birth or immigration. The MGR (Multi-Generation Register), maintained by Statistics Sweden, is a well-validated data source that has been used for studies of familial diseases.[2,18] It contains information on index individuals registered in Sweden between January 1, 1961, and December 31, 2012, and born between January 1, 1932, and December 31, 2012, and family relationships, such as siblings and parent-offspring. Patients with AF with at least one sibling alive on January 1, 1989, were included to be analyzed. Siblings were defined as individuals with the same mother and father. Spouses were identified on the basis of common children and living at the same address, registered partnership, or marriage. The Swedish NPR (National Patient Register) started in 1964 and, from 1987 and onwards, it contains information on all hospital discharge diagnoses from all counties in Sweden.[16] The NPR contains information from all specialist outpatient clinics in Sweden from 2001. The Swedish CDR (Cause of Death Register) contains information on date and cause of death from 1961 and onwards and is updated annually. The SPDR (Swedish Prescribed Drug Register) covers all filled prescriptions from 2005, including anticoagulation treatment. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Lund University, which waived the requirement of informed consent because of the use of anonymized register data.

AF Ascertainment

AF and atrial flutter are clinically related and were combined in this study.[19] For simplicity, AF and atrial flutter are below referred to as only AF. Cases with AF in the NPR were identified by the *International Classification of Diseases* (*ICD*) codes 427D (*ICD, Ninth Revision* [*ICD-9*]) and I48 (*ICD, Tenth Revision* [*ICD-10*]). The validity has been shown to be high for AF.[16,20] The analyses were based on all Swedish probands (all ages) with a sibling alive in 1989, and who had a first diagnosis of AF, diagnosed between 1989 and 2012, together with their siblings, parents, and spouses.

Outcomes

Incident ischemic stroke was identified through the NPR and defined according to the *ICD* codes 434, 436 (*ICD-9*), or I63 (*ICD-10*). Only the first hospitalization was included in this study. The proportion of correct stroke diagnoses has been shown to be >90% in data from 1999 and 2003.[21,22] Prevalent stroke was excluded. Month and year of death were derived from the Swedish CDR.

Covariate Definitions

Information on sex (classified into men and women) and age was available from the patient registers. Age at diagnosis was divided into 5 categories: <45, 45 to 54, 55 to 64, 65 to 74,

and >74 years. Period of AF diagnosis was divided into 7 categories: 1989 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, and 2008 to 2012. Comorbid conditions were defined on the basis of *ICD* codes for primary or secondary diagnoses, from the NPR, for the following conditions: hypertension, obesity, diabetes mellitus, heart failure, and coronary heart disease, as defined in Table S1. The definition of comorbid conditions was presence of a diagnosis within 2 years before and/or 3 months after study entry. CHA_2DS_2-VASc score was calculated, as previously described.[13] The definitions of variables in CHA_2DS_2-VASc criteria were based on *ICD* codes and presented in Table S1. For sensitivity analysis, the use of oral anticoagulants during follow-up time was defined as filled prescriptions of oral anticoagulants, according to the SPDR (Anatomical Therapeutic Chemical Classification [ATC] codes B01AA03, B01AE07, B01AF01, B01AF02). Information about oral anticoagulant prescription was available from 2005 and onwards.

Sibling, Parental, and Spousal Stroke and AF

Family relationships were assessed from the MGR linked to the NPR for the retrieval of diagnoses. The predictor variables were any record of a full sibling with a prevalent diagnosis, of AF, ischemic stroke, or both AF and ischemic stroke, at study entry or during the study period. For simplicity, we express this as AF_{SIB}, $stroke_{SIB}$, and AF_{SIB}+$stroke_{SIB}$, respectively. For comparison and to assess the effect of a shared environment in adulthood, spousal risks were determined. A record of a spouse with a diagnosis of either AF or ischemic stroke (expressed as AF_{SPO} or $stroke_{SPO}$) at study entry or any time during the study period was used as a predictor variable. In a secondary analysis, parental risks were also determined. In this analysis, a record of any parent of the proband with a diagnosis of ischemic stroke, AF, or both was used as a predictor variable. For parental stroke, the exposure time was limited because of incomplete coverage of the nationwide hospital registers across the parental lifespan.

Statistical Analysis

In a first analysis, Cox proportional hazards regression was used to compare incidence of ischemic stroke in subjects with siblings without AF or stroke in relation to: (1) $stroke_{SIB}$, (2) AF_{SIB}, or (3) $stroke_{SIB}$+AF_{SIB}. Subjects were followed up from the date of AF diagnosis until first ischemic stroke event, death, emigration, or the end of follow-up. Adjustment of hazard ratios (HRs) for potential confounders was conducted in several models: in a first model (model 1), adjustments were made for age at AF diagnosis and sex. In model 2, additional adjustments were made for period of diagnosis of AF (3-year intervals), time period of $stroke_{SIB}$ or AF_{SIB} (3-year intervals), proband birth order, hypertension, diabetes mellitus, obesity, heart failure, and coronary heart disease. In model 3, the analysis was additionally adjusted for a CHA_2DS_2-VASc score <2 versus ≥2 points. Model 3 was also performed with a parental predisposition to ischemic stroke or AF and with a spouse affected by ischemic stroke or AF ($stroke_{SPO}$ or AF_{SPO}) as predictor variables to assess the contribution of a shared environment in adulthood. The second analysis used mortality as an outcome, and all models were repeated. In a family with ≥2 siblings with AF, each subject was regarded as an AF case. We accounted for this dependence of cases by adjusting variance accordingly by the number of afflicted families [1/(N−M)], where N is the total number of cases and M is the number of ascertained families, as described previously.[23] In addition, incidence of ischemic stroke in relation to time of stroke onset in siblings was analyzed in subjects with AF for subjects with one sibling only. To account for anticoagulant treatment, a sensitivity analysis was also performed, including a time-dependent variable of anticoagulant treatment in the Cox model (Table S2). To assess whether any potential effect modification was present, interaction tests between $stroke_{SIB}$ and age, sex, birth order, and study period were performed. The proportionality of hazards assumption was evaluated by log-log curves. Analyses were conducted using SAS, 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics are presented in Table 1. On the basis of a cohort of 7 526 432 individuals from 2 895 193 different families (Table S3), 113 988 subjects (69% men) with at least one sibling were diagnosed with AF between 1989 and 2012. Mean age at AF diagnosis was 59.8±11.7 years.

Incidence of Ischemic Stroke

A total of 11 709 incident events of ischemic stroke occurred during a mean follow-up of 5.5 years. The Figure shows the age-specific rates of ischemic stroke by $stroke_{SIB}$, illustrating sharply increased rates with higher age. Incidence of ischemic stroke in relation to $stroke_{SIB}$, AF_{SIB}, or $stroke_{SIB}$+AF_{SIB} is presented in Table 2. After full adjustment in model 3, the HR (95% CI) for ischemic stroke in subjects with $stroke_{SIB}$ was 1.31 (1.23–1.40). Additional adjustment for anticoagulation treatment did not change the results (HR, 1.33; 95% CI, 1.19–1.49) (Table S2). The HR for ischemic stroke in subjects with AF_{SIB} was 1.09 (95% CI, 1.06–1.15) after full adjustments. For those with both $stroke_{SIB}$ and AF_{SIB}, the HR was 1.36 (95% CI, 1.24–1.49). No significant interactions were found between $stroke_{SIB}$ and age, sex, study period, or birth order, with respect to incidence of ischemic stroke.

Table 1. Characteristics of Patients With AF and Number of Ischemic Stroke Events, 1989 to 2012

Characteristic	Population		Ischemic Stroke Events	
	No.	%	No.	%
Total population	113 988	. . .	11 709	. . .
Sex				
Men	78 597	69.0	7877	67.3
Women	35 391	31.0	3832	32.7
Age at diagnosis of AF, y*				
<45	11 883	10.4	256	2.2
45–54	17 876	15.7	1188	10.1
55–64	39 245	34.4	4094	35.0
65–74	38 438	33.7	5178	44.2
≥75	6546	5.7	993	8.5
Period diagnosis of AF				
1989–1992	3898	3.4	421	3.6
1993–1995	4281	3.8	530	4.5
1996–1998	5809	5.1	728	6.2
1999–2001	10 049	8.8	1278	10.9
2002–2004	16 159	14.2	1802	15.4
2005–2007	21 760	19.1	2143	18.3
2008–2012	52 032	45.6	4807	41.1
Comorbidities				
Hypertension	33 295	29.2	4976	42.5
Diabetes mellitus	13 476	11.8	2271	19.4
Obesity	3509	3.1	328	2.8
Heart failure	14 507	12.7	2359	20.1
CHD	21 222	18.6	3276	28.0
CHA_2DS_2-VASc index				
<2	73 794	64.7	5208	44.5
≥2	40 194	35.3	6501	55.5
Sibling without $stroke_{SIB}$ or AF_{SIB}	85 724	75.2	8039	68.7
$Stroke_{SIB}$	10 114	8.9	1599	13.7
AF_{SIB}	22 672	19.9	2816	24.0
$Stroke_{SIB}$ and AF_{SIB}	4522	4.0	745	6.4

AF indicates atrial fibrillation; AF_{SIB}, a full sibling with a prevalent diagnosis of AF; CHD, coronary heart disease; $stroke_{SIB}$, a full sibling with a prevalent diagnosis of ischemic stroke.
*The registers cover subjects born after 1932, explaining the low number of subjects aged ≥75 years.

In Table 3, incidence of ischemic stroke in relation to time of stroke onset in sibling is presented. The HR (95% CI) for ischemic stroke in patients with $stroke_{SIB}$ at the time of AF diagnosis was 1.25 (1.14–1.40), and the HR (95% CI) was 1.27 (1.15–1.42) for patients with AF with $stroke_{SIB}$ during the follow-up period.

Of ischemic stroke cases, 44.5% had a CHA_2DS_2-VASc score <2. The incidence of ischemic stroke in patients with CHA_2DS_2-VASc scores <2 versus ≥2 is presented in Table 4. For patients with a CHA_2DS_2-VASc score of <2, the incidence was 17.5 per 1000 person-years for patients with $stroke_{SIB}$ versus 9.9 in patients without $stroke_{SIB}$.

All-Cause Mortality

There were 20 097 deaths during a mean follow-up period of 5.9 years. Fully adjusted, the HR (95% CI) for mortality in subjects with $stroke_{SIB}$ was 1.09 (1.05–1.14) (Table 2).

Spousal and Parental Ischemic Stroke

There was a small but significantly increased risk of ischemic stroke in patients with AF with $stroke_{SPO}$. The multivariate adjusted HRs (95% CIs) were 1.05 (1.02–1.09) and 1.05 (1.01–1.08) for patients with AF with a wife or husband $stroke_{SPO}$, respectively (Table S4). For patients with AF with a parental ischemic stroke, the risk of ischemic stroke was increased. After full adjustments in model 3, the HR (95% CI) was 1.10 (1.04–1.16) (Table S5).

Discussion

In this nationwide study, we examined the risks of ischemic stroke and mortality in patients with AF in relation to sibling ischemic stroke ($stroke_{SIB}$), AF (AF_{SIB}), or both ischemic stroke and AF ($stroke_{SIB}$+AF_{SIB}). For comparison, to estimate the contribution of a shared environment in adulthood, the analyses were repeated for patients with ischemic stroke or AF in a spouse ($stroke_{SPO}$ and AF_{SPO}).

In patients with AF, $stroke_{SIB}$ was associated with an increased risk of ischemic stroke, independently of traditional risk factors, whereas AF_{SIB} was only associated with a slightly increased risk. In contrast, the risk for ischemic stroke was only marginally increased in patients with AF with $stroke_{SPO}$, suggesting that the increased sibling risk of ischemic stroke could be explained by genetic, epigenetic, or shared childhood environmental factors, rather than shared adult environmental factors.

A challenge in stroke prevention is to identify and treat subjects with AF. Once AF is present, cardioembolic stroke is a common and severe complication, associated with a high risk of persistent disability for the individual and high costs for society.[24,25] In addition, close relatives will also be negatively affected. Several risk factors for ischemic stroke in patients with AF have been described.[11] A risk stratification score, CHA_2DS_2-VASc, is commonly used in clinical practice to assess stroke risk in patients with AF and guide decisions on whether oral anticoagulant treatment should be initiated.[14,26]

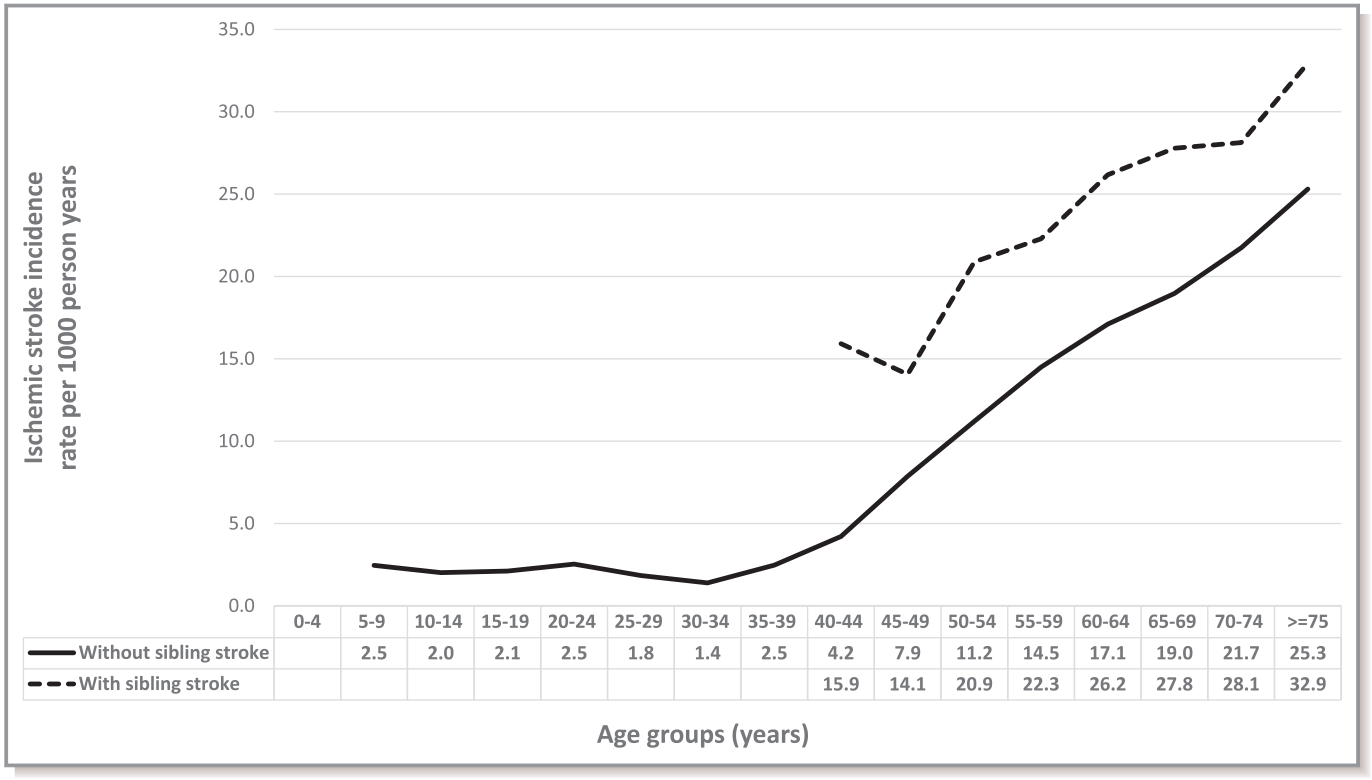

Figure. Age-specific rates of ischemic stroke by sibling ischemic stroke.

Oral anticoagulant reduces stroke risk by approximately two thirds.[11,12,27] Risk factors included in the CHA_2DS_2-VASc risk score are congestive heart failure, hypertension, age, sex, diabetes mellitus, prior stroke, and vascular disease.[13] Notably, CHA_2DS_2-VASc includes no information about family history of stroke, which could be important.

Previous studies have shown a familial aggregation of ischemic stroke, regardless of AF status.[8,9,28] In our study, sibling ischemic stroke conferred an HR (95% CI) of 1.31 (1.23–1.40) for ischemic stroke with the full set of adjustments. It should be kept in mind that the reference group for this HR was another group with AF and therefore a group with high stroke risk. The magnitude of increased risk of stroke with a sibling history of stroke in the general population was relatively similar: in the study mentioned above, the standardized incidence ratio (95% CI) was 1.82 (1.21–2.75) for ischemic

Table 2. Adjusted HRs and 95% CIs for Incident Ischemic Stroke and Death by $Stroke_{SIB}$ and AF_{SIB}

Variable	No./Cases	HR (95% CI)		
		Model 1	Model 2	Model 3
Ischemic stroke				
$Stroke_{SIB}$	10 114/1599	1.36 (1.28–1.45)	1.30 (1.23–1.40)	1.31 (1.23–1.40)
AF_{SIB}	22 672/2816	1.11 (1.06–1.17)	1.09 (1.03–1.14)	1.09 (1.06–1.15)
$Stroke_{SIB}$ and AF_{SIB}	4522/745	1.41 (1.29–1.54)	1.36 (1.24–1.49)	1.36 (1.24–1.49)
Death				
$Stroke_{SIB}$	10 114/2421	1.11 (1.06–1.16)	1.09 (1.05–1.14)	1.09 (1.05–1.14)
AF_{SIB}	22 672/4637	0.95 (0.92–0.98)	0.96 (0.92–0.99)	0.96 (0.92–0.99)
$Stroke_{SIB}$ and AF_{SIB}	4522/1047	1.03 (0.97–1.10)	1.02 (0.96–1.09)	1.02 (0.96–1.09)

Model 1 adjusted for age and sex. Model 2 adjusted for model 1+time period of AF diagnosis in patient with AF, time period of $stroke_{SIB}$ or AF_{SIB}, birth order, hypertension, diabetes mellitus, obesity, heart failure, and coronary heart disease. Model 3 adjusted for model 2+CHA_2DS_2-VASc score <2 vs ≥2 points. Data are based on 113 988 patients with AF, 11 709 ischemic stroke events, and 20 097 deaths. AF_{SIB} indicates a full sibling with a prevalent diagnosis of atrial fibrillation; HR, hazard ratio; $stroke_{SIB}$, a full sibling with a prevalent diagnosis of ischemic stroke.

Table 3. Adjusted HRs and 95% CIs for Incident Ischemic Stroke by Time of $Stroke_{SIB}$

Variable	No./Cases	HR (95% CI)
$Stroke_{SIB}$ before AF diagnosis	4126/381	1.25 (1.14–1.40)
$Stroke_{SIB}$ after AF diagnosis	2908/373	1.27 (1.15–1.42)

Adjusted for age, sex, time period of AF diagnosis in patient with AF, time period of $stroke_{SIB}$ or AF_{SIB}, birth order, hypertension, diabetes mellitus, obesity, heart failure, coronary heart disease, and CHA_2DS_2-VASc score <2 vs ≥2 points. Data are based on 2-children families only. AF indicates atrial fibrillation; HR, hazard ratio; $stroke_{SIB}$, a full sibling with a prevalent diagnosis of ischemic stroke.

stroke in relation to a sibling history of ischemic stroke.[8] In a systematic review from 2019, the relative risk (95% CI) was 1.24 (1.01–1.51) for pooled cohort studies investigating the relationship of sibling history of stroke and the risk of stroke.[29] This review included a study from the FHS (Framingham Heart Study), where the relative risk (95% CI) was 1.19 (0.61–2.32) for stroke risk in relation to sibling history of stroke.[30] Thus, our results suggest that a sibling history of stroke remains a contributor in those at high risk for cardioembolic stroke, but does not support a substantially higher heritable contribution in this population. Genome-wide association studies have identified several loci associated with stroke, many of them sharing genetic associations with other vascular traits, such as hypertension.[31] Not surprisingly, the heritability varies among the different subtypes, and seems to be highest for cardioembolic stroke (30%) and large-vessel disease (40%).[10] Our findings suggest that genome-wide studies of stroke in the context of AF may identify additional factors that specifically influence stroke risk in this context, such as factors related to hemostasis or atrial morphological characteristics.

In subjects with AF, previous studies did not find any association of sibling history of AF with risk of thromboembolic or major cardiovascular events.[15,32] This is largely consistent with the findings from our larger cohort, where an AF_{SIB} only slightly increased the risk of ischemic stroke in patients with AF. However, $stroke_{SIB}$ increased the ischemic stroke risk, independently of the CHA_2DS_2-VASc risk score, in our study. A similar magnitude of the risk increase was seen with $stroke_{SIB}$+AF_{SIB}. The risk for ischemic stroke with a $stroke_{SPO}$ was only marginally increased, indicating a limited contribution of risk from a shared environment in adulthood (Table S4).[33] The risk of ischemic stroke was increased, irrespective of whether the siblings' stroke occurred before or after the diagnosis of AF in the patient with AF. This suggests that the genetic component or a shared environment in childhood may be important. Interestingly, comparing patients with AF with a sibling with and without ischemic stroke, the rate ratios for the risk of ischemic stroke were higher in patients with AF and CHA_2DS_2-VASc score <2 and lower age (<65 years). This category of patients is estimated to have a low risk of ischemic stroke and is not routinely prescribed anticoagulants. Our results indicate that some patients with AF with a sibling with ischemic stroke in this risk category may benefit from the use of anticoagulants, and it is possible that the addition of a family predisposition of ischemic stroke could improve the precision of the CHA_2DS_2-VASc risk score.

Table 4. IRs of Ischemic Stroke (per 1000 Person-Years) by $Stroke_{SIB}$ and CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score	No $Stroke_{SIB}$		$Stroke_{SIB}$		All	
	No.	IR	No.	IR	No.	IR
<2	4557	9.9	651	17.5	5208	10.5
≥2	5553	28.7	948	38.7	6501	29.8
All	10 110	15.5	1599	26.0	11 709	16.4

IR indicates incidence rate; $stroke_{SIB}$, a full sibling with a prevalent diagnosis of ischemic stroke.

Strengths and Limitations

A major strength of the current study is the nationwide, register-based study design with almost complete records of the Swedish population.[16] In addition to spousal comparisons, the use of stroke and AF in siblings instead of parental history only also reduced potential cohort effects. The use of hospital register data also eliminates potential recall bias in the assessments of family predisposition and comorbidities.

Our study also has limitations that merit consideration. The NPR contains nationwide hospital discharge data from 1987 and outpatient data since 2001. Therefore, events before 1987 could not be recorded. However, we believe that this most likely would lead to a nondifferential bias. The SPDR contains information from 2005, and anticoagulant treatment was adjusted for in a sensitivity analysis, with essentially unchanged results. The data were based on information about filled prescriptions. However, we do not have information about patient compliance and whether the treatment was actually taken.

We did not have detailed information about the diagnostic procedures, but all diagnoses reported to Swedish nationwide registers are made by a board-certified physician and high validity has been shown for the Swedish Hospital Discharge Register, especially for cardiovascular diseases, such as AF, stroke, myocardial infarction, and heart failure, as a primary diagnosis.[16,20,34] We had no information about physical activity, renal function, cholesterol levels, smoking status, or actual blood pressure, which could influence the risk for stroke. However, we adjusted for other traditional risk factors, as well as the CHA_2DS_2-VASc score, and the included diagnoses are associated with these factors. Another limitation is the lack of information about the causative subtypes of ischemic stroke. It is likely that most stroke cases in subjects

with AF are cardioembolic, although other subtypes could also contribute to stroke burden in this context.[24]

The MGR was used in this study. This register includes individuals born after 1932, and individuals covered by this register were comparatively young during the study period of 1989 to 2012. Mean age of patients with AF in this study was 60 years, and no patients aged >80 years were included. It is therefore unclear whether the results can be generalized to older patients with AF. Prevalence of AF is high in older age groups, and these patients are more often women.[35] Hereditary factors are often assumed to be most important in young age groups, and it is possible that relative risk increase in patients with AF with sibling stroke is highest in early-onset AF.

In conclusion, subjects with AF and a sibling with ischemic stroke or both ischemic stroke and AF have an increased risk for ischemic stroke, independently of traditional risk factors. Our results suggest that family predisposition of stroke could contribute to the assessment of stroke risk in patients with AF. Whether information about family predisposition of stroke could improve the prediction of ischemic stroke compared with traditional risk factor scores, such as the CHA_2DS_2-VASc, should be examined in future studies.

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