Early recurrence in paroxysmal versus sustained atrial fibrillation in patients with acute ischemic stroke

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Abstract

Background: The relationship between different patterns of atrial fibrillation (AF) and early recurrence after an acute ischemic stroke is unclear.

Purpose: In a prospective cohort study, we evaluated the rates of early ischemic recurrence after an acute ischemic stroke in patients with paroxysmal AF (PAF) or sustained AF (SAF) which included persistent and permanent AF.

Methods: In patients with acute ischemic stroke, AF was categorized as PAF or SAF. Ischemic recurrences were the composite of ischemic stroke, transient ischemic attack and symptomatic systemic embolism occurring within 90 days from acute index stroke.

Results: A total of 2,150 patients (1,155 females, 53.7%) were enrolled: 930 (43.3%) had PAF and 1220 (56.7%) SAF. During the 90-day follow-up, 111 ischemic recurrences were observed in 107 patients: 31 in patients with PAF (3.3%) and 76 with SAF (6.2%), [Hazard Ratio (HR) 1.86 (95% CI 1.24-2.81)]. Patients with SAF were on average older, more likely to have diabetes mellitus, hypertension, history of stroke/TIA, congestive heart failure, atrial enlargement, high baseline NIHSS-score and implanted pacemaker. After adjustment by Cox proportional hazard model, SAF was not associated with early ischemic recurrences [adjusted HR 1.23 (95% CI 0.74-2.04)].

Conclusions: After acute ischemic stroke, patients with SAF had a higher rate of early ischemic recurrence than patients with PAF. After adjustment for relevant risk factors SAF was not associated with a significantly higher risk of recurrence, such suggesting that the risk profile associated with AF more than its pattern is determinant for recurrence.

Key Words: stroke, atrial fibrillation, paroxysmal atrial fibrillation, sustained atrial fibrillation, stroke recurrence, anticoagulation.

Introduction

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia and the number of patients with AF is predicted to rise steeply in the coming years.[1,2] Despite remarkable progresses in the management of patients with AF, this arrhythmia remains one of the major causes of stroke and thromboembolic events.[3]

The relationship between the different patterns of AF and the risk of stroke has been analyzed in several studies with conflicting results. Various studies reported similar risks of thromboembolism for patients with paroxysmal AF (PAF) and those with sustained AF (SAF).[4-10] However, several other studies indicated a higher risk for ischemic events in patients with non-paroxysmal AF compared to those with PAF.[11-21] Current guidelines on AF management recommend that the pattern of AF should not influence the decision on whether to treat patients with anticoagulants.[3,22]

The association of AF pattern with the risk of early recurrence after an acute ischemic stroke is unclear. By using RAF (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation) and RAF-NOAC (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation treated with Non Vitamin K Oral Anticoagulants) study databases[23,24] we evaluated the rates of ischemic recurrences in patients with PAF and those with SAF within 90 days after an acute ischemic stroke. The ultimate aim of the study was to consider if after an acute ischemic stroke different treatment approaches are needed in the presence of different patterns of AF.

Methods

For the purpose of this analysis, we combined the databases of the RAF study and the RAF-NOAC study. RAF and RAF-NOAC were prospective observational studies carried out between January 2012 and March 2014 in 29 Stroke Units and between April 2014 and June 2016 in 35 Stroke Units respectively, across Europe, United States and Asia. Both studies enrolled consecutive patients with acute ischemic stroke and known or newly diagnosed AF without contraindications to anticoagulation. The studies were approved by the local Institutional Review Boards, if required.

On admission, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). A non-contrast cerebral computed tomography (CT) or cerebral magnetic resonance (MR) scan was performed on admission for all patients to exclude intracranial hemorrhage. Revascularization treatments were given as per standard local protocol, when appropriate. Standard Stroke Unit care, monitoring and treatment were provided according to current international recommendations for acute ischemic stroke. Attending physicians made decisions regarding the type of anticoagulant to be used for secondary prevention, as well as the day of initiation of anticoagulant treatment. The RAF study included patients treated with either vitamin K antagonists or NOACs while the RAF-NOAC study included only patients who received NOACs.

A full history and clinical examination, admission ECG and prolonged ECG monitoring for 48 h after the index stroke were performed to detect non-valvular atrial fibrillation. AF was categorized as:

(1) paroxysmal: associated with episodes terminating spontaneously within 7 days;

(2) persistent: associated with episodes lasting more than 7 days or requiring pharmacological and/or electrical cardioversion;

(3) permanent: persisting for more than 1 year, either because cardioversion failed or was not pursued.[25]

For the purpose of the present study, AF was categorized into two types: paroxysmal AF or sustained (persistent or permanent) AF.

A second brain CT scan or MR was scheduled to be performed 24-72 h from stroke onset in all patients. The sites and sizes of the qualifying infarcts were determined based on standard templates as:

(1) small: when a lesion was ≤ 1.5 cm in the anterior or posterior circulation;

(2) medium: when a lesion was in a cortical superficial branch of middle cerebral artery, in the middle cerebral artery deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, in a cortical superficial branch of the anterior cerebral artery;

(3) large anterior: when a lesion involved the complete territory of middle, posterior, or anterior cerebral artery; in 2 cortical superficial branches of middle cerebral artery; in a cortical superficial branch of middle cerebral artery associated to the middle cerebral artery deep branch, or in more than 1 artery territory;

(4) large posterior: when a lesion was ≥ 1.5 cm in the brain stem or cerebellum.[26]

Left atrial enlargement and its severity was defined following the American Society of Echocardiography guidelines measuring the left atrial diameter or volume taking into account the difference between sexes.[27]

Risk factors. Data on known stroke risk factors were collected as follows: age, gender, history of hypertension (blood pressure of ≥ 140/90 mmHg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting glucose level ≥ 126 mg/dL pre-prandial on 2 examinations, glucose level ≥ 200 mg/dL

postprandial, or HbA1c ≥ 6.5%, or under antidiabetic treatment), current cigarette smoking, past smoking (cessation less than 5 years ago), hyperlipidemia (total cholesterol ≥ 200 mg/dL or triglyceride ≥ 140 mg/dL or already under lipid lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio < 0.85 in either leg at rest; or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse (≥ 300 g per week), obesity (body mass index ≥ 30 kg/m^2), or previous stroke/TIA. White matter changes [leukoaraiosis defined on the first CT (or MR) examination as ill-defined and moderately hypodense (or hyperintensity on T2-weighted on MR) areas of ≥ 5 mm according to published criteria] were investigated. Leukoaraiosis in the deep white matter was dichotomized into absent versus present (independently if mild, moderate, or severe).[28] Other baseline variables obtained at admission for all patients included: fasting serum glucose, fasting serum cholesterol (total, HDL, and LDL), platelet count, international normalized ratios (INR), activated partial thromboplastin time (aPTT), systolic blood pressure, and diastolic blood pressure.

Data on the use of any antiplatelet, anticoagulants or thrombolytic agent, prior to admission, at baseline and during the follow-up period, were recorded.

The CHA_2DS_2-VASc score (2 points for history of stroke or age ≥ 75 years and 1 point each for congestive heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years and female sex) was calculated before and after the index event.

Evaluation of outcome. Patients were followed-up prospectively by face-to-face or telephone interviews. Whether an outcome event occurred, patients were requested to bring

full documentation of it to a face-to-face appointment. Study outcome at 90 days was the composite of: recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolism.

Stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. TIA was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy.

Statistical analyses. Population characteristics were summarized as mean and SD for continuous variables and as absolute numbers and percentages for categorical variables. Differences in the baseline characteristics of patients with PAF or SAF were tested using χ^2 test for nominal variables, or ANOVA for continuous variables. Specifically, univariate tests were utilized to compare both clinical characteristics on admission and pre-existing risk factors for PAF.

A multivariate analysis was performed using logistic regression to determine independent predictors of PAF.

Differences in the characteristics of patients with or without ischemic recurrence at 90 days were tested using χ^2 test for nominal variables or ANOVA for continuous variables. Specifically, univariate tests were used to compare both clinical characteristics on admission and pre-existing risk factors for ischemic events.

The relationship between the survival function and the set of explanatory variables were explored with Cox proportional hazard model. Cox model provided estimates of AF pattern influence on survival after adjusting for other explanatory variables.

In order to measure associations, we used odds ratios (OR) for multivariate logistic models and hazard ratios (HR) for survival curve analyses with a 95% confidence interval; a two-sided P value < 0.05 was considered significant.

All statistical analyses were performed using the IBM SPSS Statistics version 22.0 (IBM Corporation, Somers, NY).

Results

PAF versus SAF patients. A total of 2,150 patients (1,155 women, 53.7%) were enrolled. Among these, 930 (43.3%) had paroxysmal (360 in RAF, 570 in RAF-NOAC) and 1,220 (56.7%) sustained AF (660 in RAF, 560 in RAF-NOAC).

812 patients with PAF (87.3%) and 976 patients with SAF (80.0%) received OAC, of which 592 and 630 were NOACs, respectively. VKAs included warfarin (518) and acenocumarol (49), whereas NOACs included rivaroxaban (414), dabigatran (410) and apixaban (396).

The baseline characteristics of the patients with PAF and SAF are summarized in Table 1. Patients with SAF were on average older and more likely to have the following: higher baseline NIHSS-score, diabetes mellitus, hypertension, a history of stroke/TIA, congestive heart failure, pacemaker implanted, CHA_2DS_2-VASc > 4 and atrial enlargement (all p < 0.05). Patients with PAF were more likely to be on OAC treatment after the index stroke.

The results from the multivariate analysis for factors associated with SAF are listed in Table 2. Older age, diabetes mellitus, history of stroke/TIA, alcoholism, history of congestive heart failure and pacemaker implant were all significant factors associated with SAF.

Ischemic recurrences. Over 90 days of follow-up, 111 ischemic recurrences were recorded in 107 patients (82 ischemic strokes, 18 TIAs and 11 systemic embolisms). The baseline characteristics of patients with and without ischemic events within 90 days from acute stroke

are listed in Table 3. Patients with ischemic recurrence were on average older and were more likely to have: higher baseline NIHSS-score, diabetes mellitus, hypertension, congestive heart failure, pacemaker implanted and CHA_2DS_2-VASc score > 4. Patients without ischemic recurrence were more likely to have small size lesions, to be on OAC treatment after the index stroke and to have PAF.

Among patients who suffered an ischemic recurrence, 9.1% (34/372) had not started anticoagulation therapy, 6.7% (38/563) were treated with a VKA and 2.9% (35/1220) with a NOAC. The median time for starting OAC was 8 days in patients with PAF and 6 days in patients with SAF.

Cox proportional hazard model was adjusted for age, sex, diabetes, hypertension, hyperlipidemia, history of stroke, current smoking, alcoholism, history of congestive heart failure, myocardial infarction, pacemaker implant, small lesion size and type of anticoagulant. SAF did not result as a risk for ischemic recurrence when compared with PAF (HR 1.23; 95% CI 0.74-2.04; p = 0.418) (Figure 1). The same result was obtained excluding TIAs from outcomes (HR 1.11; CI 0.60-2.12; p = 0.7). A sensitivity analysis performed to evaluate if our results were consistent when SAF was categorized as either persistent (HR 1.33; 95% CI 0.70-2.51; p = 0.387) or permanent AF (HR 1.12; 95% CI 0.61-2.04; p = 0.715) confirmed that AF pattern is not associated with ischemic recurrence (Figure 2).

Discussion

Among patients with acute ischemic stroke, those with SAF had a higher rate of early ischemic recurrence than patients with PAF. After adjustment for risk factors for early ischemic recurrence, SAF was not associated with a significantly higher risk of recurrence. Recent studies have reported a higher risk for ischemic events in patients with non-paroxysmal AF compared to those with PAF.[11-14,17,19-21] The large majority of the patients

included in these studies did not have a previous stroke and were evaluated for a long-term follow-up. In contrast, our study was focused on early recurrence in patients with recent ischemic stroke followed-up for 90 days.

The vast majority of patients enrolled in the RAF and RAF-NOAC studies were prescribed with anticoagulation therapy (81.6%) after the index stroke. Anticoagulation reduces the rates of ischemic outcome and therefore, although our study mirrors clinical practice, it might not reflect the natural history of the disease. Evaluating a group of AF patients in absence of anticoagulation might better reflect the recurrence risk in different types of AF,[21] but such a study design would not be feasible in populations at high risk of ischemic events, like cohorts on secondary prevention.

On average, in this cohort patients with SAF started OAC therapy 2 days before those with PAF; this could have influenced the event rate. However, this effect was, in our opinion, marginal.

The EORP-AF General Pilot Registry reported a worse outcome in patients with SAF in comparison to patients with PAF. However, this difference did not seem to be associated to the pattern of the arrhythmia, but to the worse clinical risk profile in terms of age, underlying cardiac disease, and other clinical risk factors.[29] Likewise, a sub-analysis of the J-RHYTHM Registry reported that thromboembolic events occurred more frequently in the permanent AF group, particularly in patients with higher CHA_2DS_2-VASc score. In that study, after adjusting for CHA_2DS_2-VASc score components and anticoagulation treatment, the risk of ischemic events did not differ between PAF and permanent AF.[9] Our present findings in patients on secondary prevention are in line with the results of these two primary prevention studies: in particular, patients with SAF were on average older and were more likely to have diabetes mellitus, hypertension, history of stroke/TIA, and congestive heart failure. After adjusting for established risk factors, the early thromboembolic risk in patients with acute

ischemic stroke was not associated with a particular AF pattern. These findings suggest that AF pattern should not influence the decision regarding the timing of initiating anticoagulation treatment after an acute ischemic stroke.

Study limitations. Our study had several limitations. First, the associations shown in this non-randomized study were most likely influenced by several confounders, although adjusted statistical models were used to partially control them. Second, a central adjudication of the outcome events was not performed but rather these events were assessed by the local investigators. This approach is quite common in investigator-initiated cohort prospective studies and may be justified provided that validated and internationally recognized definitions of events are actually used. This was the case of our study. Third, the inclusion of TIA as ischemic recurrence, which is considered as a soft endpoint, may have also influenced the reported associations, but sensitivity analysis performed excluding TIAs as outcome gave similar results.

Strengths of our study included the prospective design, the multicenter nature and its relatively large sample size.

Conclusions

Among patients with acute ischemic stroke, patients with PAF had a lower rate of early ischemic recurrence than patients with SAF. After adjustment for risk factors for early ischemic recurrence, SAF was not associated with a significantly higher risk of recurrence. Our results suggest that, when making decision about the timing to initiate anticoagulation treatment after an acute ischemic stroke, the patient's risk profile should be given greater relevance than the pattern of AF. These results support the need for additional comparative studies, including randomized trials.

References

1. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *American Journal of Cardiology* 2013; *112*(8), 1142–1147.

2. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *European Heart Journal* 2013; *34*(35), 2746–2751.

3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; *18*(11), 1609–1678.

4. Banerjee A, Taillandier S, Olesen JB, et al. Pattern of atrial fibrillation and risk of outcomes: The Loire Valley Atrial Fibrillation Project. *International Journal of Cardiology* 2013; *167*(6), 2682–2687.

5. Disertori M, Franzosi MG, Barlera S, et al. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSI-AF trial. *BMC Cardiovascular Disorders* 2013; *13*, 28.

6. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: Report from the Stockholm Cohort of Atrial Fibrillation. *European Heart Journal* 2010; *31*(8), 967–975.

7. Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: Incidence and predictors during aspirin therapy. *Journal of the American College of Cardiology* 2000; *35*(1), 183–187.

8. Hohnloser SH, Pajitnev D, Pogue J, et al. Incidence of Stroke in Paroxysmal Versus Sustained Atrial Fibrillation in Patients Taking Oral Anticoagulation or Combined Antiplatelet Therapy. An ACTIVE W Substudy. *Journal of the American College of*

Cardiology 2007; *50*(22), 2156–2161.

9. Inoue H, Atarashi H, Okumura K, et al. Thromboembolic Events in Paroxysmal vs. Permanent Non-Valvular Atrial Fibrillation. *Circulation Journal* 2014; *78*(10), 2388–2393.

10. Nieuwlaat R, Dinh T, Olsson SB, et al. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *European Heart Journal* 2008; *29*(7), 915–922.

11. Al-Khatib SM, Thomas L, Wallentin L, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: Results from the ARISTOTLE trial. *European Heart Journal* 2013; *34*(31), 2464–2471.

12. Chen Y, Zhao Y, Dang G, et al. Stroke Event Rates and the Optimal Antithrombotic Choice of Patients With Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine* 2015; *94*(52), e2364.

13. Chiang CE, Naditch-Brûlé L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circulation: Arrhythmia and Electrophysiology* 2012; *5*(4), 632–639.

14. Deguchi I, Hayashi T, Fukuoka T, et al. Features of cardioembolic stroke with persistent and paroxysmal atrial fibrillation - a study with the Japan Stroke Registry. *European Journal of Neurology* 2015; *22*(8), 1215–1219.

15. Koga M, Yoshimura S, Hasegawa Y, et al. Higher Risk of Ischemic Events in Secondary Prevention for Patients with Persistent Than Those with Paroxysmal Atrial Fibrillation. *Stroke* 2016; *47*(10), 2582–2588.

16. Lip GYH, Frison L, Grind M. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *Journal of Internal Medicine* 2008; *264*(1), 50–61.

17. Ntaios G, Vemmou A, Koroboki E, et al. The type of atrial fibrillation is associated with long-term outcome in patients with acute ischemic stroke. *International Journal of Cardiology* 2013; *167*(4), 1519–1523.

18. Senoo K, Lip GYH, Lane DA, et al. Residual Risk of Stroke and Death in Anticoagulated Patients According to the Type of Atrial Fibrillation: AMADEUS Trial. *Stroke* 2015; *46*(9), 2523–2528.

19. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: Results from the ROCKET-AF Trial. *European Heart Journal* 2015, *36*(5), 288–296.

20. Takabayashi K, Hamatani Y, Yamashita Y, et al. Incidence of stroke or systemic embolism in paroxysmal versus sustained atrial fibrillation: The fushimi atrial fibrillation registry. *Stroke* 2015; *46*(12), 3354–3361.

21. Vanassche T, Lauw MN, Eikelboom JW, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: Analysis of 6563 aspirin-treated patients in active-a and averroes. *European Heart Journal* 2015; *36*(5), 281–287.

22. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American college of Cardiology/American heart association task force on practice guidelines and the heart rhythm society. *Journal of the American College of Cardiology* 2014; *64*(21), e1–e76.

23. Paciaroni M, Agnelli G, Falocci N, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: Effect of anticoagulation and its timing: The RAF study. *Stroke* 2015; *46*(8), 2175–2182.

24. Paciaroni M, Agnelli G, Caso V, et al. Prediction of Early Recurrent Thromboembolic Event and Major Bleeding in Patients With Acute Stroke and Atrial Fibrillation by a Risk Stratification Schema. *Stroke* 2017; STROKEAHA.116.015770.

25. Lévy S, Camm AJ, Saksena S, et al. International consensus on nomenclature and classification of atrial fibrillation: A collaborative project of the Working Group on Arrhythmias and the Working Group of Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Journal of Cardiovascular Electrophysiology* 2003; *14*(4), 443–5.

26. Paciaroni M, Agnelli G, Corea F, et al. Early Hemorrhagic Transformation of Brain Infarction: Rate, Predictive Factors, and Influence on Clinical Outcome: Results of a Prospective Multicenter Study. *Stroke* 2008; *39*(8), 2249–2256.

27. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography* 2005; *18*(12), 1440–1463.

28. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; *32*(6), 1318–22.

29. Boriani G, Laroche C, Diemberger I, et al. "Real-world" management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: The EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Pilot Registry. *Europace* 2016; *18*(5), 648–657.

Figures

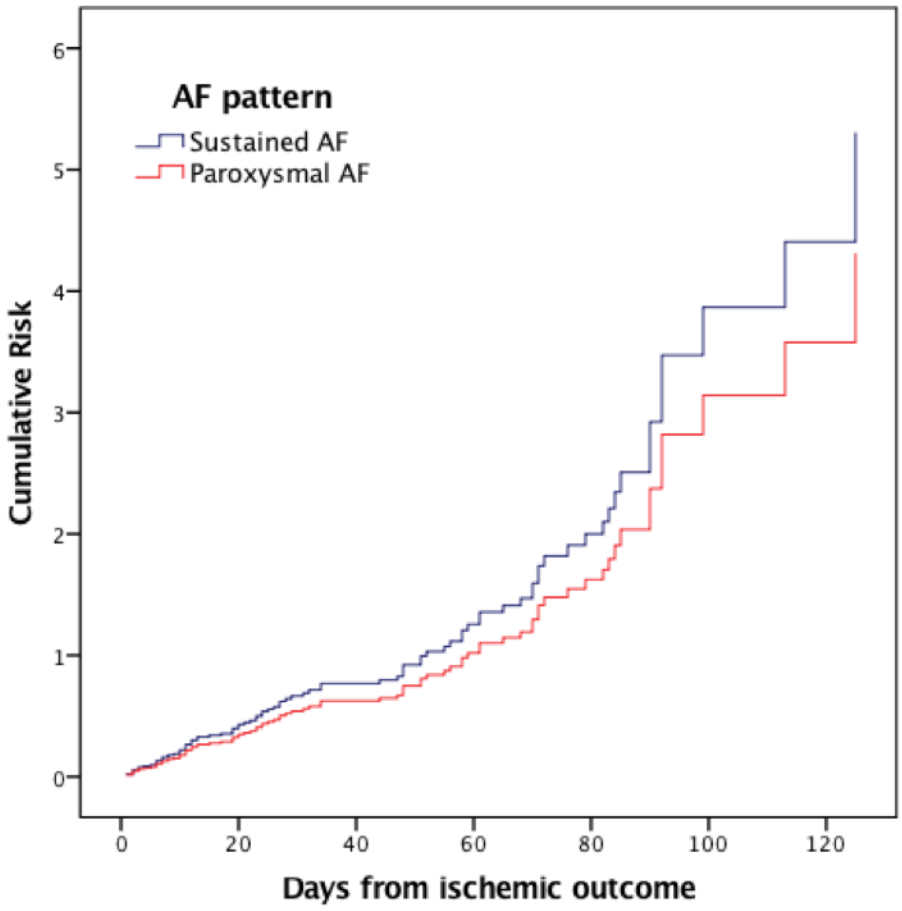

Figure 1: Adjusted cumulative risk for ischemic recurrence (stroke, transient ischemic attack, systemic embolism) in patients with SAF compared with patients with PAF (HR 1.23; 95% CI 0.74-2.04; p = 0.418). AF = atrial fibrillation; HR = hazard ratio; PAF = paroxysmal atrial fibrillation; SAF = sustained atrial fibrillation.

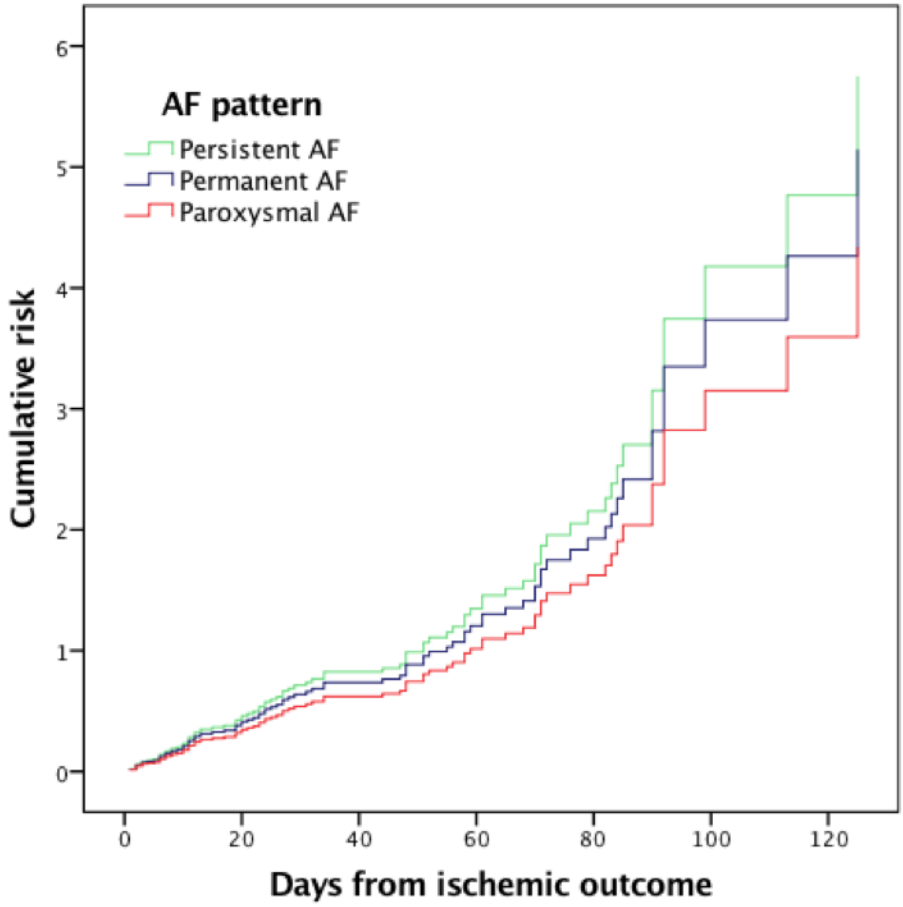

Figure 2: Adjusted cumulative risk for ischemic recurrence in patients with paroxysmal, permanent and persistent AF; AF = atrial fibrillation.

Table 1. Baseline characteristics of patients with PAF and SAF

	PAF (n = 930)	**SAF** (n = 1220)	**p***
Age (mean, years)	74.5 ± 9.8	77.7 ± 9.5	< 0.0001
Sex M	422 (45.4%)	573 (47.0%)	
NIHSS (mean)	8.0 ± 6.7	8.7 ± 6.8	0.026
Diabetes mellitus	181 (19.5%)	301 (24.7%)	0.004
Hypertension	709 (76.2%)	978 (80.2%)	0.026
Hyperlipidemia	318 (34.2%)	405 (33.2%)	
History stroke/TIA	211 (22.7%)	357 (29.3%)	0.001
Current smoker	110 (11.8%)	95 (7.8%)	
Alcoholism	50 (5.4%)	92 (7.5%)	
History congestive heart failure	89 (9.6%)	281 (23.0%)	< 0.0001
History myocardial infarction	116 (12.5%)	180 (14.8%)	
History peripheral artery disease	71 (7.6%)	111 (9.1%)	
Pacemaker	39 (4.2%)	111 (9.1%)	< 0.0001
Lesion size			
Small	350 (37.6%)	471 (38.6%)	
Medium	310 (33.3%)	428 (35.1%)	
Large Anterior	173 (18.6%)	225 (18.4%)	
Large Posterior	62 (6.7%)	74 (6.1%)	
Leukoaraiosis	465 (50.0%)	632 (51.8%)	
OAC	812 (87.3%)	976 (80.0%)	< 0.0001
VKA	220 (23.7%)	346 (28.4%)	
NOAC	592 (63.7%)	630 (51.6%)	< 0.0001
CHA_2DS_2-VASc > 4	682 (73.3%)	988 (81.0%)	< 0.0001
Atrial enlargement †	510 (62.5%)	739 (74.6%)	< 0.0001

* p-values are given only if < 0.05; † 1806 patients with trans-thoracic echocardiogram performed.

NIHSS = National Institutes of Health Stroke Scale; PAF = paroxysmal atrial fibrillation; SAF = sustained atrial fibrillation; TIA = transient ischemic attack.

Table 2. Multivariate logistic regression analysis of factors potentially associated with SAF

	OR	**95% CI**	**p***
Age (for each year increase)	1.03	1.02-1.04	< 0.0001
Sex	1.15	0.94-1.39	
NIHSS	1.01	1.00-1.03	
Diabetes mellitus	1.28	1.03-1.61	0.026
Hypertension	1.05	0.79-1.25	
Hyperlipidemia	3.85	0.73-1.09	
History stroke/TIA	1.25	1.01-1.54	0.042
Smoking	3.85	0.79-1.06	
Alcoholism	1.69	1.14-2.50	0.009
History congestive heart failure	2.70	2.04-3.57	< 0.0001
History myocardial infarction	3.85	0.64-1.12	
Pacemaker	1.85	1.23-2.78	0.003

* p-values are given only if < 0.05. CI = confidence interval; OR = odds ratios; other abbreviations as in Table 1.

Table 3. Baseline characteristics of patients with and without ischemic recurrences

	With event (n = 107)	**Without event** (n = 2040)	**p***
Age (mean, years)	78.3 ± 9.4	76.2 ± 9.8	0.034
Sex M	47 (43.9%)	945 (46.3%)	
NIHSS (mean)	10.4 ± 8.0	8.3 ± 6.7	0.001
Diabetes mellitus	38 (35.5%)	443 (21.7%)	0.020
Hypertension	93 (86.0%)	1597 (78.3%)	0.026
Hyperlipidemia	37 (34.6%)	697 (34.2%)	
History stroke/TIA	35 (32.7%)	528 (25.9%)	
Current smoker	8 (7.5%)	196 (9.6%)	
Alcoholism	9 (8.4%)	131 (6.4%)	
History congestive heart failure	29 (27.1%)	340 (16.7%)	0.008
History myocardial infarction	17 (15.9%)	275 (13.5%)	
History peripheral artery disease	14 (13.1%)	163 (8.0%)	
Pacemaker	13 (12.1%)	133 (6.5%)	0.029
Lesion size			
Small	31 (29.0%)	796 (39.0%)	0.050
Medium	42 (39.3%)	705 (34.6%)	
Large Anterior	27 (25.2%)	368 (18.0%)	
Large Posterior	3 (2.8%)	132 (6.5%)	
Leukoaraiosis	61 (57.0%)	1013 (49.7%)	
PAF	31 (29.0%)	886 (43.4%)	0.003
OAC	73 (68.2%)	1710 (83.9%)	0.001
VKA	38 (35.5%)	525 (25.7%)	0.041
NOAC	35 (32.7%)	1185 (58.1%)	0.001
CHA_2DS_2-VASc > 4	94 (87.9%)	1573 (77.0%)	0.008

* p-values are given only if < 0.05. CHA_2DS_2-VASc = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack,

vascular disease, 65 to 74 years of age, female; OAC = oral anticoagulation; other abbreviations as in Table 1.