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Atrial Fibrillation in Transient Ischemic Attack Versus Ischemic Stroke

A Swedish Stroke Register (Riksstroke) Study

Fredrik Buchwald, MD; Bo Norrving, MD; Jesper Petersson, MD

Background and Purpose—Compared with ischemic stroke (IS), the association of atrial fibrillation (AF) with transient ischemic attack (TIA) is less well established. We aimed to assess the proportion of AF in patients with TIA, and these patients' characteristics and secondary preventive treatment in comparison to patients with IS.

Methods—Hospital-based data on TIA and IS events, registered from July 2011 to June 2013, were obtained from the Swedish Stroke Register (Riksstroke). A time-based TIA definition (duration of symptoms <24 hours) was applied. AF was registered as present when previously known or diagnosed at the time of assessment.

Results—AF was present in 2779 of 14 980 (18.6%) patients with TIA and 13 258 of 44 173 (30.0%) patients with IS. The proportion of AF increased with age, reaching 32.9% in TIA and 46.6% in IS patients ≥85 years. Both in TIA and IS, age, hypertension, a history of stroke, and TIA, and being a nonsmoker were associated with the presence of AF. In contrast to IS, AF was less common in female than in male patients with TIA. At discharge, 64.2% of TIA and 50.0% of IS patients with AF were treated with oral anticoagulants. Proportions of AF patients treated with oral anticoagulants decreased substantially with increasing age.

Conclusions—AF is highly prevalent not only in IS but also in TIA patients, with proportions steeply increasing with age. In both TIA and IS, a substantial proportion of patients with AF were discharged without anticoagulant therapy. (*Stroke*. 2016;47:2456-2461. DOI: 10.1161/STROKEAHA.116.013988.)

Key Words: anticoagulants ■ atrial fibrillation ■ hypertension ■ stroke ■ transient ischemic attack

Atrial fibrillation (AF) increases the risk of stroke 5-fold, but it is effectively reduced by the use of vitamin K antagonist and non-vitamin K antagonist oral anticoagulants (OACs) as recommended in current guidelines.¹⁻³ The proportion of AF among patients with ischemic stroke (IS) has been reported to range from 19% to 38%, with variability because of ethnicity, age, and detection mode.⁴⁻⁹ Men carry a higher burden of AF,¹⁰ whereas women are more at risk of AF-associated IS,^{4,9} the reasons for which are not completely understood.¹¹

Whereas the role of AF in IS is well established, there are fewer reports on its contribution to transient ischemic attack (TIA). Substantially lower proportions of AF have been reported for TIA patients ranging from 6.7% to 17.2%.¹²⁻²³ A cardioembolic pathogenesis in TIA according to TOAST (Trial of Org 10172) criteria,²⁴ that is, AF and other cardiac causes, was reported to be likely in 14.7% to 19.4% of patients, whereas the percentage of patients with undetermined cause could be as high as 46.4%.^{17,20}

By evaluating population-based data from a large national register (The Swedish Stroke Register; Riksstroke), we wish to assess the proportion of AF in TIA in comparison to IS and clarify patient characteristics and secondary preventive measures.

Methods

Study Population

Data on TIA events, registered from July 1, 2011 to June 30, 2013, were obtained from the Swedish Stroke Register TIA module (Riksstroke-TIA, RS-TIA); 59 of 72 Swedish hospitals contributed with data to this register.²⁵ TIA diagnosis was based on a time-based definition, that is, an acute focal neurological deficit of presumed vascular origin with complete remission of symptoms <24 hours irrespective of neuroimaging findings. Data on IS events, registered during the same period of time, were obtained from the stroke module in the Swedish Stroke Register (Riksstroke, RS),²⁶ to which all Swedish hospitals involved in acute stroke care contributed.

Patients aged ≥18 years with *International Classification of Diseases Tenth Revision* diagnoses of TIA (G45, excluding G45.4) and IS (I63) were included. For patients with >1 stroke during the course of 28 days, only the first event was included. All patients included in this study were taken care of in-hospital.

Registered Items

Both in RS-TIA and RS, data on demography, risk factors, diagnostic measures, medical treatment at arrival and discharge, and follow-up were registered. In RS-TIA the ABCD2 score was recorded, and in RS details on functional ability and symptoms preadmission, level of medical care, acute stroke treatment,

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stroke-related complications, rehabilitation, and mortality. In RS, an item on continuous cardiac arrhythmia detection in-hospital was only registered from 2012 onwards, whereas it was available for the whole study period in RS-TIA. Results of continuous cardiac arrhythmia detection post discharge were not registered.

Definition of Items

AF was registered as present or absent without specification whether it was previously known or diagnosed during the current hospital admission. Subtypes of AF were not recorded in separate. In RS-TIA, instead of hypertension, blood pressure-lowering medication at arrival and discharge was registered. The registered item of a previous stroke did not specify whether it was hemorrhagic or ischemic. Carotid ultrasound, computed tomographic angiography, and magnetic resonance angiography were registered as performed when done within 28 days before or 7 days after the qualifying event. Continuous cardiac rhythm monitoring methods included Holter ECG, telemetry, and any other continuous monitoring method. As a measure of stroke severity at admittance, the Reaction Level Scale RLS-85²⁷ was used, with categories of fully awake (RLS 1), somnolent (RLS 2–3), and comatose (RLS 4–8), in addition to the NIHSS (National Institutes of Health Stroke Scale). Vitamin K antagonist and non-vitamin K antagonist OACs are referred to as OACs.

Descriptive and Statistical Analysis

SPSS 22.0 and Excel were used for statistical analyses. Categorical variables are summarized as proportions and quantitative variables as means or medians. Proportions were derived from the total of patients in whom the respective item was registered. Baseline data were compared with prevalence differences (PDs) and 95% confidence intervals (CIs).

Ethics

The study was approved by the local ethics committee (Dnr 2013/719).

Results

Proportions of AF

In the 2-year study period, 15064 patients were registered in the TIA module (RS-TIA) and 44416 patients with IS in the acute stroke module (RS); the presence or absence of AF was documented in >99% of TIA and IS patients. AF was present in 18.6% (2779/14980) of patients with TIA compared with 30.0% (13258/44173) of patients with IS (PD, -11.5; CI, -12.2 to -10.7). The proportion of AF in patients with TIA increased with age, from 1.9% (6/324) in patients aged <45 years to 32.9% (909/2763) in patients aged ≥85 years. AF was less common in TIA compared with IS in all age groups (Figure 1). In female patients with TIA, the proportion of AF was 17.7% (1283/7229), in male patients it was 19.1% (1478/7751; PD, 1.3; CI, -2.6 to -0.1; Figure 2A). In contrast, female patients admitted due to IS had a higher proportion of AF with 33.3% (7089/21297) versus 27.0% (6169/22876; PD, 6.3; CI, 5.5–7.2) in men (Figure 2B).

Patient Characteristics

Mean age in patients with TIA was 73.1 years compared with 75.7 years in patients with IS. In TIA patients with AF, the mean age was 79.2 years; and in IS patients with AF, the mean age was 81.1 years. Patients with TIA had lower proportions of hypertension, diabetes mellitus, and previous stroke than patients with IS, and they were less likely to be smokers. A history of TIA, however, was more common in patients with TIA than in those with IS (Table 1).

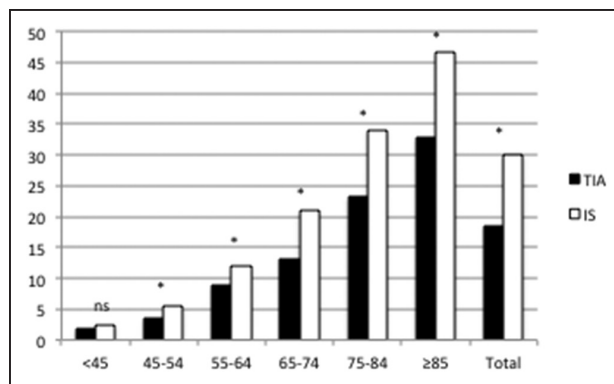


Figure 1. Proportion (%) of atrial fibrillation in patients with transient ischemic attack (TIA) and ischemic stroke in relation to age. Above the columns, the significance of difference is indicated, as tested by prevalence difference and 95% confidence interval. IS indicates ischemic stroke; and ns, not significant. *Significant.

Both in TIA and IS patients, age, hypertension, being a nonsmoker, and a history of stroke and TIA were associated with the presence of AF. Among patients with TIA, women had lower proportions of AF than men, whereas they had higher proportions of AF than men when admitted due to IS. Diabetes mellitus was associated with AF in TIA; in IS, no such association was observed (Table 2).

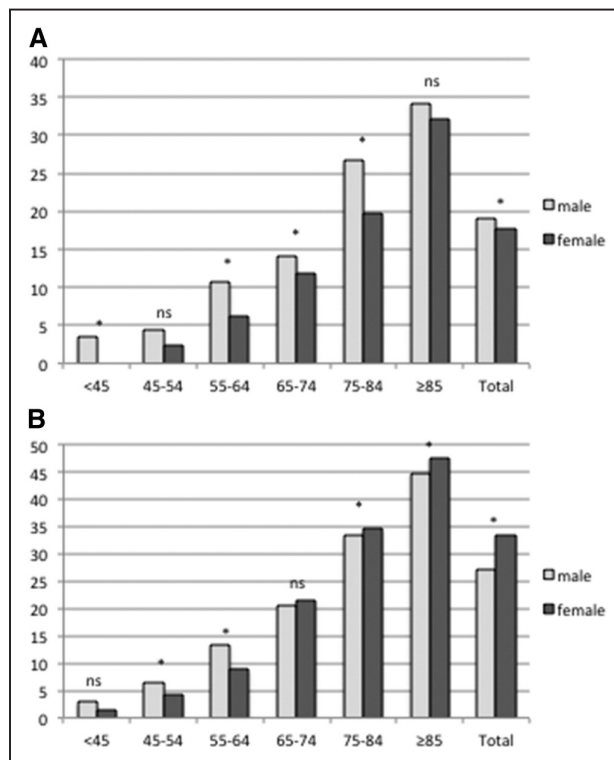


Figure 2. A, Proportion (%) of atrial fibrillation in male and female patients admitted for transient ischemic attack in relation to age. Above the columns, the significance of difference is indicated, as tested by prevalence difference and 95% confidence interval. **B,** Proportion (%) of atrial fibrillation in male and female patients admitted for ischemic stroke in relation to age. Above the columns, the significance of difference is indicated, as tested by prevalence difference and 95% confidence interval. ns indicates not significant. *Significant.

Table 1. Baseline Characteristics in Patients Admitted With TIA and Ischemic Stroke

	TIA	IS	Difference TIA–IS; PD % (95% CI)
Female, n (%)	7229/14 980 (48.3)	21 297/44 173 (48.2)	0.0 (–0.9 to 1.0)
Age, mean (SD)	73.1 (12.3)	75.7 (12.3)	...
Atrial fibrillation, n (%)	2779/14 980 (18.6)	13 258/44 173 (30.0)	–11.5 (–12.2 to –10.7)
Hypertension, n (%)*	9033/14 926 (60.5)	27 629/44 015 (62.8)	–2.3 (–3.2 to –1.4)
Diabetes mellitus, n (%)	2345/14 903 (15.7)	9342/44 130 (21.2)	–5.4 (–6.1 to –4.7)
Smoking, n (%)	1653/13 899 (11.9)	5848/41 103 (14.2)	–2.3 (–3.0 to –1.7)
History of stroke, n (%)	2868/14 945 (19.2)	10 806/44 031 (24.5)	–5.4 (–6.1 to –4.6)
History of TIA, n (%)	2707/14 850 (18.2)	3968/43 653 (9.1)	9.1 (8.5 to 9.8)
Consciousness level at admission			
Fully awake, n (%)	...	37 473/43 636 (85.9)	...
Somnolent, n (%)	...	4768/43 636 (10.9)	...
Comatose, n (%)	...	1395/43 636 (3.2)	...
NIHSS at admission†			
Mean (SD)	...	5.79 (6.6)	...
Median	...	3	...

CI indicates confidence interval; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; PD, prevalence difference; and TIA, transient ischemic attack.

*In patients with TIA defined by item blood pressure–lowering medication at admission.

†Data available in 21 633 of 44 173 patients with IS.

Diagnostic Procedures

In-hospital continuous cardiac monitoring was performed in 47.7% (7054/14 792) of patients with TIA and in 45.0% (14 622/32 507) of patients with IS. As shown in Table 3, TIA patients with AF underwent a computed tomographic head scan in >97%, and IS patients with AF in >98%. In TIA patients with AF, magnetic resonance imaging and computed tomographic angiography were less often utilized, whereas carotid ultrasound was more often done compared with IS patients with AF.

Antithrombotic Treatment at Admission

At admission, the presence or absence of ongoing antithrombotic treatment was registered in >99% of patients with TIA and >98% of patients with IS. Treatment with OACs was ongoing in 8.7% (1292/14 922) of patients with TIA, antiplatelet medication alone (without concomitant OAC) in 40.1% (5989/14 922), and 51.2% (7641/14 922) did not have any antithrombotic treatment. TIA patients with AF were on OAC medication in 36.8% of cases (1019/2766). Women and men were equally often treated (454/1276, 35.6% versus 565/1490, 37.9%; PD, –2.3; CI, –5.9 to 1.3).

In patients admitted for IS, 8.8% (3803/43 317) were on OAC, 42.4% (18 346/43 317) on antiplatelet drugs only, whereas 48.9% (21 168/43 317) were not on any antithrombotic medication. The proportion of ongoing OAC treatment in IS patients with AF was lower than in patients with TIA, that is, 23.7% (3074/12 945). Female patients with AF were less likely to be treated with OAC than men (1389/6852, 20.3% versus 1685/6093, 27.7%; PD, –7.4; CI, –8.9 to –5.9).

Antithrombotic Treatment at Discharge

Antithrombotic treatment at discharge was registered in >99% of TIA and surviving IS patients. TIA patients with AF were treated with OAC in 64.2% (1778/2771) of cases, ranging from 80.5% (177/220) in patients aged <65 years to 45.5% (412/905) when aged ≥85 years. Only 4.6% (126/2769) were discharged without any antithrombotic medication. The proportion of OAC treatment in female TIA patients with AF was lower than in male patients (785/1279; 61.4% versus 993/1492; 66.6%; PD, –5.2; CI, –8.8 to –1.6).

In comparison to TIA, a lower proportion of IS patients with AF was treated with OAC at discharge, that is, 50.0% (5502/10 899) of cases, and a higher proportion was discharged without any antithrombotic treatment (9.3%, 1011/10 899). As in the TIA group, women with IS and AF were less likely to be treated with OAC at discharge than men (Table 4).

Discussion

On the basis of data from large national TIA and stroke registers in Sweden, we have shown that the proportion of known or recently diagnosed AF in patients with TIA is 18.6%, which is higher than previously reported. Earlier population-based and multicenter studies on patients with TIA have reported proportions of AF ranging from 9% to 17.2%,^{14–18,21–23} whereas data from single centers or specialist services tended to be even lower.^{12,13,19,20} In our study, the proportion of AF in patients with TIA markedly increased with age reaching about a quarter in the age group of 75 to 84 years and a third in patients aged ≥85 years. This age pattern is in line with previous reports on TIA²³ and IS.⁴ Among our patients with IS, we found a higher proportion of AF than in patients with TIA. We

Table 2. Proportions of Atrial Fibrillation According to Patient Characteristics in Patients With TIA Compared With Patients With Ischemic Stroke

Characteristics		TIA		IS		Difference TIA-IS	
		AF Present		AF Present		PD % (95% CI)	PValue*
		n	% (95% CI)	n	% (95% CI)		
Sex	Female	1283/7229	17.7 (16.9–18.6)	7089/21 297	33.3 (32.7–33.9)	–15.5 (–16.6 to –13.2)	†
	Male	1496/7751	19.3 (18.4–20.2)	6169/22 876	27.0 (26.4–27.5)	–7.7 (–8.7 to –5.4)	†
Hypertension	Yes	2261/9033	25.0 (24.1–26.0)	9639/27 629	34.9 (34.3–35.5)	–9.9 (–10.9 to –7.8)	†
	No	509/5893	8.6 (7.9–9.4)	3544/16 386	21.6 (21.0–22.3)	–13.0 (–14.0 to –12.0)	†
Diabetes mellitus	Yes	497/2345	21.2 (19.5–22.9)	2760/9342	29.5 (28.6–30.5)	–8.4 (–10.3 to –4.4)	†
	No	2265/12 558	18.0 (17.4–18.7)	10 471/34 788	30.1 (29.6–30.6)	–12.1 (–12.9 to –10.3)	†
Smoking	Yes	162/1653	9.8 (8.4–11.2)	944/5848	16.1 (15.2–17.1)	–6.3 (–8.1 to –1.2)	†
	No	2362/12 246	19.3 (18.6–20.0)	11 157/35 255	31.7 (31.2–32.1)	–12.4 (–13.2 to –10.6)	†
History of stroke	Yes	785/2868	27.4 (25.7–29.0)	3896/10 806	36.1 (35.2–37.0)	–8.7 (–10.6 to –5.2)	†
	No	1983/12 077	16.4 (15.8–17.1)	9311/33 225	28.0 (27.5–28.5)	–11.6 (–12.4 to –9.7)	†
History of TIA	Yes	551/2707	20.4 (18.8–21.9)	1281/3968	32.3 (30.8–33.7)	–11.9 (–14.0 to –7.7)	†
	No	2191/12 143	18.0 (17.4–18.7)	11 764/39 685	29.6 (29.2–30.1)	–11.6 (–12.4 to –9.8)	†
Age, y	<65	222/3306	6.7 (5.9–7.6)	711/7634	9.3 (8.7–10.0)	–2.6 (–3.7 to –1.5)	†
	65–74	554/4204	13.2 (12.2–14.2)	2206/10 504	21.0 (20.2–21.8)	–7.8 (–9.1 to –4.5)	†
	75–84	1094/4707	23.2 (22.0–24.5)	4824/14 197	34.0 (33.2–34.8)	–10.7 (–12.2 to –7.9)	†
	≥85	909/2763	32.9 (31.2–34.7)	5517/11 838	46.6 (45.7–47.5)	–13.7 (–15.7 to –10.4)	†

AF indicates atrial fibrillation; CI, confidence interval; IS, ischemic stroke; PD, prevalence difference; and TIA, transient ischemic attack.

*Fisher exact test with 2-sided P values.

†P<0.0001.

here report the occurrence of AF in 30% of our patients with IS, a proportion that agrees well with other studies.⁴⁻⁹

According to a recent meta-analysis, choice of diagnostic method and timing have an impact on AF detection in IS and TIA patients with no known AF.²⁸ In this meta-analysis, AF was diagnosed by a default ECG in the emergency department in 7.7% of patients, and during in-hospital stay in 5.1%; in addition, a substantial number of diagnoses were made in the ambulatory phase after discharge. In our study, we included AF diagnosed during the current hospital stay but no postdischarge results, which is in line with most previous reports. All our patients with TIA were admitted to hospital, which was the case in only one of the referred studies,¹⁷ whereas in the others, when stated, 50% of patients or more were discharged home from the emergency department.^{15,16,18,21} Thus, it is likely that

the high proportion of in-hospital care in our study contributes to a higher AF detection rate in patients with TIA.

The mean age of our patients with TIA could, in part, explain the high proportion of AF. Compared with data from other population-based and multicenter studies,^{14-18,21} our patients' mean age was older (73.1 years) with the exception of the OXVASC study (Oxford Vascular Study; 73.7 years).²² Notably, this latter study also reported a relatively high proportion of AF, that is, 16%. Distribution of AF with respect to sex was comparable to referred studies as were proportions of vascular risk factors, including hypertension, diabetes mellitus, smoking, and previous TIA and stroke.

Contrary to the female predominance in AF-associated IS,^{4,9} female patients with TIA had a significantly lower proportion of AF than men. This was an unexpected finding, and

Table 3. Evaluation of TIA and IS Patients With Atrial Fibrillation

	TIA		IS		Difference TIA-IS
	n	% (95% CI)	n	% (95% CI)	PD % (95% CI)
CT	2699/2779	97.1 (96.5–97.7)	13104/13 254	98.9 (98.7–99.1)	–1.8 (–2.4 to –1.1)
MRI	108/2773	3.9 (3.2–4.6)	1015/13 196	7.7 (7.2–8.2)	–3.8 (–4.7 to –3.0)
Carotid ultrasound	1295/2773	46.7 (44.8–48.6)	3318/13 164	25.2 (24.5–26.0)	21.5 (19.5 to 23.5)
CTA	249/2771	9.0 (7.9–10.1)	1746/13 144	13.3 (12.7–13.9)	–4.3 (–5.5 to –3.1)
MRA	33/2767	1.2 (0.8–1.6)	147/13 144	1.1 (0.9–1.3)	0.1 (–0.4 to 0.5)

CI indicates confidence interval; CT, computed tomography; CTA, computed tomographic angiography; IS, ischemic stroke; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PD, prevalence difference; and TIA, transient ischemic attack.

Table 4. Oral Anticoagulation Treatment in Female and Male Patients With Atrial Fibrillation at Discharge, Separately for TIA and Ischemic Stroke

	Age, y	Female		Male		Difference; Female–Male
		n	% (95% CI)	n	% (95% CI)	PD % (95% CI)
TIA	<65	51/61	83.6 (74.3–92.9)	126/159	79.2 (72.9–85.6)	4.4 (–6.9 to 15.6)
	65–74	162/208	77.9 (72.2–83.5)	253/346	73.1 (68.5–77.8)	4.8 (–2.6 to 12.1)
	75–84	329/471	69.9 (65.7–74.0)	445/621	71.7 (68.1–75.2)	–1.8 (–7.3 to 3.7)
	≥85	243/539	45.1 (40.1–49.3)	169/366	46.2 (41.1–51.3)	–1.1 (–7.7 to 5.5)
	Total	785/1279	61.4 (58.7–64.0)	993/1492	66.6 (64.2–69.0)	–5.2 (–8.8 to –1.6)
IS	<65	123/172	71.5 (64.8–78.3)	349/492	70.9 (66.9–75.0)	0.6 (–7.3 to 8.4)
	65–74	470/717	65.6 (62.1–69.0)	847/1232	68.8 (66.2–71.3)	–3.2 (–7.5 to 1.1)
	75–84	1072/1984	54.0 (51.8–56.2)	1245/2084	59.7 (57.6–61.9)	–5.7 (–8.8 to –2.7)
	≥85	854/2769	30.8 (29.1–32.6)	542/1449	37.4 (34.9–39.9)	–6.6 (–9.6 to –3.5)
	Total	2519/5642	44.7 (43.4–45.9)	2983/5257	56.7 (55.4–58.1)	–12.1 (–14.0 to –10.2)

CI indicates confidence interval; PD, prevalence difference; and TIA, transient ischemic attack.

further studies will be necessary to clarify this sex difference between TIA and IS.

The presence of AF in TIA and IS patients was associated with age, hypertension, and nonsmoking, whereas AF was associated with diabetes mellitus only in patients with TIA but not in patients with IS. Prevalence of hypertension and diabetes mellitus increase with age,^{29,30} and both risk factors are reported to be independently associated with AF.^{31–33} In previous studies on AF in TIA and IS, however, patients with AF were not more likely to be hypertensive or diabetic.^{4,7,23} These findings might need further clarification. Smoking rates decrease significantly by age³⁴ and are, therefore, expected to be lower in patients with AF.

Both TIA and IS events occurred in patients with AF in spite of ongoing OAC treatment. More than a third of TIA patients with AF and almost a fourth of IS patients with AF were on OAC medication at admission. This proportion in patients with IS is comparable to a previous study⁹; but to our knowledge, there are no previous reports on patients with TIA. Our results are limited by the fact that we have not got access to international normalized ratio levels. Roughly, 80% of Swedish patients with AF treated with warfarin are within the therapeutic range³⁵; among Swedish patients admitted with TIA and IS, this proportion might be lower; but to our knowledge, there is no data on this group of patients with AF. Our results suggest that TIA, too, occurs in a significant number of treated patients with AF.

Although the proportion of AF in TIA and IS patients increases markedly with age, we found a marked decrease of OAC treatment in older patients. Female patients with AF were less often anticoagulated than men, both when discharged after IS and TIA. Similar age- and sex-related variations of treatment have previously been highlighted in patients with IS⁹ and in the overall group of patients with AF.¹⁰ To our knowledge, there are no previous reports on TIA. In IS, it is not recommended to start anticoagulants immediately after the event.³⁶ In TIA, however, direct initiation of antithrombotic and anticoagulant medication is recommended.³⁷ It is, thus, unlikely that the decision to start OAC treatment was postponed. Our results in TIA patients with AF showed that ≈30% of patients aged 75 to 84 years and >50% of patients aged ≥85 years were

discharged without OAC. Age is a strong predictor of major bleeding complications³⁸ and no treatment may be justified in some of the elderly patients. Still, our data indicate a substantial undertreatment of patient groups with a high risk of stroke.

There are limitations to our study. Because of the low number of magnetic resonance imaging scans among patients with TIA, we were not able to apply a tissue-based definition but had to rely on the traditional one based on time (duration of symptoms). Because our data did not include results on monitoring for AF after discharge, the proportion of AF for both TIA and IS may be considered a conservative estimate. AF was registered as a dichotomous variable (present or absent); therefore, we did not have access to information whether it was a previously known condition or newly diagnosed nor on its subtypes. These details might have had an impact on treatment decisions, although, according to guidelines,^{1–3} treatment would have been recommended irrespective of these details. Furthermore, we did not have access to international normalized ratio results (or other coagulation tests) and therefore no information on the effectiveness of OAC treatment; the proportion of patients effectively treated with OAC medications is likely to be lower than the reported proportions of treatment.

The strength of this study is that data were obtained from the comprehensive Swedish Stroke Register (Riksstroke) with its consistent data registration.

Conclusions

AF is highly prevalent not only in IS but also in TIA. TIA patients with AF are substantially undertreated, especially the elderly and women.

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Disclosures

None.

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