

Atrial Fibrillation, Stroke Risk, and Warfarin Therapy Revisited

A Population-Based Study

Staffan Björck, MD, PhD; Bo Palaszewski, PhD; Leif Friberg, MD, PhD; Lennart Bergfeldt, MD, PhD

Background and Purpose—Atrial fibrillation (AF) is a major risk factor for ischemic stroke. This study aims to update the knowledge about AF and associated stroke risk and benefits of anticoagulation.

Methods—We extracted data from the hospital, specialized outpatient, and primary healthcare and drug registries in a Swedish region with 1.56 million residents. We identified all individuals who had received an AF diagnosis during the previous 5 years; all stroke events during 2010; and patients with AF aged ≥ 50 years who had received warfarin during 2009.

Results—AF had been diagnosed in 38 446 subjects who were alive at the beginning of 2010 (prevalence of 3.2% in the adult [≥ 20 years] population); $\approx 46\%$ received warfarin therapy. In 2010, there were 4565 ischemic stroke events and 861 intracranial hemorrhages. AF had been diagnosed in 38% of ischemic events ($\geq 50\%$ among those aged ≥ 80 years) and in 23% of intracranial hemorrhages. An AF diagnosis was often lacking in hospital discharge records after stroke events. Warfarin therapy was associated with an odds ratio of 0.50 (confidence interval, 0.43–0.57) for ischemic stroke and, despite an increased risk of intracranial hemorrhage, an odds ratio of 0.57 (confidence interval, 0.50–0.64) for the overall risk for stroke.

Conclusions—AF is more common than present guidelines suggest. The attributable risk of AF for ischemic stroke increases with age and is close to that of hypertension in individuals aged ≥ 80 years. Because a majority of patients with AF with increased risk for stroke had not received anticoagulation therapy, there is a large potential for improvement. (*Stroke*. 2013;44:3103–3108.)

Key Words: atrial fibrillation ■ diabetes mellitus ■ hypertension ■ intracranial hemorrhage ■ risk assessment ■ stroke ■ thromboembolism

Atrial fibrillation (AF) is the most common arrhythmia, and until recently, it was estimated to affect around 1% of the population.¹ This estimate was mainly based on persistent or permanent forms of AF while transient AF was excluded because of the widespread assumption that stroke risk was dependent on AF type. However, a post hoc analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I to III studies,² subsequently corroborated by others,^{3,4} led to a paradigm shift: all types of AF seem to carry similar risk of ischemic stroke and should be regarded equivalent regarding stroke prophylaxis. This concept was rapidly incorporated in international AF guidelines.^{5–7} Considering that nonpermanent forms of AF are more common than permanent forms (eg, in the Euro Heart Survey only 30% of all patients with AF had permanent AF),⁸ it is likely that AF is more common than previous estimates.

The presence of AF is considered to increase the stroke risk 4 to 5 times,⁹ and based on the earlier estimates of AF prevalence, 15% to 20% of all stroke events are thought to be attributable to AF.¹⁰ Although the beneficial effects of anticoagulation therapy are well established, many patients do not receive such therapy even if their risk profile motivates anticoagulation according to the present guidelines.¹¹ This is assumed to be partly due to the problems related to warfarin therapy. With the advent of alternatives to warfarin, such as dabigatran, rivaroxaban, and apixaban, it is pertinent to update the knowledge about the association between AF and stroke to determine how AF-related stroke can be minimized most efficiently and cost-effectively. This is even more relevant as AF becomes more common with increasing longevity in many countries.

The aim of this study was, therefore, to define the association between AF and stroke in a population sample of 1.6

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From the Department of Health Care Evaluation, Regionens Hus, Gothenburg, Sweden (S.B., B.P.); Department of Cardiology, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden (L.F.); and Department of Molecular and Clinical Medicine/Cardiology, Sahlgrenska Academy, University of Gothenburg, Sweden (L.B.).

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Correspondence to Lennart Bergfeldt, MD, PhD, Department of Cardiology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden. E-mail lennart.bergfeldt@hjl.gu.se

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million (1.2 million adults) and the benefit and risk of anticoagulation therapy.

Methods

Registries

Sweden has a long tradition of administrative registries, and all Swedish residents have a unique personal identification number that is used in these registries. We extracted data from the database on healthcare contacts of the Västra Götaland (VG) Region (17% of the Swedish population). The VG Region is situated in the southwest of Sweden and includes both rural and urban areas. The demographic composition is similar to the whole of Sweden. Within this region, there are no long distances to healthcare and all hospitals are open for acute care of patients with stroke. The regional healthcare database includes place of residence, age, sex, principal and ancillary diagnoses, and codes for surgical procedures. It covers all hospitals, specialized outpatient care, and all private and publicly owned primary healthcare centers. Since 2005, the completeness of data in the regional database has been greatly enhanced because the reimbursement system to primary healthcare providers is partly based on the disease burden, which in turn is dependent on reported diagnoses. The VG Region forwards information concerning all hospital or hospital-affiliated outpatient care in the region to the national patient register. The validity of this register is evaluated annually, and <1% of hospital contacts lack a proper discharge record with at least 1 principal diagnosis as the cause for care.¹² A diagnosis of AF or atrial flutter in the national patient register has been shown to be 97% accurate.¹³

We used *International Classification of Diseases, Tenth Revision* (ICD-10) code I 489 with or without subcodes A to F to identify healthcare contacts with an AF diagnosis. Our definition of AF therefore includes atrial flutter, but these 2 arrhythmias are closely related, often appear in the same patients, and have a similar stroke risk.^{14,15}

We also used the national register on all prescribed and dispensed drugs. This register covers all purchases of prescribed drugs nationwide and lists information about, for example, date of purchase, dispensed drug, quantity, and dosing instructions. Because the reporting to this register is automatic and no pharmacy can operate outside this system, it may be regarded as almost 100% complete.

Study Population

The study consists of 2 parts with partly overlapping cohorts. In the first part, data from the entire population in the VG Region were analyzed and used to estimate the risk for stroke associated with AF and other medical conditions. In the second part, we studied all stroke events during 2010 to assess the role of AF.

The first cohort consists of all 1.56 million residents in the VG Region listed at a primary care center on December 31, 2009. For each individual, the regional healthcare database was searched for a diagnosis of AF, hypertension (ICD I10–I15), ischemic heart disease (ICD I20–I25), cardiac failure (ICD I50), diabetes mellitus (ICD E10–E14), and a previous stroke during the preceding 5 years. Together with age ≥ 75 years, these are the constituent factors used in the widely applied cardiac failure, hypertension, age ≥ 75 years, diabetes, and stroke (CHADS₂) stroke risk assessment score.¹⁶ In the AF cohort alive at the beginning of 2010, we identified those with an incident stroke during 2010 and also those who had purchased warfarin at least once during the preceding year. Some calculations were limited to individuals aged ≥ 50 years as specified.

The second cohort consists of all events recorded in 6 VG Region hospitals with a primary diagnosis of ischemic stroke or intracranial hemorrhage (ICH) during 2010. The ICD-10 codes I61 and I62 were used for ICH and I63 and I64 for ischemic stroke. An event appearing more than once during a 28-day period in the same individual was counted only once in order to exclude duplicate reporting after transfer between hospitals. For all of these events, we searched the registries for a diagnosis of AF during the preceding 5 years. First-time stroke was defined when no diagnosis of stroke had been assigned during 5 preceding years.

Statistical Methods

Attributable risk was calculated according to Benichou¹⁷ and Walter¹⁸ within each 10-year age stratum. Attributable risk represents the percentage of events (in this case, stroke) that could be prevented in a population if the condition (eg, AF, hypertension) was removed. It is dependent on the prevalence of the condition and the associated risk for individuals with or without the condition, and it increases if either the prevalence or the associated risk increases.

Binary logistic regression was used to calculate the risk contribution of different factors for ischemic stroke and ICH in patients with AF and the general population. Odds ratios (ORs) for stroke in the presence or absence of cofactors were calculated within 10-year age strata ≥ 50 years.

Results

AF Prevalence in the General Population

During the 5-year inclusion period, 66 292 individuals in the VG Region received an AF diagnosis on 416 122 occasions (on average 6.3 occasions per patient). Of these, 38 446 (58%) were alive and living in the VG Region at the beginning of 2010. This corresponds to a prevalence of 2.5% of the total population (n=1 564 627) and 3.2% of the population aged ≥ 20 years (n=1 199 683). Figure 1 shows the prevalence in relation to age stratum and sex.

AF Prevalence in Ischemic Stroke

During 2010, there were 5426 diagnosed stroke events in the VG Region of which 4565 (84%) were ischemic and 3525 (77%) were first-time events. AF was more common among the elderly and diagnosed in at least 50% from 80 years of age (Figure 2).

A diagnosis of AF was recorded in the hospital discharge note in 29% of the ischemic stroke events (1299/4565). However, when we searched for AF recorded by all healthcare contacts, AF was diagnosed in 38% of the ischemic stroke events (1733/4565). In the 434 stroke events without hospital discharge

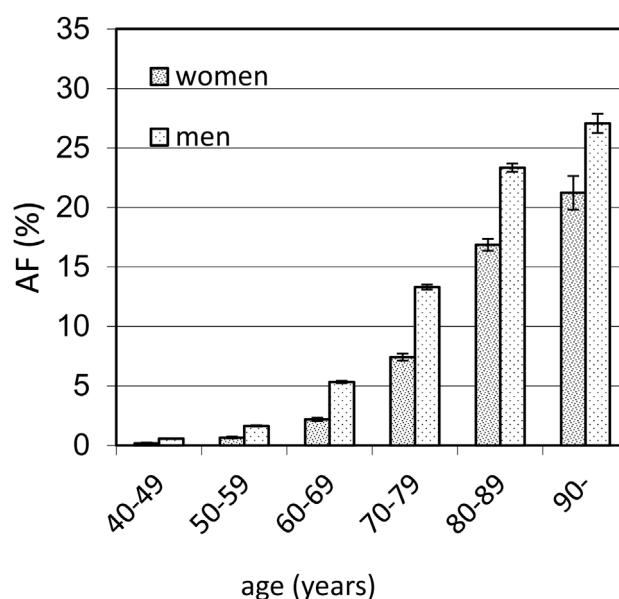


Figure 1. Prevalence of atrial fibrillation (AF) in the general population in relation to age and sex. Error bars denote 95% confidence intervals.

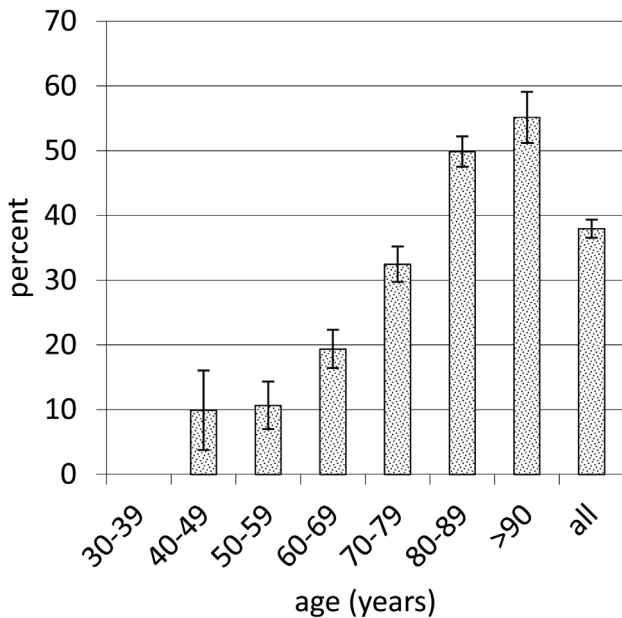


Figure 2. Prevalence of atrial fibrillation among 4565 acute ischemic stroke events. Error bars denote 95% confidence intervals.

codes for AF, an AF diagnosis had been recorded on average 4.2 times before the stroke occurred. The proportion of AF in ischemic stroke events according to the discharge notes for the 6 hospitals in the VG Region compared with information from all healthcare contacts is presented in Figure I in the online-only Data Supplement.

AF Prevalence in ICH

During 2010, there were 861 ICHs in the VG Region and AF was diagnosed in 23% (195/861) of these events according to all available information. Again, a substantial proportion of AF diagnoses (28%) was not recorded in the discharge notes but obtained from primary care records.

Concomitant Diseases: Prevalence, OR, and Attributable Risk for Ischemic Stroke

The prevalence of AF, ischemic stroke, and comorbidities is presented in Table I in online-only Data Supplement. This information is included in the OR and attributable risk estimates presented below. Note that they were calculated against a background of oral anticoagulant therapy in 46% of patients with AF (see below).

Table 1 shows the ORs of stroke associated with specified medical conditions (AF, diabetes mellitus, cardiac failure,

hypertension, and ischemic heart disease) in relation to advancing age (logistic regression analysis). The OR is approximately the same as the relative risk if the outcome of interest is rare.

Table 2 shows the attributable risks for specified medical conditions with regard to ischemic stroke during 2010 by 10-year age strata from 50 years of age. Hypertension was the most important risk factor and similar for all age strata. The AF attributable risk for stroke increased significantly with age in contrast to that of the other medical conditions and approached hypertension in the highest age stratum. The figures for diabetes mellitus and ischemic heart disease were similar. Cardiac failure had its highest attributable risk in the oldest age stratum.

Anticoagulation and Risk for Stroke

Anticoagulant therapy with warfarin, the only oral anticoagulant available during the study period, was received by 46% (17023/37200) of patients with AF aged ≥ 50 years during 2009, the year before the stroke events were counted. Figure 3 shows the number of patients with AF with at least 1 stroke (ischemic or ICH) during 2010 with/without warfarin therapy ($n=1170$; 3% of 37200 with AF). The proportion treated with warfarin in this subgroup was only 33%, and this proportion decreased markedly >80 years of age; however, this figure is based on individual patients and with very few individuals aged >90 years. Warfarin was taken by 57.8% of patients with AF with ICH compared with 29.9% of patients with AF with ischemic stroke.

Figure 4A shows the OR for ischemic stroke during 1 year (2010) in different age groups after adjustment for cardiac failure, hypertension, diabetes mellitus, and previous stroke. Warfarin therapy reduced the risk for ischemic stroke by, on average, 50.4% (43.3%–56.6%). Figure 4B shows the OR for ischemic stroke and ICH together. Warfarin therapy reduced the risk of ischemic stroke or ICH by 43.5% (36.0%–50.1%). This calculation is based on a worst case scenario and assumes that all ICHs in the 57.8% of patients with AF receiving warfarin were because of the anticoagulation therapy.

Ischemic stroke was almost 9 times more common than ICH in all patients with AF (195 versus 1733 events during 2010). ICH was more common in patients with AF with versus without warfarin. The risk increase with warfarin use was 63% after adjustment for comorbidities according to the CHADS₂ score (OR, 1.63; confidence interval, 1.13–2.36). There was, however, a net benefit of 43% in favor of warfarin treatment for avoiding a composite end point of ischemic stroke or ICH (OR, 0.57; confidence interval, 0.50–0.64).

Table 1. Odds Ratios for Ischemic Stroke in the Västra Götaland Region

Age, y	n	Events	Odds Ratios for Ischemic Stroke (95% CI)				Ischemic Heart Disease
			Atrial Fibrillation	Diabetes Mellitus	Cardiac Failure	Hypertension	
50–59	193817	265	2.7 (1.5–4.7)	1.5 (1.0–2.2)	2.5 (1.3–4.8)	2.6 (2.0–3.4)	1.7 (1.1–2.7)
60–69	184134	689	1.9 (1.4–2.4)	1.8 (1.5–2.2)	2.2 (1.6–2.9)	1.6 (1.4–1.9)	1.7 (1.4–2.1)
70–79	112733	1143	1.8 (1.6–2.1)	1.5 (1.3–1.7)	1.2 (1.0–1.5)	1.4 (1.3–1.6)	1.4 (1.2–1.6)
80–89	69672	1591	2.1 (1.9–2.3)	1.3 (1.1–1.4)	1.1 (1.0–1.3)	1.3 (1.2–1.5)	1.1 (1.0–1.3)

95% confidence intervals (CIs) within brackets.

Table 2. Attributable Risk (%) for Ischemic Stroke in Relation to Age

Age, y	Attributable Risk for Ischemic Stroke, % (95% CI)				
	Atrial Fibrillation	Diabetes Mellitus	Cardiac Failure	Hypertension	Ischemic Heart Disease
50–59	4.6 (1.8–7.4)	8.7 (4.3–13.1)	4.2 (1.6–6.9)	26.2 (19.3–33.2)	7.4 (3.6–11.1)
60–69	7.9 (5.4–10.3)	14.5 (11.0–17.9)	7.7 (5.5–10.0)	27.5 (22.1–32.9)	12.8 (9.6–16.0)
70–79	11.6 (9.0–14.2)	11.1 (8.2–14.0)	6.6 (4.5–8.7)	26.2 (20.8–31.6)	12.1 (9.1–15.1)
80–89	20.2 (17.3–23.0)	6.4 (4.1–8.7)	10.2 (7.7–12.8)	23.0 (17.6–28.4)	9.4 (6.4–12.4)

95% confidence intervals (CIs) within brackets.

Discussion

The major findings of this population-based study are that AF is more common than previously thought, its association with stroke increases with age, and is stronger than can be appreciated from hospital discharge data alone. There is a significant undertreatment with anticoagulants and therefore a potential for substantial improvement.

The attributable risk is dependent on the prevalence of the conditions being studied and their associated risks.¹⁷ We found a prevalence of AF in the adult population of 3.2%, >3 times higher than that reported in the Anticoagulation and Risk Factors in AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,¹ which is often used as reference for the AF prevalence. The discrepancy is partly attributable to different inclusion criteria: the ATRIA study counted only patients with sustained AF, whereas we counted all individuals with a diagnosis of AF, whether it was paroxysmal, persistent, or permanent. Because the AF type no longer should influence decisions about stroke prophylaxis according to current guidelines,^{7,19} all patients with AF should be included. The mean age of the patients in the ATRIA study was 71 years, compared with 76.8 years in our population-based cohort. Because AF is more common with increasing age, this age difference probably contributed to the different estimates. An increase of the mean age of the general population by only 1 year would increase the AF prevalence by 7.2%; for example, from 2.5% to 2.62% in our entire population and from 3.2% to 3.4% among adults. The prevalence of 3.2% in this study

is most likely an underestimation of the actual prevalence, as judged from results of a recent screening study. In that study on subjects aged 75 to 76 years with at least 2 risk factors for stroke according to CHADS₂ in a small Swedish community, the baseline prevalence was 9.6%, which increased to 14% after 2 weeks of handheld ECG recording for 20 to 30 seconds twice a day plus at palpitations.²⁰ In our study, some patients with asymptomatic AF have probably been diagnosed when seeing their physicians for different other complaints, but there is likely a substantial number of asymptomatic and undiagnosed individuals with AF in the VG Region.

The condition with the highest attributable risk for stroke is hypertension, which is even more common than AF and also increases with age (Table 1 in the online-only Data Supplement). The importance of AF and hypertension, however, becomes more equal with increasing age. The prevalence of hypertension in our study was similar to that observed in the Framingham study,⁹ despite the fact that the criteria for hypertension has changed over time and now is 140/90 compared with 165/95 in the Framingham study. However, the relation between hypertension and stroke was less strong in the present study compared with the Framingham study, which may partly be related to improved antihypertensive therapy. Recent results of the INTERnational STROKE (INTERSTROKE) study underscore the importance of hypertension as a risk factor for stroke.²¹

We also found that patients with AF treated with anticoagulation therapy the year before the observation period had a 54%

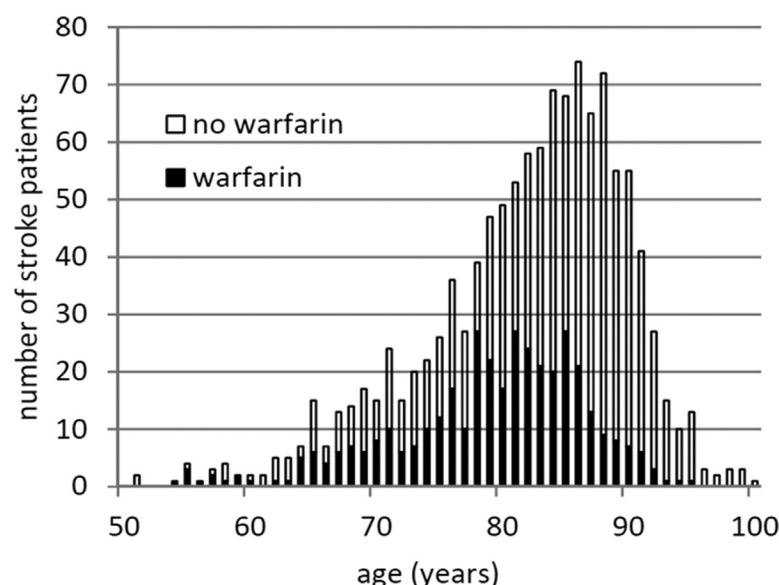


Figure 3. Number of patients with atrial fibrillation who during 2010 had a stroke (either ischemic stroke or intracranial hemorrhage) in relation to age and warfarin treatment.

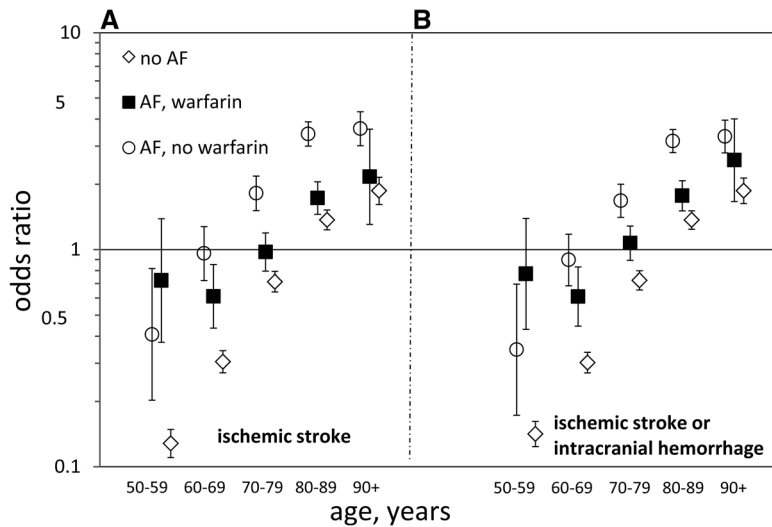


Figure 4. Odds ratios (95% confidence interval) for ischemic stroke (A) and ischemic stroke plus intracranial hemorrhage (B) in relation to atrial fibrillation (AF), warfarin treatment and age, adjusted for cardiac failure, hypertension, diabetes mellitus, and previous stroke.

lower risk of ischemic stroke compared with patients with AF who did not receive such therapy. This result is quite similar to the 62% that was found in the meta-analysis of placebo-controlled studies by Hart et al²² that established the role of vitamin K antagonists for stroke prophylaxis in AF. However, in our analysis, the patients had not been randomized to warfarin treatment, and we cannot verify the quality of their actual treatment (see below). Although warfarin therapy was the most important risk factor for ICH (followed by diabetes mellitus and >75 years of age), the overall risk for patients with AF was almost 9 times higher for ischemic stroke than for ICH (ie, when combining the patients with AF regardless of whether or not they took warfarin). Our findings thus verify the high benefit–risk ratio for warfarin treatment, except in the age stratum 50 to 59 years (Figure 4).

Methodological Considerations and Limitations

Both Hospital and Primary Care

Early studies of AF prevalence simply counted the fraction of patients who had AF during a 10-second 12-lead ECG.^{23–25} Later studies used healthcare registers but mostly included only hospital-based populations. Our study is unique because we also had access to data from primary care and from private practitioners, which cared for ≈20% of the patients. A considerable proportion of AFs were identified from nonhospital-based registers only. The records from the 6 hospitals within the VG Region thus underestimated the presence of AF in patients with ischemic stroke at the time of this event; further study is needed to determine whether this influenced the therapy/secondary prophylaxis.

Dependence on Validity of Registers

Our analyses cannot account for all clinical variables or for changes in therapy over time, and are reliant on the accuracy of diagnostic recording. There are as yet no studies of the diagnostic validity of the primary healthcare register in our region. However, the VG Region forwards information concerning all hospital or hospital-affiliated outpatient care in the region to the national patient register. The validity of this register is high as is a diagnosis of AF or atrial flutter (see Methods).^{12,13} For some other important diagnoses such as

myocardial infarction and cardiac failure, external validation of the diagnostic accuracy is also good,¹² but some comorbidities might have been under-reported (especially hypertension), whereas over-reporting probably is much rarer. Thus, patients might have had more risk factors than we were aware of and could adjust for, but this limitation is inherent in all registry studies.

Confounding by Indication

Notably, the patients in this study were not randomized to receive warfarin therapy, and we have no information about the time within the therapeutic interval for individual patients. Warfarin-treated patients with AF may differ from those who do not receive warfarin, which might have affected our results. This was certainly the case for older patients with AF, who were less likely to receive warfarin. A recent study shows that they are more likely to receive acetylsalicylic acid, which might suggest that the stroke risk has been recognized, but that the risk–benefit ratio was perceived unfavorable with warfarin.²⁶ Although, undertreatment with anticoagulation in patients with AF has been internationally recognized, its reasons have not been fully elucidated, an issue that requires further research.

Conclusions

AF was found to be more common, by a factor ≥2 to 3, than present guidelines suggest. The older the stroke patient, the more likely stroke was associated with AF, with an attributable risk close to that of hypertension. Because a majority of patients with AF with an increased risk for stroke and an actual stroke had not received anticoagulation, there is a large potential for improvement.

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Disclosures

Dr Bergfeldt has received advisory board and lecture honoraria from Sanofi-Aventis, Boehringer–Ingelheim, and MSD. Dr Friberg has received research grants from Boehringer-Ingelheim, Sanofi-Aventis, Bristol-Myers-Squibb, and Bayer and has participated in advisory boards with Boehringer-Ingelheim and Sanofi-Aventis. The other authors have no conflicts to report.

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