ORIGINAL INVESTIGATIONS

Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA$_2$DS$_2$-VASc Score of 1

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ABSTRACT

BACKGROUND Patients with atrial fibrillation (AF) and ≥1 point on the stroke risk scheme CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) are considered at increased risk for future stroke, but the risk associated with a score of 1 differs markedly between studies.

OBJECTIVES The goal of this study was to assess AF-related stroke risk among patients with a score of 1 on the CHA$_2$DS$_2$-VASc.

METHODS We conducted this retrospective study of 140,420 patients with AF in Swedish nationwide health registries on the basis of varying definitions of "stroke events."

RESULTS Using a wide "stroke" diagnosis (including hospital discharge diagnoses of ischemic stroke as well as unspecified stroke, transient ischemic attack, and pulmonary embolism) yielded a 44% higher annual risk than if only ischemic strokes were counted. Including stroke events in conjunction with the index hospitalization for AF doubled the long-term risk beyond the first 4 weeks. For women, annual stroke rates varied between 0.1% and 0.2% depending on which event definition was used; for men, the corresponding rates were 0.5% and 0.7%.

CONCLUSIONS The risk of ischemic stroke in patients with AF and a CHA$_2$DS$_2$-VASc score of 1 seems to be lower than previously reported. (J Am Coll Cardiol 2015;65:225–32) © 2015 by the American College of Cardiology Foundation.

Current guidelines for the management of atrial fibrillation (AF) recommend a risk-based approach toward stroke prevention with oral anticoagulant (OAC) agents (1–5). Unfortunately, large differences exist among the estimates of risk of AF-related stroke without protective treatment (6–13). For patients at high risk, such differences will not affect practical management because all patients will be considered for OAC treatment; for patients at low risk, however, therapeutic decisions will depend on the estimated stroke risk.

Both the European and U.S. guidelines advocate the use of the CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular

disease, age 65-74 years, sex category) scheme for risk stratification. Points are given for these various factors (6). For low-risk patients with a score of 1 on the CHA$_2$DS$_2$-VASc, the European Society of Cardiology recommends treatment with either an adjusted-dose vitamin K antagonist (e.g., warfarin) or, preferably, 1 of the new OAC agents (i.e., dabigatran, rivaroxaban, apixaban). However, stroke risk estimates for AF patients with a CHA$_2$DS$_2$-VASc score of 1 and no OAC treatment varies by a factor of 3 among different studies, from 0.6% to >2.0% (6-13). At an annual unprotected risk of 0.6%, it is unlikely that patients will realize the benefits of treatment, whereas patients with an annual risk >1% are more likely to benefit from treatment (14-16).

The goal of the present study was to assess the risk of AF-related stroke among patients without OAC treatment and a CHA$_2$DS$_2$-VASc score of 1.

METHODS

This was a retrospective study of unselected patients in nationwide, cross-matched Swedish health registries. The study population consisted of all patients with a diagnosis of nonvalvular AF in the Swedish National Patient Register between July 1, 2005, and June 31, 2010, who had not been exposed to warfarin at any time during follow-up. Patients with valvular AF were excluded because these patients have an obligate indication for OAC treatment. The codes used to identify patients with valvular AF are listed in Table 1. The index date was defined by first contact with a diagnosis of AF in the National Patient Register during the study period. Follow-up lasted until the specified event, death, or July 1, 2010, whichever came first.

Stroke events during follow-up were identified in the National Patient Register, which was cross-matched with the Swedish national stroke register (known as Riks-Stroke). We evaluated how the estimated event rates were affected by the various ways of counting these events that were used in previous studies. We thus investigated how much the estimate of the annual "stroke" rate was affected by the inclusion of other diagnoses such as TIA or pulmonary embolism, as in some of the earlier studies (Table 1). We also evaluated how varying degrees of inclusiveness in the counting of secondary diagnoses affected the estimate, under the assumption that a low secondary diagnosis of acute ischemic stroke has lower validity than one given as a principal diagnosis.

Last, we examined how the estimated annual stroke risk was affected by quarantine periods of varying lengths. Quarantine periods are commonly used in registry studies and consist of initial blanking periods after the index AF diagnosis, postponing the counting of days at risk. During this period, no events or deaths are counted. Because patients can only be identified as AF patients when they seek medical care, there will be patients who do not primarily seek medical attention due to AF but do so because of unrelated acute disease. Some of these patients may have done so because of acute stroke, myocardial infarction, imminent death, or some other reason not directly related to AF. If such patients also receive a secondary diagnosis of AF, they will enter the study, and their stroke, myocardial infarction, or death will be attributed to AF. If no blanking period is used, this classification would lead to overestimation of the risks associated with AF. To assess true long-term risks, it is therefore essential to ensure that the study population is stable when the observation period starts. Similar run-in periods are common in clinical drug trials in which it is essential to ascertain that there is no selection bias associated with patient recruitment.

Another reason for using a quarantine period is that acute stroke diagnoses are used in conjunction

TABLE 1 Patient Baseline Characteristics and Applicable ICD-10 Codes

	Study Population	ICD-10 Code or Swedish Procedure Code Beginning With:
Age, mean	77.2	
≥75 yrs	67.3	
65–74 yrs	15.5	
Female	50.1	
Mean CHA$_2$DS$_2$-VASc score	3.61	I50, I10-15, E10-14, I21, I252, I70-73, I63-64, G45, I74 (and age and sex)
Heart failure	31.9	I50
Hypertension	43.8	I10-15
Diabetes	16.4	E10-14
Vascular disease (as in CHA$_2$DS$_2$-VASc)	23.4	I21, I252, I70-73
Thromboembolism (previous)	22.8	I63-64, I69, G45, I74
Ischemic stroke	15.2	I63
Unspecified stroke	3.0	I64
TIA	5.7	G45
Sequelae of old stroke	7.6	I69
Peripheral emboli	1.2	I74
Pulmonary embolism	1.8	I26
Valvular AF	(exclusion criterion)	I342, I050, I052, Q232, Z952, Z954 procedure codes FG, FJE, FJF, FK, FM

Values are mean or %.

AF = atrial fibrillation; CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65–74 years, sex category; ICD-10 = International Classification of Diseases-10th Revision.

with transfers between clinics during the first days or weeks. Absence of a quarantine period may therefore result in double-counting of stroke events and subsequently an exaggerated estimate of the stroke rate.

THE PATIENT REGISTER. The National Patient Register holds detailed information about all hospitalizations and visits to hospital-affiliated open clinics in Sweden. For characterization of previous and current disease, the study considered diagnoses given after 1997 when the International Classification of Diseases-10th Revision (ICD-10), was introduced in Sweden. The specific codes applied are listed in Table 1. Information about previous diagnoses was used to calculate individual risk scores for AF-related stroke.

Validation studies of the quality of diagnoses in the Swedish National Patient Register have shown a positive predictive value of 97% for a diagnosis of AF (17,18) and 88.1% for a diagnosis of stroke (19,20).

RIKS-STROKE. The national stroke register, Riks-Stroke (21), is on the basis of active registration of stroke patients in all 72 hospitals in Sweden admitting patients with acute stroke. Active reporting makes double-counting of old events as new events unlikely. The coverage, compared with the National Patient Register, is 88.2% (22). After adjusting for overreporting in the National Patient Register (e.g., due to transfer between clinics), the coverage in Riks-Stroke is estimated to be 94%.

THE DISPENSED DRUG REGISTER. The Dispensed Drug Register accumulates details of nearly every prescription handled in pharmacies in Sweden since July 1, 2005, and is almost 100% complete given that all pharmacies in the country are required by law to participate. Information is transferred electronically whenever a drug is dispensed. The only registered

OAC agent in Sweden during the study period was warfarin with phenprocoumon, a derivative of coumarin, as an alternative on special license for a small number of patients intolerant to warfarin. Warfarin use at baseline was defined as any purchase of warfarin later than 6 months before and up to 28 days after the index date.

Cross-matching of data in these registers was made by the National Board of Health and Welfare according to unique civic registration numbers that are given to all residents in Sweden, irrespective of citizenship. Before data were made available to us, these numbers were replaced by anonymized numbers to assure participants' personal integrity.

The study was approved by the regional ethics committee (EPN 2010/852-31/3) and conformed to the Declaration of Helsinki. Individual patient consent was not required or obtained.

STATISTICAL METHODS. Baseline characteristics were presented descriptively and differences were tested with Student *t* tests and the chi-square test. Values of p < 0.05 were considered significant. Rates are calculated as events per 100 years at risk but expressed as annualized rates in percents for comprehensiveness. All analyses were performed by using SPSS version 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

During the 5-year study period, 287,512 unique individuals in the National Patient Register received a diagnosis of AF; 11,814 were excluded because of valvular AF. After having studied the prevalence of anticoagulant treatment at baseline, all patients who had been exposed to warfarin any time within

TABLE 2 Annualized Ischemic Stroke Rates in Relation to Duration of Quarantine Period

	n	Riks-Stroke*	Ischemic Stroke (I63)			Thromboembolism Excluding TIA (I63, I64, I74, I26)	Thromboembolism Including TIA (I63, I64, I74, I26, G45)
			Swedish National Patient Register			Swedish National Patient Register	
			Principal Diagnosis Only	Principal or First Secondary Diagnosis	Principal or Any Secondary Diagnosis	Principal or First Secondary Diagnosis	Principal or First Secondary Diagnosis
0 week	140,420	5.4	6.3	6.7	7.2	8.3	9.3
1 week	135,937	3.0	3.7	4.0	4.3	5.0	5.7
2 weeks	132,315	2.9	3.5	3.7	4.1	4.7	5.4
4 weeks	127,292	2.8	3.4	3.6	3.9	4.5	5.2
6 weeks	123,510	2.8	3.3	3.6	3.9	4.4	5.1
8 weeks	120,306	2.8	3.3	3.5	3.8	4.4	5.0
10 weeks	117,554	2.7	3.3	3.5	3.8	4.3	5.0

Values are percent of events per year. *Diagnosis not applicable.

Abbreviation as in Table 1.

6 months before the index date or during the study period (n = 144,111) were excluded from further study. Thus, a total of 140,420 patients were included in the main analysis.

DURATION OF QUARANTINE PERIOD. The overall ischemic stroke event rate, as diagnosed by Riks-Stroke, was 5.4% if no quarantine period was used, 3.0% with a quarantine period of 1 week, and 2.8% with a 4-week quarantine period (**Table 2**). The overall rates were slightly higher if the National Patient Register was used for event detection rather than Riks-Stroke, but the effects of quarantine periods on rates were similar. After ~4 weeks, event rates had stabilized at a level almost one-half as high as if no quarantine period had been used (**Figure 1**). For the purposes of reporting our results, the 4-week quarantine period was chosen as the most representative for long-term stroke risk beyond the first month.

CONSIDERATION OF SECONDARY DIAGNOSES. When a diagnosis of ischemic stroke (I63) was used in the National Patient Register, it was placed as the principal diagnosis in 82% of the cases. Using both the principal and the first secondary diagnoses to identify patients with ischemic stroke classified 90% of cases. A minority had the diagnosis placed far down among the secondary diagnoses; the maximum was a patient with ischemic stroke as the 13th diagnosis. In these cases, circumstances indicated that the appropriate ICD-10 code should have been I69 for sequelae of old stroke, rather than I63 for acute ischemic stroke

(**Figure 1**, **Table 2**). For this reason, only principal and first secondary diagnoses were considered in this analysis.

WIDELY OR STRICTLY DEFINED ENDPOINTS. The addition of unspecified stroke and systemic and pulmonary embolism to the strictly defined endpoint of ischemic stroke increased the event rate estimate at 4 weeks by 25%. Further addition of TIAs increased the estimated rate by 44% (**Table 2**).
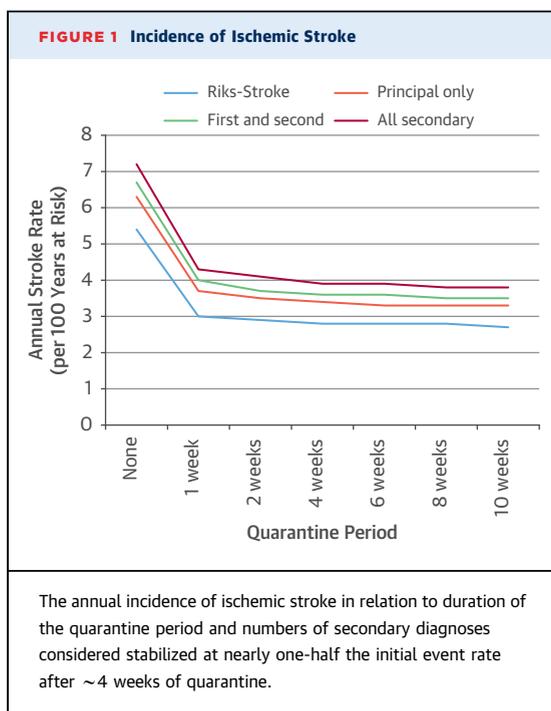
EVENT RATES AT A CHA$_2$DS$_2$-VASc SCORE OF 1. At a CHA$_2$DS$_2$-VASc score of 1, the annual event rates in the Swedish National Patient Register varied between 0.5% and 0.9%, depending on whether only ischemic strokes were counted or a more inclusive endpoint was used (**Central Illustration**); the event rate dropped to 0.3% in Riks-Stroke. European guidelines are clear that women with a CHA$_2$DS$_2$-VASc score of 1 should not be given anticoagulation therapy on the basis of their sex alone (2); the risks of men and women with CHA$_2$DS$_2$-VASc scores of 1 were therefore assessed separately. Indeed, we found that women were truly low risk, with an annual ischemic stroke rate of only 0.1% to 0.2%. For men, the ischemic stroke rate was 0.5% according to Riks-Stroke and 0.7% according to the National Patient Register. When the endpoint was enriched with diagnoses of TIA, pulmonary embolism, arterial embolism, and stroke not specified as ischemic or hemorrhagic, the annual event rate for men was 1.3%.
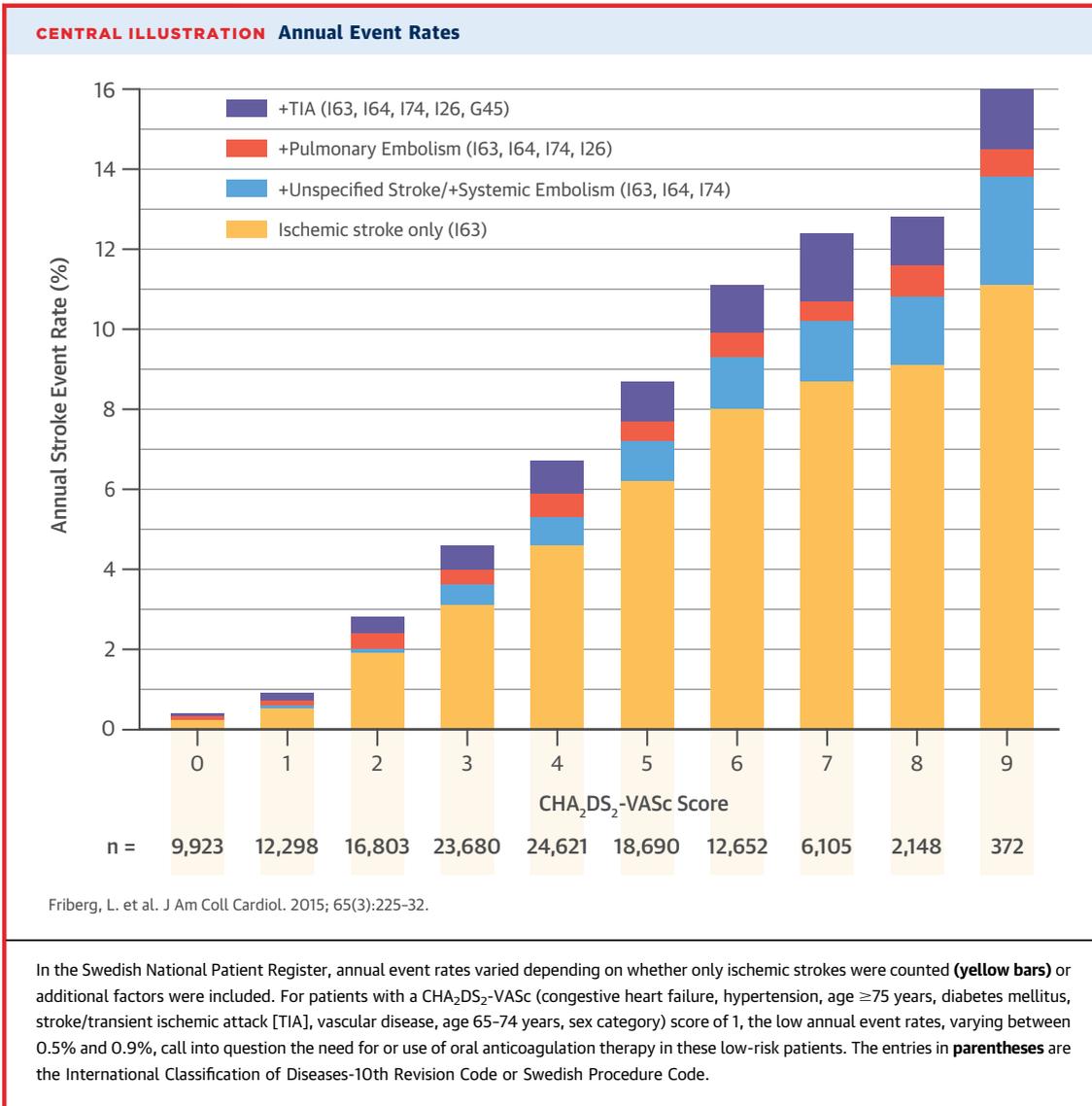
WARFARIN USE AMONG PATIENTS WITH A CHA$_2$DS$_2$-VASc SCORE OF 1. Cross-matching the National Patient Register with the Dispensed Drug Register found that 46.2% of the men and 22.5% of the women with a CHA$_2$DS$_2$-VASc score of 1 had taken warfarin at baseline. Overall, warfarin use was more common among these low-risk patients than among patients with a CHA$_2$DS$_2$-VASc score ≥3 (**Figure 2**).

DISCUSSION

The risk of ischemic stroke among patients with AF and a CHA$_2$DS$_2$-VASc score of 1 seems to be lower than previous studies have indicated. This earlier finding may have led to unnecessary, and potentially harmful, OAC treatment of low-risk patients.

The present study found that diverging estimates of stroke risks associated with AF are partly due to differences in study methods. Although event rates in previous studies generally are thought of as describing stroke risk, the figures actually represent much more diverse endpoints. Several of the studies included pulmonary embolism in the "stroke" endpoint (6,8–10) and some included TIAs (9,13). We do not agree on the inclusion of pulmonary

FIGURE 1 Incidence of Ischemic Stroke

The annual incidence of ischemic stroke in relation to duration of the quarantine period and numbers of secondary diagnoses considered stabilized at nearly one-half the initial event rate after ~4 weeks of quarantine.

CENTRAL ILLUSTRATION **Annual Event Rates**

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In the Swedish National Patient Register, annual event rates varied depending on whether only ischemic strokes were counted (**yellow bars**) or additional factors were included. For patients with a CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category) score of 1, the low annual event rates, varying between 0.5% and 0.9%, call into question the need for or use of oral anticoagulation therapy in these low-risk patients. The entries in **parentheses** are the International Classification of Diseases-10th Revision Code or Swedish Procedure Code.
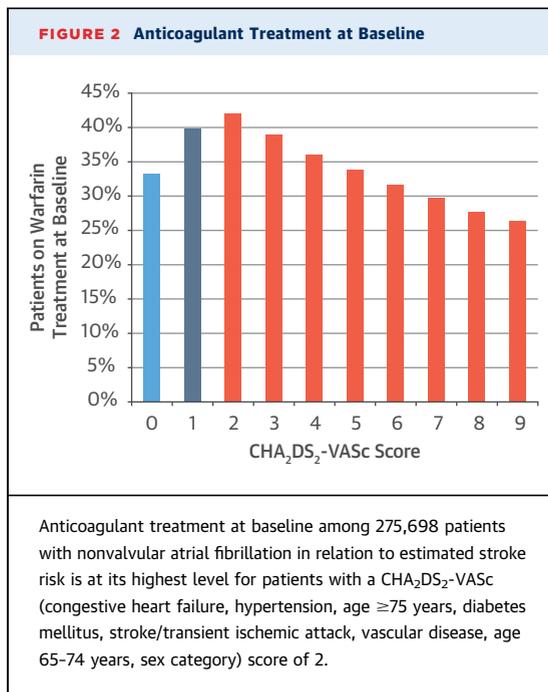
embolism. Although OAC treatment also protects against pulmonary embolism, a general desire to avoid pulmonary embolism should not affect decisions regarding anticoagulation in patients with AF. Primary prevention of pulmonary embolism among patients with AF has, to the best of our knowledge, not been studied and is not an approved indication for OAC treatment.

We also did not find it relevant to count TIA as an endpoint in studies that describe stroke risk. As a diagnosis, TIA is difficult to validate. Patients with diffuse symptoms or dizziness may be diagnosed at times with TIA when no other diagnosis seems applicable, especially if the diagnosis is made by less experienced physicians working in areas other than neurology and stroke care (23). TIAs are important as

markers of increased risk for future stroke and should be counted in risk scores such as CHA$_2$DS$_2$-VASc. Although TIAs should be used to alert physicians to the need to initiate OAC treatment, TIAs remain poor endpoints for studies of stroke risk.

Some older studies did not specify what was included in the endpoint (7,10,12,13) but incorporating more diagnoses inevitably serves to inflate the estimated stroke risk. We found that the overall event rate increased by 44% if TIA, pulmonary embolism, systemic embolism, and unspecified strokes were added to the endpoint. In some studies, all patients were receiving anticoagulant treatment, and extrapolation was used to estimate what the stroke risk would have been without anticoagulant agents (7,9). Most studies do not mention quarantine periods;

FIGURE 2   Anticoagulant Treatment at Baseline

Anticoagulant treatment at baseline among 275,698 patients with nonvalvular atrial fibrillation in relation to estimated stroke risk is at its highest level for patients with a CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) score of 2.

however, a lack of quarantine periods will result in higher risk estimates than would be the case after the first few weeks. It is the long-term risk that is relevant for decisions regarding anticoagulation.

The extreme estimates of stroke risk in the Danish registry study (8) are difficult to explain; the 2.01% risk at a CHA$_2$DS$_2$-VASc score of 1 is 2 or 3 times higher than other studies (6,7,9-12). However, these figures have been extensively used as a reference and thus have exerted considerable influence on the European decision to recommend treatment to patients with CHA$_2$DS$_2$-VASc scores of 1. Even when we include pulmonary embolism in the endpoint (which we oppose), our estimates only reach an annual risk of 0.7% (**Central Illustration**). In the Danish study, a quarantine period of 7 days was used, which may have increased the estimates. The Danish study also seems to have identified thromboembolic events from secondary diagnoses in any position, whereas in the main analysis, we used only the principal and first secondary diagnoses to avoid the common confusion in which patients with sequelae of stroke (code I69) incorrectly receive codes for acute stroke (I63 or I64). The Danish study also reported much lower prevalence of heart failure and diabetes (about one-half of that in the present study); these findings suggest that the Danish patients may have been given risk scores that were too low.

With an annual stroke risk of 2.0%, as in the Danish study (8), anticoagulant treatment is expected to be of benefit, unless the bleeding risk is extreme (14-16).

In a study of the net benefit of OAC treatment in AF, Eckman et al. (24) found that an annual stroke risk of 1.7% constitutes a tipping point at which treatment with warfarin becomes beneficial. If one of the newer safer drugs is chosen instead of warfarin, the tipping point could be as low as 0.9% annually. In the present study, men with a CHA$_2$DS$_2$-VASc score of 1 had an annual stroke risk well below both the 1.7% and 0.9% limits. Treatment benefit is therefore unlikely with warfarin or even with the newer drugs (dabigatran, rivaroxaban, or apixaban). Subsequently, the cost-effectiveness of treatment will be low, or even negative, if treatment causes more harm than good.

Guidelines do not recommend OAC treatment of women with AF and CHA$_2$DS$_2$-VASc scores of 1 because they are considered to be low risk and are not expected to benefit from anticoagulation therapy (25,26). Our results confirm this view. Nevertheless, 22.5% of these low-risk patients were on warfarin therapy. Among men with CHA$_2$DS$_2$-VASc scores of 1, the annual stroke risk ranged between 0.5% and 0.7%; almost one-half of them, however, were on OAC treatment, a much higher proportion than seen among high-risk patients who are likely to have much larger benefit from anticoagulation.

European guidelines favor OAC treatment at CHA$_2$DS$_2$-VASc scores of 1, whereas the newly adopted U.S. guidelines recommend treatment from 2 points and higher, with an option to treat with OAC, aspirin, or nothing at 1 point (27). Our results indicate that the European recommendation for OAC treatment at a CHA$_2$DS$_2$-VASc score of 1 may be unwise.

STUDY LIMITATIONS. The present study assessed hospital-based registers and does not include data on patients managed exclusively in primary care or data on patients with silent, undiagnosed AF. The result may therefore not be applicable to these groups. Nevertheless, the present study is twice as big as the largest study conducted thus far (8) and >100 times larger than the original CHA$_2$DS$_2$-VASc study (6).

Unlike prospective registries, such as GARFIELD (Global Anticoagulant Registry in the FIELD) (28), GLORIA-AF (Global Registry on Long-Term Oral Anti-Thrombotic Treatment in Patients With Atrial Fibrillation) (29), PREFER-AF (Prevention of Thromboembolic Events-European Registry in Atrial Fibrillation) (30), and ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) (31), this was a retrospective study (although information was collected prospectively). However, with this approach, we were unable to verify diagnoses directly, prescribe examinations, or obtain other information than what had been coded into binary ICD-10 codes or drug prescriptions. However, the study did have all

the advantages of working with "big data," including no selection bias because all AF patients in the country were included, not just those subjects considered cooperative and suitable for participation in a study.

In addition, it should be recognized that CHA$_2$DS$_2$-VASc and other major risk stratification schemes were developed and validated in retrospective registries. Swedish health databases include detailed information about all residents; hence, there are no selection biases. Availability of such details makes characterization of comorbidity more complete, which will render higher risk scores than if less well-managed registries or databases were used. Working with population registries means that virtually no patients are lost to follow-up, and detection of events during the study will be higher than if more limited registers are used. Together, this makes it necessary to exercise caution when comparing registry studies from different countries.

Although the Swedish registries are mostly correct about a diagnosis when it is given (18-20,32), under-reporting of diagnoses are common. Establishing the negative predictive value is difficult because it entails screening the general population for each diagnosis. Thus, some patients classified as having a CHA$_2$DS$_2$-VASc score of 1 would rightly have been classified higher if all information had been available. If these misclassified patients were to be analyzed according to their true higher score, the estimated risk for patients with a true score of 1 would have been lower than our results indicate.

Using quarantine periods means that patients with true recurrent strokes within the quarantine period will not be recognized as such. However, this will not affect the estimates of long-term risks because the counting of time at-risk did not start before the quarantine period ended. In addition, not all patients had their diagnosis verified by cerebral imaging, perhaps leading to some misclassifications. To help control against this issue, information from both registries was compared. As a sensitivity analysis, we also performed analyses with different degrees of inclusiveness and discussed how this affected the estimates.

It is possible that some deaths were due to unrecognized stroke. Autopsies are seldom performed in Sweden if there is a known severe disease that is a likely cause of death. Patients dying outside the hospital under uncertain circumstances, however, are generally subjected to autopsy to determine the cause of death. It is therefore unlikely that such underestimation could have affected estimates more than marginally.

Information about drug exposure from the Dispensed Drug Register does not list medicine given during hospital stays, although drugs used by patients in long-term care are included in the register. Thus, some patients allegedly not exposed to warfarin may, in fact, have been administered warfarin for a short period while in the hospital. This action may have acted to reduce the risk estimates to some degree.

CONCLUSIONS

The risk of ischemic stroke in patients with AF and a CHA$_2$DS$_2$-VASc score of 1 seems to be lower than previously thought. No benefit is anticipated for routine administration of OAC agents to these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Stroke risk in AF varies with age and comorbidity. OAC agents offer efficient protection against stroke, but they are associated with increased risk of bleeding.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The stroke risk assessment scheme CHA$_2$DS$_2$-VASc is used to identify genuinely low-risk patients who will not benefit from anticoagulant treatment.

TRANSLATIONAL OUTLOOK: Improved individualized risk assessment is essential when making decisions about anticoagulant treatment of patients with AF.

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