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Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation

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Aims Knowledge about stroke risk in paroxysmal atrial fibrillation (PxAF) is limited. Although current guideline recommendations advocate the same treatment as in permanent atrial fibrillation (PermAF), most patients with PxAF do not receive prophylactic anticoagulation. The aim of this study is to investigate whether there are differences in stroke risk between PxAF and PermAF.

Methods and results All patients with PxAF ($n = 855$) and PermAF ($n = 1126$) treated for atrial fibrillation (AF) during 2002 at one of Scandinavia's largest hospitals were followed-up for 3.6 years regarding incidence of stroke. Information about type of AF, comorbidity, medication, and clinical events during follow-up was acquired from medical records and the National Register of Hospital Discharges. The incidence of ischaemic stroke was similar in PxAF and PermAF (26 vs. 29 events/1000 patient years). The multivariable-adjusted hazard ratio (HR) for ischaemic stroke in PxAF compared with PermAF was 1.07 (95% CI 0.71–1.61) in subjects without prior stroke. The corresponding HR for any stroke, ischaemic or haemorrhagic, was 0.89 (95% CI 0.61–1.30). Compared with the general population, ischaemic stroke was twice as common as expected in PxAF after standardization for age and sex (standardized incidence ratio 2.12, 95% CI 1.52–2.71). PxAF patients who took warfarin had approximately half as many ischaemic strokes as those who did not take warfarin (HR 0.44, 95% CI 0.30–0.65).

Conclusion Ischaemic stroke is about as common in PxAF as in PermAF, and about twice as common as in the general population. Yet, PxAF patients do not receive protective anticoagulant treatment as often as patients with PermAF do. It is therefore important to increase the use of anticoagulants among PxAF patients in accordance with current guideline recommendations.

Keywords Atrial fibrillation • Paroxysmal atrial fibrillation • Stroke • Systemic embolization • Cerebral haemorrhage • Anticoagulation • Warfarin • Cohort study

Introduction

The stroke risk in paroxysmal atrial fibrillation (PxAF) has not been extensively studied. Most studies on the association between atrial fibrillation (AF) and thrombo-embolic stroke have been made on patient groups consisting mainly of patients with permanent AF (PermAF), or where differentiation between AF types has not been made.[1–4] Knowledge of this risk is important for decisions regarding anticoagulation for this important group of patients, comprising approximately one-third of all patients with symptomatic AF.[5,6]

Warfarin, and other vitamin K antagonists, offer efficient protection against ischaemic stroke, but are associated with increased risks of cerebral bleedings.[7–11] It has repeatedly been demonstrated that AF patients do not get warfarin as often as they should,[12–16] according to current guideline recommendations.[17] Such underprescription is even more common in PxAF than in PermAF.[12] Yet, the stroke risk in PxAF may be the same as in PermAF.[9,18]

Methods

During the early spring 2003, we identified all patients who had received a diagnosis of AF or flutter while treated as inpatients or outpatients during 2002 at the South Hospital in Stockholm, Sweden, or at

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the Gustavsberg Primary Care Centre in a small town close to Stockholm. The patients were identified from the local patient registers at the hospital and at the primary care centre, respectively. After verification of the diagnosis, 2912 patients remained for the study. The study population has previously been presented in reports from the Stockholm Cohort Study on Atrial Fibrillation (SCAF).[12,19] During the inclusion year, 85% of the patients were hospitalized at least once. The complete digitally stored information was examined and validated according to a predefined protocol. Complementary information about previous and current diseases was obtained from the National Hospital Discharge Register going back to 1987 nationally and to 1972 for Stockholm County. The study population has since been followed with re-examinations of medical records and through national registers of hospital discharges and death.

Patients who had a stroke ($n = 93$) in conjunction with the index generating hospital period were excluded. The rationale was that it was likely that the endpoint stroke, which we were studying, was the reason why these patients came to hospital and thus became eligible for the study. Furthermore, it is not acceptable to have an endpoint event as a starting point of an observation period. We also excluded patients who died ($n = 88$) during the hospital period, which gave the diagnosis that made them enter the study. Clearly, patients with AF as part of a terminal illness are not representative of AF patients in general. Furthermore, we also excluded patients who had neither PxAF nor PermAF, as these were the two groups we were studying. This resulted in the exclusion of 619 patients with persistent AF (PersAF) and 148 patients whose type of AF was not possible to determine from the records by the end of the inclusion year. A few patients were excluded because of several of these criteria. After exclusions 1981 patients remained with either PxAF ($n = 855$) or PermAF ($n = 1126$) during the inclusion year 2002. Separate analyses were carried out for patients without a history of stroke at the index generating contact. The mean follow-up was 2.8 $\pm$ 13 years (median 3.3 years, interquartile range 1.7 years). During follow-up, we searched locally in the patient records for information about changes in medication and rhythm status. From the National Register of Hospital Discharges, we gathered information about patients who had received endpoint diagnoses of ishaemic or haemorrhagic stroke. The diagnoses we searched for were I63 (ischaemic stroke), I64 (stroke, undetermined whether stroke or bleeding), and the diagnoses I60 and I61 (cerebral and subarachnoid haemorrhages). Information about deaths was obtained through the civic registration authority. All information about changes in cardiac rhythm or changes in medication during follow-up was dependent on the patients spontaneous contacts with the hospital. Thus, some patients had frequent contacts and others had just one single contact at index.

The study was approved by the ethical committee of Karolinska Institutet.

Definitions

We defined stroke by the ICD-10 codes I63 (ischaemic stroke), I64 (unspecified stroke), and I60–61 (subarachnoid and cerebral haemorrhages). The follow-up period was 3.6 $\pm$ 0.3 years (mean $\pm$ SD). Although some patients had more than one event, only the first stroke episode during follow-up was used in the analyses.

We adhered to the definition of PxAF used in the ACC/AHA/ESC Guidelines,[17] which says that PxAF is the one that terminates spontaneously within 7 days, most often within 24 h. Termination with pharmacological or DC cardioversion does not change this designation if done within the time limits. We used that definition while extracting information from the medical records, but during the process we found that exact information about the duration of the current episode of AF was often lacking. In order to avoid ambiguity in the distinction between PxAF and PersAF, we therefore considered all patients with whom we underwent cardioversion as having PersAF. PermAF was defined as long-standing AF, where attempts to restore sinus rhythm had failed or else been considered meaningless. For patients with first occurrence of AF during 2002, we used the accumulated information available by the end of that year for the classification. All patients were analysed according to the AF type in 2002 irrespective of later changes during follow-up.

Statistical methods

For comparisons within the study population, we used independent sample *t*-tests (two-sided), and χ^2 tests. For stroke-free survival time, Kaplan–Meier analysis with log-rank tests were used. For multivariable analyses, we used Cox regression. Each patient was only represented once in each analysis, i.e. only the first stroke event of the type in question was counted. We ascertained that the proportional hazards assumption was not violated by making sure that regression curves did not cross and that hazard ratios (HR) were reasonably constant across time.

The strategy for the multivariable analyses was to successively introduce variables in the models as needed in order to adjust for confounding factors as far as possible. In the first step, adjustment was only made for age and sex. In the second step adjustment was made for $CHADS_2$ score, which is a scoring system for prediction of stroke risk in AF patients.[17,20] One point is given for each of congestive heart failure, hypertension, age >75 years, and diabetes. Two points are given for any previous stroke or embolic episode. Thirdly, adjustments were made for $CHADS_2$ score and warfarin use on the occasion of a cerebrovascular event, or if the patient had no event, at the latest known contact during follow-up. Finally, extensive adjustment was made for factors known to be associated with the outcome, with the addition of age, sex, and the cofactor of interest, as presented in the legend to the respective table. *P*-values <0.05 were considered significant. Confidence intervals (CI) are 95%. All analyses were performed in SPSS (SPSS Inc., Chicago, IL, USA) 15.0 and 16.0.

Results

Patients with PxAF were younger and had fewer other risk factors for stroke, than patients with PermAF. They were also less often treated with warfarin (*Table 1*). During follow-up, 697 (35%) of the patients died, 152 (8%) had a diagnosis of an ischaemic stroke, 29 (1%) with an unspecified stroke, and 23 (1%) with a haemorrhagic stroke. PxAF patients who had a stroke were younger than PermAF patients with stroke, and less often they had heart failure, had smaller atria, and used statins more often. Otherwise, the groups were similar (*Table 1*).

Stroke in paraoxysmal atrial fibrillation vs. permanent atrial fibrillation

The incidence of a first ischaemic stroke occurred at a rate of 21 vs. 25 events per 1000 patient-years in PxAF and PermAF, respectively ($P = 0.54$). If recurrent strokes were included, the rates were 26 and 29 events, respectively ($P = 0.45$; *Table 2* and *Figure 1*). After adjustment for cofactors there was essentially no difference in the incidence of ischaemic stroke between PxAF and PermAF (used as reference), irrespective of whether patients with a previous history of stroke were included (HR 1.10, 95% CI

Table 1 Baseline characteristics

	All patients					Patients with ischaemic stroke (I63) during follow-up				
	n	PxAF (means ± SD)	*n*	PermAF (means ± SD)	*P*	*n*	PxAF (means ± SD)	*n*	PermAF (means ± SD)	*P*
Age (years)	855	73 ± 13	1126	78 ± 10	<0.0001	66	79 ± 8	86	82 ± 7	0.003
Years since first diagnosis of AF	855	1.4 ± 2.7	1126	2.8 ± 4.0	<0.0001	66	1.4 ± 2.8	86	2.9 ± 4.4	0.021
Days at hospital last 3 years	855	11 ± 25	1126	18 ± 26	<0.0001	66	13 ± 19	86	21 ± 29	0.035
$CHADS_2$ score	855	1.7 ± 1.3	1126	2.4 ± 1.3	<0.0001	66	2.5 ± 1.4	86	2.9 ± 1.3	0.071
LVEF[a]	562	0.49 ± 0.09	762	0.43 ± 0.13	<0.0001	47	0.47 ± 0.09	55	0.42 ± 0.13	0.036
Left atrial diameter[a]	520	42 ± 6	739	48 ± 8	<0.0001	38	43 ± 5	55	48 ± 7	<0.0001
	n	%	*n*	%		*n*	%	*n*	%	
Women	432	51	529	47	0.12	37	56	51	59	0.67
Lone atrial fibrillation	55	6	23	2	<0.0001	0	0	0	0	-
Previous ischaemic stroke/TIA	91	11	207	18	<0.0001	17	26	25	29	0.65
Previous cerebral haemorrhage	5	0.6	21	1.9	0.013	1	1.5	1	1.2	0.85
Previous myocardial infarction	147	17	269	24	0.0003	19	29	21	24	0.54
Heart failure	275	32	720	64	<0.0001	29	44	62	72	0.0004
Valvular defect	187	22	17	37	<0.0001	17	26	30	35	0.23
Mitral stenosis	5	0.6	13	1.2	0.19	0	0	0	0	-
Prior valve surgery	35	4	61	5	0.17	3	4.5	2	2.3	0.45
Pacemaker	108	13	154	14	0.50	5	8	8	9	0.71
Hypertension	409	48	533	47	0.82	39	59	47	55	0.58
Peripheral arterial disease	91	11	165	15	0.008	8	12	14	16	0.47
Diabetes mellitus	140	16	231	21	0.019	13	20	13	15	0.46
Renal failure	28	3	29	3	0.37	1	1.5	3	3.5	0.45
Chronic pulmonary disease	149	17	259	23	0.002	11	17	21	24	0.25
Thyroid disease (incl. previous)	99	12	137	12	0.69	8	12	19	22	0.11
Cancer <3 years	54	6	98	9	0.048	4	6	8	9	0.46
Alcohol/drug abuse	26	3	54	5	0.049	2	3	4	5	0.61
Contraindication against warfarin	134	16	308	27	<0.0001	18	27	30	3	0.32
Medication at index										
Warfarin	238	28	555	49	<0.0001	21	32	33	38	0.40
Aspirin	415	49	460	41	<0.0001	39	59	43	50	0.27
No prophylaxis	187	22	97	9	<0.0001	4	6	6	7	0.82
Beta-blocker	424	50	628	56	0.0063	36	55	53	62	0.38
ACE-I/A2-blocker	240	28	469	42	<0.0001	17	26	34	40	0.075
Statin	208	24	178	16	<0.0001	24	36	13	15	0.0025

[a]Echocardiography performed on 61% of PxAF and 67% of PermAF patients.

Table 2 Incidence of first and recurrent stroke in relation to type of atrial fibrillation (AF)

	Ischaemic stroke I63						Any stroke (ischaemic, haemorrhagic, or unspecified)					
	New and recurrent stroke[a] (*n* = 1981)			First stroke only[b] (*n* = 1668)			New and recurrent stroke[a] (*n* = 1981)			First stroke only[b] (*n* = 1668)		
	PxAF Events/ (events per 1000 patient-years)	PermAF Events/ (events per 1000 patient-years)	*P*	PxAF Events/ (events per 1000 patient-years)	PermAF Events/ (events per 1000 patient-years)	*P*	PxAF Events/ (events per 1000 patient-years)	PermAF Events/ (events per 1000 patient-years)	*P*	PxAF Events/ (events per 1000 patient-years)	PermAF Events/ (events per 1000 patient-years)	*P*
Age group												
<60	2 (5)	0 (−)	0.35	1 (2)	0 (−)	0.50	3 (7)	2 (10)	0.64	2 (5)	2 (11)	0.41
60–69	5 (10)	4 (11)	0.87	4 (8)	4 (12)	0.61	5 (10)	5 (13)	0.59	4 (8)	5 (15)	0.37
70–79	29 (35)	20 (19)	0.040	21 (27)	13 (16)	0.11	32 (38)	29 (28)	0.22	24 (31)	20 (24)	0.38
80–89	26 (40)	54 (46)	0.54	19 (35)	37 (40)	0.69	33 (51)	66 (57)	0.61	23 (43)	42 (45)	0.83
90+	4 (47)	8 (45)	0.94	4 (49)	7 (47)	0.96	4 (47)	14 (81)	0.36	4 (49)	12 (83)	0.39
$CHADS_2$ score												
0–1	14 (10)	9 (10)	0.98	14 (10)	9 (11)	0.96	17 (13)	16 (19)	0.25	17 (13)	15 (18)	0.33
2–3	42 (42)	52 (32)	0.20	34 (41)	48 (33)	0.48	48 (48)	67 (42)	0.43	39 (44)	61 (42)	0.77
4–6	10 (57)	25 (54)	0.84	1 (20)	4 (33)	0.67	12 (69)	33 (71)	0.93	1 (21)	5 (41)	0.53
Warfarin												
Yes	13 (16)	22 (14)	0.72	9 (13)	14 (11)	0.63	15 (18)	31 (20)	0.57	10 (15)	21 (16)	0.80
No	53 (31)	64 (46)	0.047	40 (25)	47 (42)	0.023	62 (36)	85 (55)	0.005	47 (29)	60 (53)	0.003
All patients	66 (26)	86 (29)	0.54	49 (21)	61 (25)	0.45	77 (31)	116 (40)	0.092	57 (25)	81 (33)	0.11

TIA, transient ischaemic attack; PxAF, paraoxysmal AF; PermAF, permanent AF.

[a]All patients included, also patients with earlier ischaemic stroke, TIA, or cerebral bleeding.

[b]Same analyses as explained in footnote 'a' with the exclusion of 313 patients with a history of ischaemic stroke, TIA, or cerebral bleeding before index date.

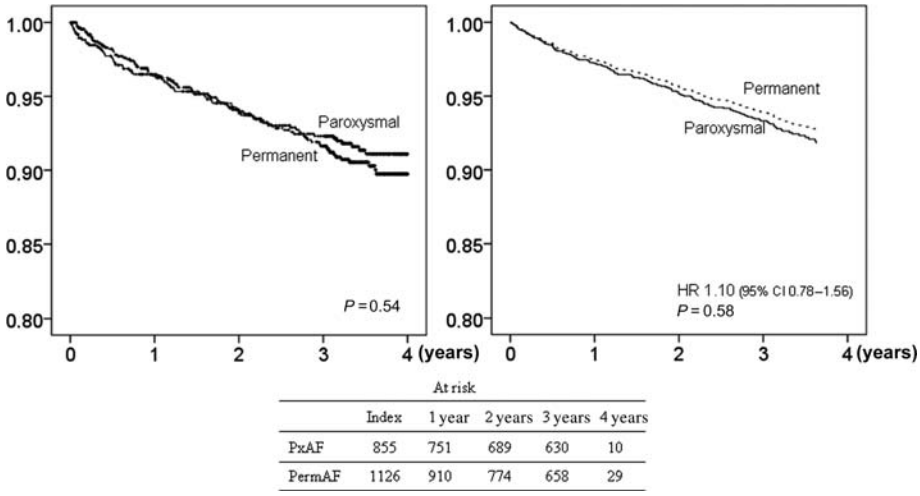

Figure 1 Survival free from ischaemic stroke (I63) in paraoxysmal atrial fibrillation (AF) and permanent AF. Unadjusted incidence to the left, multivariably adjusted to the right. Note abbreviation of scale

0.78–1.56) or excluded (HR 1.07, 95% CI 0.71–1.61) from the analysis (*Table 3*).

The diagnostic code I64 ('stroke, not specified as haemorrhage or infarction') was seldom used. When used, it was mostly in elderly patients where the diagnosis was based on clinical examination only. The incidence of a first diagnosis of unspecified stroke was 1.7 and 4.8 events per 1000 patient-years in PxAF and PermAF, respectively ($P = 0.063$). Multivariable adjustment for cofactors showed that this apparent difference was non-significant (HR 0.60, 95% CI 0.22–1.64).

In all 23 patients were diagnosed with cerebral bleeding during follow-up. Of these six had PxAF and 17 had PermAF, representing two and six events/1000 patient-years, respectively. Ischaemic strokes in PxAF patients were more than 10 times as common as haemorrhagic ones. Most of the patients with cerebral bleedings were not treated with warfarin when the bleeding occurred (13/23). After adjustment for cofactors, the risk of cerebral haemorrhage tended to be lower in PxAF than in PermAF, irrespective of whether patients with previous cerebral bleedings were included in the analysis or not (*Table 3*). When all ischaemic, unspecified, and haemorrhagic strokes were combined, the incidence was about the same in patients with PxAF and PermAF after adjustment for cofactors (HR 0.96, 95% CI 0.70–1.31; *Table 3*).

Stroke in paroxysmal atrial fibrillation vs. the general population

The incidence of a first ischaemic stroke in PxAF was twice as high as expected in an age- and sex-standardized comparison with the general population in Stockholm County during the study period. The standardized incidence ratio (SIR) for ischaemic stroke in patients with PxAF was 2.12 (95% CI 1.52–2.71) compared with the general population (*Table 4*). The excess risk appeared to be about the same in younger and older patients and among men and women. Cerebral bleedings were about as common in PxAF as in the general population.

Women, but not men, with PermAF showed an elevated SIR for ischaemic stroke and for cerebral haemorrhages.

Warfarin

Warfarin was used by less than one-third of PxAF patients. Those who took warfarin on the latest contact during follow-up, had less than half as many ischaemic strokes as those who did not (13/254 vs. 53/601). The difference was significant after adjustment for age and other cofactors (HR 0.44, 95% CI 0.30–0.65). When 313 patients with a prior stroke, transient ischaemic attack (TIA), or cerebral bleeding were excluded from the analysis, confidence intervals increased and significance was no longer met (HR 0.56, 95% CI 0.27–1.16). Cerebral bleedings occurred in two warfarin-treated PxAF patients and four non-warfarin-treated PxAF patients, representing a rate of 2.3 events/1000 patient-years in both groups alike.

Discussion

The incidence of ischaemic stroke appears to be similar in PxAF and PermAF (26 vs. 29 events/1000 patient-years). This is similar to what was found in the SPAF study, where the corresponding rates for PxAF patients were 32 and 33 events/1000 patient-years.[18] Considering that all of the patients in the SPAF study had aspirin prophylaxis, while almost one-third in our study had the more efficacious warfarin prophylaxis, there is a good agreement in the results of these two studies.

It was most likely that the results of the SPAF study of 460 PxAF patients who had been followed for 2 years who made the ACC/AHA/ESC issue a Class IIa, Level B recommendation that 'It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e. paroxysmal, persistent, or permanent) of AF.'[17] Our results, which are based on almost twice as many

Table 3 Hazard ratios for stroke in paraoxysmal atrial fibrillation (PxAF) compared with permanent atrial fibrillation (PermAF) (used as reference)

	First and recurrent stroke[a] (*n* = 1981)					First stroke only[b] (*n* = 1668)			
	Unadjusted HR (95% CI)	Age + sex HR (95% CI)	$CHADS_2^c$ HR (95% CI)	$CHADS_2$ + warfarin[d] HR (95% CI)	Extended[e] HR (95% CI)	Unadjusted HR (95% CI)	Age + sex HR (95% CI)	Age + sex + warfarin HR (95% CI)	Extended HR (95% CI)
Ischaemic stroke (I63)	0.91 (0.66–1.25)	1.15 (0.83–1.60)	1.18 (0.85–1.64)	1.02 (0.73–1.42)	1.10 (0.78–1.56)	0.86 (0.59–1.26)	1.10 (0.75–1.62)	0.94 (0.64–1.40)	1.07 (0.71–1.61)
Stroke unspecified (I64)	0.62 (0.29–1.33)	0.84 (0.39–1.83)	0.85 (0.39–1.86)	0.69 (0.31–1.52)	0.74 (0.33–1.66)	0.64 (0.25–1.62)	0.82 (0.32–2.12)	0.67 (0.25–1.78)	0.60 (0.22–1.64)
Cerebral bleeding (I60–61)	0.43 (0.17–1.11)	0.43 (0.17–1.14)	0.46 (0.18–1.21)	0.46 (0.17–1.22)	0.39 (0.14–1.09)	0.36 (0.12–1.11)	0.34 (0.11–1.10)	0.35 (0.11–1.16)	0.35 (0.10–1.20)
Any stroke	0.79 (0.59–1.05)	0.99 (0.74–1.33)	1.02 (0.76–1.37)	0.88 (0.65–1.19)	0.96 (0.70–1.31)	0.76 (0.54–1.06)	0.95 (0.67–1.34)	0.81 (0.57–1.16)	0.89 (0.61–1.30)

[a]All patients included, also patients with earlier ischaemic stroke, transient ischaemic attack (TIA), or cerebral bleeding.
[b]Same analyses as in footnote 'a' with the exclusion of 313 patients with a history of ischaemic stroke, TIA, or cerebral bleeding before index date.
[c]$CHADS_2$ scoring for stratification of stroke risk in atrial fibrillation. One point each for age >75 years, heart failure, hypertension, diabetes. Two points for previous thrombo-embolic stroke.[19]
[d]Warfarin use on the occasion of the event, or else on the latest documented contact.
[e]Extended adjustment included AF-type, age (continuous), sex, and factors known to be risk factors for the outcome. For I63 and I64 these factors were previous ischaemic stroke or TIA, heart failure, hypertension, diabetes mellitus, mitral stenosis, previous myocardial infarction, and warfarin treatment on the latest documented contact or on the occasion of the event. For cerebral haemorrhages, I60–61, additional adjustment was made for previous cerebral bleeding, hypertension, apparent contraindication against warfarin in 2002, warfarin and/or aspirin on latest contact/on event. For any stroke we made adjustments for all factors used in the above analyses.

Table 4 Standardized incidence ratios (SIR) for ischaemic stroke and cerebral haemorrhage

	Paroxysmal AF			Permanent AF		
	Experiment	Observed	SIR (95% CI)	Experiment	Observed	SIR (95% CI)
Ischaemic stroke (I63)						
Age (years)						
≤75	6.59	15	2.27 (1.27–3.75)	5.59	9	1.61 (0.74–3.06)
>75	16.6	34	2.05 (1.36–2.75)	27.9	52	1.86 (1.36–2.37)
Sex						
Men	10.6	21	1.98 (1.13–2.82)	17.6	23	1.31 (0.84–1.84)
Women	12.5	28	2.24 (1.41–3.07)	16.0	38	2.38 (1.62–3.14)
All	23.1	49	2.12 (1.52–2.71)	33.5	61	1.82 (1.36–2.28)
Cerebral bleeding (I60–61)						
Age (years)						
≤75	1.95	3	1.54 (0.32–4.50)	1.71	3	1.76 (0.36–5.13)
>75	3.68	3	0.82 (0.17–2.38)	6.36	13	2.04 (1.09–3.49)
Sex						
Men	2.82	2	0.71 (0.09–2.56)	4.47	7	1.56 (0.63–3.22)
Women	2.80	4	1.43 (0.39–3.65)	3.60	9	2.50 (1.14–4.75)
All	5.62	6	1.07 (0.39–2.32)	8.07	16	1.98 (1.13–3.22)

Patients aged >30 years with no previous stroke or cerebral bleeding were compared regarding age- and sex-adjusted incidence in the general population of Stockholm County for the years 2002–2005.

PxAF patients who have been followed for almost twice as long, thus further support the conclusions of the SPAF study and the guideline recommendations regarding warfarin prophylaxis in AF.

The strength of our observations is further supported by comparisons with the stroke incidence in the general population in the same area and during the same years as our study was going on. These comparisons showed that PxAF patients suffered ischaemic stroke about twice as often as expected from the general population, but that cerebral bleedings were rare and not more frequent than expected.

The results of our study are also in agreement with the incidence of stroke risk reported in the Framingham study (29 events/1000 patient-years), although no differentiation was made between PxAF and PermAF in that study.[21]

When we compared stroke incidence in PxAF with the incidence in PermAF, we found that the original unadjusted results did not change much with multivariable adjustment (*Table 3*). PxAF patients are certainly younger and healthier. They are therefore expected to suffer fewer strokes than PermAF patients do. On the other hand, PxAF patients do not receive warfarin prophylaxis as often as PermAF patients do, i.e. they have less-efficient protection against stroke than PermAF patients have.

The PxAF group is heterogenous. Some patients have daily relapses, others just a few each year. Some patients have relapses that last a couple of days, in others just a couple of minutes. How these factors affect stroke risk is largely unknown. Available information indicates that once a patient has got a diagnosis of symptomatic PxAF, he or she is at an increased risk of ischaemic stroke.[22]

We do not know why the stroke risk appears to be almost the same in PxAF and PermAF. One aspect may be that the two arrhythmias are manifestations of one structural, fibrotizing heart disease with different clinical manifestations at different stages of the disease progress. Patients with PxAF also often have a higher AF burden than is immediately evident.[23] Asymptomatic relapses of AF in patients with symptomatic PxAF may be more than 10 times as frequent as the symptomatic episodes.[24,25] Furthermore, it may be that the period directly after spontaneous cessation of AF is a vulnerable period for embolization. If so, the increased risk associated with rhythm shifts in PxAF patients may possibly balance a lower stroke risk during prolonged periods of sinus rhythm. This, however, remains to be investigated.

We found that the stroke incidence in PxAF patients varied from five strokes per 1000 patient-years at risk in the youngest and healthiest group up to over 50 strokes per 1000 patient-years in elderly patients with multiple risk factors. Our study confirms earlier studies regarding the efficacy of the $CHADS_2$ scoring system for the proper identification of patients at high-risk as well as low-risk for ischaemic stroke.[17,20]

Although our study was not designed to evaluate the efficacy and safety of warfarin treatment, it was evident that PxAF patients treated with warfarin suffered far less strokes than those without warfarin, and that the proportions were similar to that in PermAF. After adjustment for age and important cofactors PxAF patients treated with warfarin had about half as many strokes, as for those without warfarin. Cerebral bleedings were rare in the study group and not more frequent among patients using warfarin

than who did not, or higher than what was expected from the incidence in the general population. However, these findings have to be interpreted with great caution since only a minority of all PxAF patients took warfarin, since there were very few cerebral bleedings during follow-up and since the knowledge about the actual exposure to warfarin is fragmentary.

There are several reasons of why it is unlikely that the relatively low incidence of cerebral bleedings in PxAF patients is merely owing to deficient reporting of cerebral bleedings. First, cerebral bleedings are life-threatening acute conditions with an assumed high probability of hospital treatment and thus a diagnosis in the National Hospital Discharge Register from which we obtained information about bleedings that occurred during follow-up. Secondly, there is no reason to believe that under-reporting of bleedings is more common in one type of AF than the other. Furthermore, the incidence of bleedings among patients with PermAF using warfarin (five strokes per 1000 patient-years) is similar to that which was reported by the BAFTA trial[26] in which the anticoagulant treatment was of the same intensity as the therapeutic range, which is recommended for AF prophylaxis in Sweden (INR 2.1–3.0). Earlier studies that compared warfarin and aspirin treatment reported over 10 cerebral bleedings per 1000 patient-years at risk. These studies were however mostly made on study populations with PermAF and with higher therapeutic INR values than those currently recommended, e.g. 4.5 in the SPAF trial and 4.2 in the AFASAK trial.[7,10,27] In later studies, the incidence of cerebral bleedings has been lower, often in the range of 1–6 bleedings/1000 patient-years.[26,28,29] Apparently, this change is because of more stringent controls of INR, and because of a lower recommended target range for INR. We thus found that warfarin use was associated with a better prognosis regarding cerebral catastrophies in all patient subgroups but for the youngest and healthiest, where the incidence of stroke is very low.

Limitations

Most of the patients in our study (78%) were treated as inpatients at South Hospital on at least one occasion during 2002. The remaining 22% of the patients were treated as outpatients only, either at South Hospital or at Gustavsberg Primary Care Centre or at both places. It is likely that patients treated as inpatients at a hospital are more symptomatic or else of poorer health than patients who only seek medical help at an outpatient clinic. Indeed, those who only had been treated as outpatients were younger (68 vs. 76 years) and healthier (e.g. 5% had a previous myocardial infarction vs. 22% among hospitalized patients). Therefore, the findings in this study may not be applicable on a population consisting mostly of outpatients.

PxAF is, by nature, an elusive disease, which comes and goes. Since this a study based on medical records and registers, we have no other source of information about the rhythm of the patients during follow-up, than what was documented when, and if, patients had a reason to be in contact with the hospital or with the primary care centre. All analyses regarding the type of AF were based on the type of arrhythmia determined at the time of the latest contact during the inclusion year. This analysis is analogous with an 'intention-to-treat' analysis. In such an analysis cross-over, i.e. patients who change from PxAF to PermAF will obscure differences that may be owing to AF status.

Our information about exposure to warfarin during follow-up is incomplete. Medication was recorded at the last contact of each calendar year and on the occasion of an ischaemic or haemorrhagic stroke. Thus, we have more detailed and presumably better information about the medication of patients with poorer health and many hospital contacts than those who do not need the hospital's services. Incompleteness of information about warfarin exposure during follow-up is likely to make real differences, if such exists, appear smaller than they really are. In the comparison of patients with and without warfarin use, we adjusted for a number of confounding factors, but it is likely that some residual confounding remained after multivariable adjustment. This could involve undocumented circumstances that constitute contraindications against warfarin treatment, or life-style factors like smoking, drinking, obesity, etc. that have not been explicitly documented in the medical records and registers. It seems less likely, however, that this should be a greater problem in patients with PxAF than in patients with PermAF, where the reduction of stroke risk by warfarin treatment is firmly established.

For the classification of stroke events we have relied on clinically assigned diagnoses. The correctness of such diagnoses may vary depending on use of computed tomography (CT) scan, magnetic resonance imaging (MRI), or autopsy. During the study period, stroke diagnoses in hospitalized patients in Sweden were in general based on CT-scan or MRI. It is likely that some cases of stroke were not recognized, especially if they were minor strokes. In support of this there are several studies showing multiple minor cerebral infarctions in AF patients without a previous diagnosis of stroke.[8,30–33] Thus, the stroke incidence estimates in the present study most likely are lower than the real incidence in AF patients.

Conclusion

Ischaemic stroke is about as common in PxAF as in PermAF, and about twice as common as in the general population. Yet, PxAF patients do not receive protective anticoagulant treatment as often as patients with PermAF do. It is therefore important to increase the use of anticoagulants among PxAF patients in accordance with current guideline recommendations.

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Conflict of interest: N.H. is a part-time employee of AstraZeneca R&D, Mölndal, Sweden. M.R. has been lecturing and acted as a national coordinator in clinical trials sponsored by AstraZeneca. He is also a member of the Boehringer Ingelheim Swedish advisory committee regarding haemostasis.

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