March, 2018

AF after stroke and the Neurogenic hypothesis

Gustavo Saposnik
Luciano A. Sposato

ARTICLE

Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence

Luciano A. Sposato, MD, MBA, FRCPC, Joshua O. Cerasuolo, MSc, Lauren E. Cipriano, PhD, Jiming Fang, PhD, Sebastian Fridman, MD, MPH, Maryse Paquet, MSc, PhD, and Gustavo Saposnik, MD, MSc, FRCPC, On behalf of the PARADISE Study Group

Correspondence
Dr. Sposato
lsposato@uwo.ca

Neurology® 2018;90:e924-e931. doi:10.1212/WNL.0000000000005126

Abstract

Objective

To compare the risk of 1-year ischemic stroke recurrence between atrial fibrillation (AF) diagnosed after stroke (AFDAS) and sinus rhythm (SR) and investigate whether underlying heart disease is as frequent in AFDAS as it is in AF known before stroke (KAF).

Methods

In this retrospective cohort study, we included all ischemic stroke patients admitted to institutions participating in the Ontario Stroke Registry from July 1, 2003, to March 31, 2013. Based on heart rhythm assessed during admission, we classified patients as AFDAS, KAF, or SR. We modeled the relationship between heart rhythm groups and 1-year ischemic stroke recurrence by using Cox regression adjusted for multiple covariates (e.g., oral anticoagulants). We compared the prevalence of coronary artery disease, myocardial infarction, and heart failure among the 3 groups.

Results

Among 23,376 ischemic stroke patients, 15,885 had SR, 587 AFDAS, and 6,904 KAF. At 1 year, 39 (6.6%) patients with AFDAS, 661 (9.6%) with KAF, and 1,269 (8.0%) with SR had recurrent ischemic strokes ($p = 0.0001$). AFDAS-related ischemic stroke recurrence adjusted risk was not different from that of SR (hazard ratio 0.90 [95% confidence interval 0.63, 1.30]; $p = 0.57$). Prevalence of coronary artery disease (18.2% vs 34.7%; $p < 0.0001$), myocardial infarction (11.6% vs 20.5%; $p < 0.0001$), and heart failure (5.5% vs 16.8%; $p < 0.0001$) were lower in AFDAS relative to KAF.

Conclusions

The lack of difference in 1-year ischemic stroke recurrence between AFDAS and SR and the lower prevalence of heart disease in AFDAS compared to KAF suggest that the underlying pathophysiology of AFDAS may differ from that of KAF.

MORE ONLINE

Podcast
Dr. Mark McAllister interviews Dr. Luciano Sposato about his paper on atrial fibrillation and ischemic stroke.
NPub.org/o4cmei

RELATED ARTICLE

Editorial
Insights into atrial fibrillation newly diagnosed after stroke: Can the brain rule the heart?
Page 493

From the Department of Clinical Neurological Sciences, London Health Sciences Centre (L.A.S., S.F.), Department of Anatomy and Cell Biology (L.A.S.), and Department of Epidemiology and Biostatistics (L.A.S., J.O.C., L.E.C.), Schulich School of Medicine and Dentistry, Stroke, Dementia, and Heart Disease Lab (L.A.S., M.P.), and Ivey Business School (L.E.C.), Western University, London; Institute for Clinical Evaluative Sciences (J.F., G.S.), Toronto; Stroke Outcomes & Decision Neuroscience Research Unit (G.S.), Division of Neurology, Department of Medicine, St. Michael's Hospital and Institute of Health Policy, Management and Evaluation, Faculty of Medicine, Institute for Clinical Evaluative Sciences, University of Toronto; and Li Ka Shing Knowledge Institute (G.S.), Toronto, Canada.

Coinvestigators are listed at links.lww.com/WNL/A242.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AF = atrial fibrillation; **AFDAS** = atrial fibrillation detected after stroke; **CI** = confidence interval; **HR** = hazard ratio; **KAF** = atrial fibrillation known prior to the stroke.

Ischemic stroke patients fall into 3 possible categories of heart rhythm: (1) sinus rhythm: no history of atrial fibrillation (AF) and no AF identified after cardiac monitoring, (2) AF known prior to the stroke (KAF), or (3) AF detected after stroke (AFDAS).[1] Despite the increasing detection of AFDAS,[2] the incident risk of recurrent stroke and its pathophysiology remain unknown.

KAF is a primarily cardiogenic form of AF, with minimal or no participation of central neurogenic mechanisms. Conversely, AFDAS may comprise a heterogeneous mix of AF phenotypes,[1] some of them likely representing AF that existed before the stroke, but remained undiagnosed until poststroke ECG monitoring was completed. This preexisting or cardiogenic AFDAS is essentially an undiagnosed form of KAF and, therefore, it is caused by underlying heart disease. The neurogenic phenotype is characterized by involvement of brain or brainstem structures implicated in the regulation of heart rhythm[3–5] in patients without previously known heart disease. We have proposed that the presence of a given proportion of relatively more benign neurogenic AFDAS phenotypes may dilute the overall AFDAS-associated risk of recurrent ischemic stroke, resulting in similar recurrence rates as those of patients without AF.[1,6,7]

We hypothesized that there would be no differences in the risk of ischemic stroke recurrence between AFDAS and sinus rhythm. Based on the neurogenic AFDAS premise[1] (e.g., neurogenic AFDAS with less frequent heart disease but more frequent insular involvement compared to KAF), we also expected a lower prevalence of cardiac comorbidities among patients with AFDAS relative to those with KAF.

Methods

This observational study is part of a translational initiative investigating AFDAS, Pathophysiology and Risk of Atrial Fibrillation Diagnosed after Stroke (PARADISE), which comprises experimental, clinical, and epidemiologic studies.[8]

Study cohort

For the present analysis, we included clinically confirmed acute ischemic stroke patients admitted between July 1, 2003, and March 31, 2013, to 11 participating institutions of the Ontario Stroke Registry. The Ontario Stroke Registry comprises information regarding patient-level demographics, risk factors, comorbidities, processes of care, as well as hospital-level characteristics. This clinical registry is managed by the Institute for Clinical Evaluative Sciences (Toronto, Canada), which has approved the prespecified analytical plan and study hypotheses. Data were systematically collected during hospitalization and at discharge by using comprehensive case report forms. We excluded patients younger than 18 years, diagnosed with hemorrhagic stroke, cerebral venous thrombosis, or a brain tumor, presenting with an in-hospital stroke, or with invalid or missing key number for database linkage. Patients who were dead at discharge were excluded from the analysis, as stroke severity or early death may have precluded cardiac monitoring.

Cohort stratification into heart rhythm subgroups

All patients had at least one ECG. Participants without KAF underwent further in-hospital ≥24 hours ECG monitoring (e.g., Holter, telemetry) based on the discretion of the treating physician. Based on their history of AF and on the results of ECG monitoring during hospitalization, patients were stratified into 3 main groups: (1) AFDAS (no history of AF but AF detected during hospital stay after the index ischemic stroke), (2) KAF (history of AF known before the index ischemic stroke, regardless of whether it was documented during admission), and (3) sinus rhythm (no history of AF and no AF identified during admission). A history of AF was determined as per a specific field in the Ontario Stroke Registry case report form, which was clinically ascertained during hospital stay. To further validate this, we looked at 3 available administrative datasets (Ontario Health Insurance Plan, Discharge Abstract Database, and the National Ambulatory Care Reporting System) to determine whether each participant had been diagnosed with AF within 5 years before the index ischemic stroke (figure e-1, links.lww.com/WNL/A240).[9] Datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences.

Outcome measures

The primary outcome of this study was the risk of a recurrent ischemic stroke at 1 year after discharge, which was ascertained by using a previously validated algorithm.[10,11] The algorithm involves multiple linkable databases in Ontario, Canada, including the Discharge Abstract Database and the National Ambulatory Care Reporting System.[9] We considered any admission or emergency department visit due to a main diagnosis of ischemic stroke after the index discharge dates. Accordingly, recurrent ischemic stroke was defined as a single entry in the Discharge Abstract Database or the National Ambulatory Care Reporting System with most responsible diagnosis of ischemic stroke.

Analyses

We developed cumulative incidence function curves for recurrent ischemic stroke among patients in each of the 3

heart rhythm groups. We estimated the association between each AF subgroup (AFDAS and KAF) and recurrent ischemic stroke at 1 year after discharge by using cause-specific Cox proportional hazards. We developed 3 different models by using variables known to influence the risk of recurrent ischemic stroke. Model 1 was adjusted for age, sex, stroke severity, and prescription of oral anticoagulants at discharge. Model 2 was adjusted for the same variables as model 1 plus systemic hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, and history of stroke or TIA. Model 3 was adjusted for the same variables as model 2 plus history of dementia and modified Rankin Scale score at discharge. All-cause death following the index ischemic stroke was adjusted as a competing risk. Death within 1 year of the incident ischemic stroke was determined by using the Ontario Registered Persons Database, a population-based registry maintained by the Ministry of Health and Long-Term Care in Ontario, Canada, which captures individuals' date of birth, sex, address, and date of death, among other demographic variables.[9] Sinus rhythm was the comparator for both types of AF (AFDAS and KAF). We used a robust sandwich covariance matrix estimate to account for the intracluster dependence of hospitals. We selected the model based on the lowest Akaike Information Criteria values. Because patients who had a stroke before the index ischemic stroke may constitute a specific population at particularly high risk, we ran sensitivity analyses restricted to patients with first-ever ischemic strokes, adjusted for the same variables as those used in the models for the overall cohort.

To provide a more intuitive adjusted estimate of the annual risk of recurrent ischemic stroke at 1 year, we calculated the adjusted proportion of patients experiencing a recurrence in each group by using subdistribution Cox proportional hazards, which allow for estimating the effect of covariates on the absolute risk of a given time-to-event outcome.[12] We developed 3 different subdistribution Cox models, adjusted for the same variables as those used for the cause-specific Cox analyses.

To assess the hypothesis of neurogenic vs cardiogenic AFDAS, we compared the prevalence of available cardiovascular comorbidities (e.g., congestive heart failure, myocardial infarction, and coronary artery disease) between AFDAS and KAF, and between AFDAS and sinus rhythm. We used the z test with 2-tailed probabilities for comparing proportions. We estimated the difference in proportions with asymptotic (normal approximation) 95% confidence intervals (CIs) (based on a significance level of 0.05). All statistical analyses were done with SAS Enterprise Guide 6.1 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Results

We assessed 23,376 acute ischemic stroke patients from the Ontario Stroke Registry who were alive at discharge (table 1 and figure e-2, links.lww.com/WNL/A240). A total of 6,904 (29.5%) participants had KAF. Among 16,472 patients without history of AF before the index ischemic stroke, 5,793 (35.2%) underwent >24 hours of in-hospital ECG monitoring (e.g., admission ECG, telemetry, and Holter). At discharge, 587 were deemed to have AFDAS (282 cases were detected with continuous ECG monitoring), whereas 15,885 were not diagnosed with AF at the time of discharge and were thus classified as having sinus rhythm. The overall AFDAS detection yield during hospitalization for all ECG monitoring methods (admission ECG, ECG during hospital stay, and in-hospital continuous ECG monitoring) considered together was 10.1% (587 AF cases identified among 5,793 patients monitored).

Overall, 1,969 (8.4%) participants had a recurrent ischemic stroke at 1 year: 39 (6.6%) with AFDAS, 661 (9.6%) with KAF, and 1,269 (8.0%) with sinus rhythm (p = 0.0001). Accounting for the competing risk of death, the unadjusted cumulative incidence of recurrent ischemic stroke within 1 year after discharge for patients with AFDAS was lower than for participants with KAF and sinus rhythm (figure 1).

Adjusted risk of recurrent ischemic stroke at 1 year

Patients with KAF had a consistently higher risk (hazard ratio [HR] 1.25 [95% CI 1.12, 1.39]; p = 0.001) of recurrent ischemic stroke at 1 year than those with sinus rhythm in all the cause-specific Cox regression models (figure 2). The risk of recurrent ischemic stroke at 1 year in patients with AFDAS was not different from that of patients with sinus rhythm (HR 0.90 [95% CI 0.63, 1.30]; p = 0.57; figure 2). Age, female sex, stroke severity, a history of stroke or TIA before the incident ischemic stroke, and the use of oral anticoagulants at the time of discharge were all associated with ischemic stroke recurrence at 1 year (table 2). Uncertainty in the influence of AFDAS on the risk of recurrent ischemic stroke, represented by the width of the CIs, was not reduced by including more covariates known to contribute to stroke risk such as hypertension, diabetes mellitus, coronary artery disease, prior stroke, or congestive heart failure (models 2 or 3 relative to model 1).

Sensitivity analyses in patients with first-ever ischemic stroke

A total of 19,266 first-ever ischemic stroke patients were included in sensitivity analyses excluding patients with a prior cerebrovascular event before the index ischemic stroke. Among them, 510 had AFDAS, 5,371 had KAF, and 13,385 had sinus rhythm (table e-1, links.lww.com/WNL/A241). The risk of recurrent ischemic stroke at 1 year in patients with AFDAS was not different from that

Table 1 Characteristics of patients with KAF, AFDAS, and sinus rhythm

	Total (n = 23,376)	KAF (n = 6,904)	AFDAS (n = 587)	Sinus rhythm (n = 15,885)	*p* Value
Age, y	71.4 (14.1)	77.4 (11.1)	77.4 (10.8)	68.6 (14.5)	<0.0001
Female sex	10,909 (46.7)	3,589 (52.0)	317 (54.0)	7,003 (44.1)	<0.0001
Stroke severity, CNS					
Mild (CNS ≥ 8)	17,425 (74.5)	4,710 (68.2)	313 (53.3)	12,402 (78.1)	<0.0001
Moderate (CNS 7-5)	3,819 (16.3)	1,287 (18.6)	157 (26.7)	2,375 (15.0)	
Severe (CNS 4-1)	2,132 (9.1)	907 (13.1)	117 (19.9)	1,108 (7.0)	
Risk factors					
Hypertension	16,100 (68.9)	5,312 (76.9)	409 (69.7)	10,379 (65.3)	<0.0001
Diabetes mellitus	5,984 (25.6)	1,805 (26.1)	105 (17.9)	4,074 (25.6)	<0.0001
Dyslipidemia	9,302 (39.8)	3,004 (43.5)	209 (35.6)	6,089 (38.3)	<0.0001
Prestroke CHA_2DS_2-VASc stratification					
Low risk	2,292 (9.8)	155 (2.2)	25 (4.3)	2,112 (13.3)	<0.0001
Intermediate risk	2,692 (11.5)	371 (5.4)	41 (7.0)	2,280 (14.4)	
High risk	18,392 (78.7)	6,378 (92.4)	521 (88.8)	11,493 (72.4)	
Median CHA_2DS_2-VASc score	3 (2–5)	4 (3–5)	4 (3–4)	3 (2–4)	<0.0001
Mean CHA_2DS_2-VASc score	3.4 (1.9)	4.2 (1.7)	3.6 (1.6)	3.1 (1.8)	<0.0001
IV thrombolysis	3,694 (15.8)	1,252 (18.1)	225 (38.3)	2,217 (14.0)	<0.0001
Antithrombotics before admission					
No antithrombotics	18,002 (77.0)	4,772 (69.1)	468 (79.7)	12,762 (80.3)	<0.0001
Antiplatelet agents or oral anticoagulants	5,374 (23.0)	2,132 (30.9)	119 (20.3)	3,123 (19.7)	
Antithrombotics at discharge					
No antithrombotics	1,852 (7.9)	620 (9.0)	35 (6.0)	1,197 (7.5)	<0.0001
Antiplatelet agents only	14,620 (62.5)	2,451 (35.5)	125 (21.3)	12,044 (75.8)	
Oral anticoagulants only	3,285 (14.1)	2,118 (30.7)	211 (35.9)	956 (6.0)	
Antiplatelet agents and oral anticoagulants	3,619 (15.5)	1,715 (24.8)	216 (36.8)	1,688 (10.6)	

Abbreviations: AFDAS = atrial fibrillation detected after the index stroke; CNS = Canadian Neurologic Scale; KAF = atrial fibrillation known before the index stroke.
Data are mean (SD), n (%), median (interquartile range), or n/N (%). CHA_2DS_2-VASc (age, sex, hypertension, diabetes, history of stroke or TIA, heart failure, peripheral artery disease) stratification: low risk (men = 0 or women = 1), intermediate risk (men = 1 or women = 2), high risk (men ≥ 2 or women ≥ 3).

of patients with sinus rhythm (HR 0.92 [95% CI 0.59, 1.43]; $p = 0.71$; table e-2). Participants with KAF had a higher risk of recurrent ischemic stroke compared to those with sinus rhythm (HR 1.27 [95% CI 1.08, 1.49]; $p = 0.005$).

Adjusted incidence of recurrent ischemic stroke at 1 year

Patients with AFDAS (6.8% [95% CI 4.8, 8.9%]) had similar adjusted incidence of recurrent ischemic stroke as those with sinus rhythm. In contrast, the adjusted incidence of recurrent ischemic stroke at 1 year (model 1; figure e-3, links.lww.com/WNL/A240) was higher for KAF (9.6% [95% CI 8.9, 10.4%]) than for sinus rhythm (7.9% [95% CI 7.5, 8.4]).

Prevalence of cardiac comorbidities in each heart rhythm group

Overall, 5,262 (22.5%) patients had coronary artery disease, 3,195 (13.7%) had a myocardial infarction, and 1,732 (7.4%) had congestive heart failure prior to the index ischemic stroke. Relative to participants with KAF, those with AFDAS had a significantly lower prevalence of coronary artery disease (18.2% vs 34.7%; $p < 0.0001$), prior myocardial infarction (11.6% vs 20.5%; $p < 0.0001$), and congestive heart failure (5.5% vs 16.8%; $p < 0.0001$) (figure 3 and table e-3, links.lww.com/WNL/A241). Compared to sinus rhythm, AFDAS had a similar prevalence of myocardial infarction and coronary artery disease, but a slightly higher frequency of congestive heart failure (5.5% vs 3.4%; $p = 0.009$).

Figure 1 Cumulative incidence function curve for recurrent ischemic stroke in atrial fibrillation known prior to the stroke (KAF), atrial fibrillation detected after stroke (AFDAS), and sinus rhythm

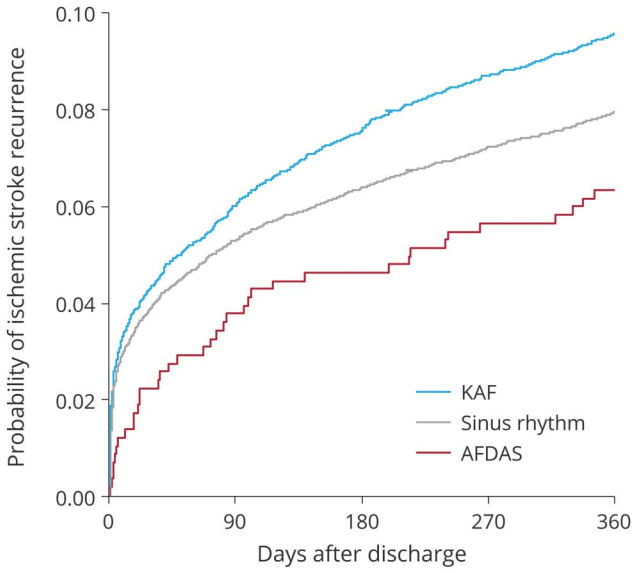
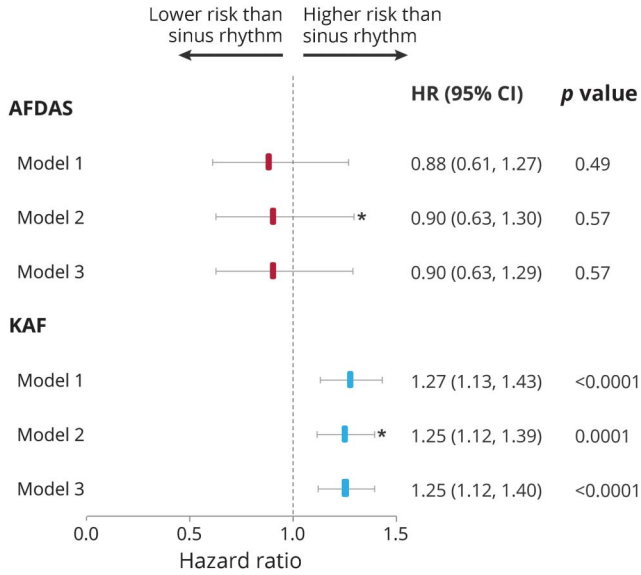


Figure 2 Adjusted risk of recurrent ischemic stroke at 1 year for atrial fibrillation known prior to the stroke (KAF) and atrial fibrillation detected after stroke (AFDAS) in Cox regression models



Error bars denote 95% confidence intervals. * denotes the best fitting model as per the lowest Akaike information criteria. Hazard ratios for each outcome shown in the figure were estimated in separate models (one model for each outcome) applied to the whole study cohort. Model 1 was adjusted for age, sex, stroke severity, and prescription of oral anticoagulants at discharge. Model 2 was adjusted for age, sex, stroke severity, systemic hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, prior history of stroke or transient ischemic attack, and prescription of oral anticoagulants at discharge. Model 3 was adjusted for age, sex, stroke severity, systemic hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, prior history of stroke, prior history of TIA, history of dementia, modified Rankin Scale score at discharge, and prescription of oral anticoagulants at discharge.

Discussion

In this study comprising 23,376 patients with an acute ischemic stroke admitted to tertiary care institutions participating in the Ontario Stroke Registry, ADFAS was identified in 587 of 16,472 patients who had no history of AF and were alive at discharge. Relative to participants with sinus rhythm, those with AFDAS had no difference in the risk of recurrent ischemic stroke at 1 year after adjusting for multiple confounders. Importantly, the adjustment for the exposure to oral anticoagulants did not alter the results. Patients with AFDAS had a significantly lower prevalence of cardiac comorbidities than those with KAF, but there were no significant differences vs those who had sinus rhythm, except for a slightly higher prevalence of congestive heart failure. The results were consistent through multiple levels of adjustment.

We observed a higher risk of recurrent ischemic stroke at 1 year in patients with KAF than in those with sinus rhythm, but we did not find a difference between patients with AFDAS and those with sinus rhythm (figure e-3, links.lww.com/WNL/A240). Our findings support the hypothesis that AFDAS is different from KAF, at least in terms of outcomes. Specifically, we suggest that AFDAS comprises a wide spectrum of AF with dissimilar associated risks of recurrent ischemic stroke. Additional findings from our study contribute to support this idea. The relatively large uncertainty in the HRs for AFDAS, even after adjusting for oral anticoagulant use and factors known to affect stroke risk, suggests substantial heterogeneity in stroke risk across patients with AFDAS. As such, AFDAS-associated risk of recurrent ischemic stroke seems to be determined not only by risk factors in classical risk stratification schemes, but also by other elements. Differing pathophysiologic mechanisms could account for part of the heterogeneity of AFDAS-associated risk. Accordingly, neurogenically triggered AFDAS may have a lower risk, whereas cardiogenic AFDAS is possibly associated with the well-known high risk of stroke in patients with AF caused by underlying heart disease.[1] Indeed, markers of heart disease were significantly more prevalent among patients with KAF compared to those with AFDAS in our study, while there were no differences in the prevalence of coronary artery disease and myocardial infarction in participants with AFDAS relative to those with sinus rhythm, meaning that a considerable proportion of patients in the AFDAS group had AF in the absence of evident heart disease. Although this explanation is in line with our a priori study hypothesis,[1,6,13] our results may be explained by other yet unidentified factors.

A recent study reported an increased risk of ischemic and TIA at 1 year in patients with ischemic stroke or TIA who were newly diagnosed with AF in the year after the index stroke, as identified by ambulatory ECG monitoring.[14] Different from ours, the patient cohort in this study included participants with TIA, who are known to have a lower prevalence or smaller

Table 2 Cox regression models for ischemic stroke recurrence at 1 year after discharge

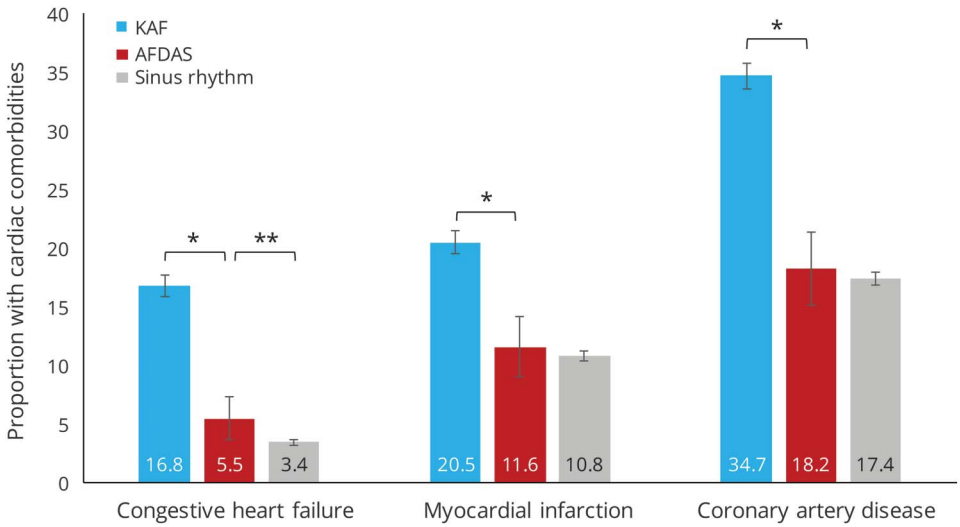
Outcome	HR (95% CI)	*p* Value	AIC
Model 1			39,172.3
Heart rhythm			
Sinus rhythm	Ref	—	
KAF	1.27 (1.13, 1.43)	<0.0001	
AFDAS	0.88 (0.61, 1.27)	0.49	
Age	1.006 (1.003,1.009)	<0.0001	
Female sex	1.07 (1.00, 1.16)	<0.0001	
Severe stroke (CNS 4-1)	1.25 (1.07, 1.47)	0.06	
Anticoagulants at discharge	0.83 (0.78, 0.89)	<0.0001	
Model 2			39,147.9
Heart rhythm			
Sinus rhythm	Ref	—	
KAF	1.25 (1.12, 1.39)	0.0001	
AFDAS	0.90 (0.63, 1.30)	0.57	
Age	1.005 (1.002, 1.008)	0.002	
Female sex	1.09 (1.01, 1.17)	0.025	
Severe stroke (CNS 4-1)	1.25 (1.06, 1.47)	0.007	
Hypertension	1.00 (0.93, 1.06)	0.94	
Diabetes mellitus	1.05 (0.99, 1.12)	0.09	
Congestive heart failure	1.00 (0.77, 1.29)	0.98	
Coronary artery disease	1.04 (0.94, 1.15)	0.45	
Prior stroke or TIA	1.32 (1.19, 1.46)	<0.0001	
Anticoagulants at discharge	0.83 (0.78, 0.89)	<0.0001	
Model 3			39,162.1
Heart rhythm			
Sinus rhythm	Ref	—	
KAF	1.25 (1.12, 1.40)	<0.0001	
AFDAS	0.90 (0.63, 1.29)	0.57	
Age, y			
<55	Ref	—	
55–65	1.13 (0.94, 1.35)	0.21	
66–75	1.20 (1.01, 1.42)	0.038	
76–85	1.23 (1.08, 1.40)	0.002	
>85	1.22 (1.05, 1.42)	0.009	
Female sex	1.09 (1.02, 1.17)	0.014	
Hypertension	0.99 (0.93, 1.06)	0.88	
Diabetes mellitus	1.04 (0.98, 1.11)	0.19	
Congestive heart failure	1.00 (0.77, 1.30)	0.99	
Prior stroke	1.31 (1.17, 1.46)	<0.0001	
Prior TIA	1.18 (1.06, 1.30)	0.002	
Diagnosis of dementia before stroke	1.00 (0.87, 1.16)	1.00	
Stroke severity (CNS)			
Mild (CNS ≥ 8)	Ref	—	
Moderate (CNS 7-5)	1.00 (0.92, 1.08)	0.93	
Severe (CNS 4-1)	1.24 (1.06, 1.44)	0.005	
Modified Rankin Scale score at discharge	1.03 (0.94, 1.14)	0.49	
Anticoagulants at discharge	0.83 (0.77, 0.88)	<0.0001	

Abbreviations: AFDAS = atrial fibrillation detected after the index stroke; AIC = Akaike Information Criteria; CI = confidence interval; CNS = Canadian Neurologic Scale; HR = hazard ratio; KAF = atrial fibrillation known before the index stroke.

brain infarcts, resulting in milder autonomic and inflammatory responses. Also, while in our study the main outcome was recurrent ischemic stroke at 1 year, in the study by Lip et al.[14] was the composite of ischemic and TIA. Finally, while we included only AFDAS detected during admission, in the other study, AFDAS was ascertained between 8 days and 1 year after stroke.

This study has limitations. First, patients who died during hospital stay were excluded from the study because their stroke severity or a premature death may have precluded them from undergoing cardiac monitoring. Despite this, the study cohort represents real-world data from stroke patients discharged from hospital in Ontario, Canada. Second, some patients in the sinus rhythm group may have had covert AF, which remained undiagnosed because AFDAS was not systematically investigated in this cohort. This could have weakly biased statistical comparisons of AFDAS and sinus rhythm towards the null hypothesis of no difference. However, the comparison between KAF and sinus rhythm would similarly be biased towards a null finding; but in this case, we found a consistently significant difference. Furthermore, the strongly significant lack of difference in the risk of stroke recurrence between AFDAS and sinus rhythm, as shown by the CI (0.63–1.30; $p = 0.57$), renders a considerable influence of this bias on our results highly unlikely. Third, we did not account for AFDAS detected a long time after the hospital discharge

Figure 3 Cardiac comorbidities in atrial fibrillation known prior to the stroke (KAF), atrial fibrillation detected after stroke (AFDAS), and sinus rhythm



Data are proportions, error bars are 95% confidence intervals constructed by the Wilson method. *$p < 0.0001$; **$p < 0.01$.

(e.g., during ambulatory ECG monitoring). Ambulatory AF screening remains low in real-world medical practice,[14] even in regions with adequate availability of resources such as Ontario.[15] Consequently, in most instances, therapeutic decisions are made before or at the time of discharge, and are based on AF detected during admission. In addition, the pathophysiology and outcome of AFDAS detected months after the index stroke may differ significantly from that detected immediately after the event, and the clinical significance is uncertain.[1] Fourth, there were some limitations inherent to the nature of the dataset, which did not allow us to identify specific patient characteristics that could have helped to explain the findings of this study: (1) the mechanism of incident or recurrent ischemic strokes, (2) the proportion of patients with paroxysmal vs sustained AF in each group, and (3) the topography of brain infarcts. Despite the absence of some variables of interest, these previously validated and large clinical and administrative datasets comprising a sizable and up to date sample size with population coverage including long observational periods offer the possibility of reliably addressing the prespecified hypothesis. However, further research in other cohorts is needed to externally validate these results.

If the explanation for the lack of differences in the risk of recurrent ischemic stroke in patients with AFDAS relative to patients with sinus rhythm is that the pathophysiology of some types of AFDAS is different from that of KAF, involving inflammatory[16] and dysautonomic[17] mechanisms, the use of drugs known to have anti-inflammatory properties (e.g., statins, low-dose steroids) or to modulate the autonomic nervous system (e.g., β-blockers) could also be tested in the hyperacute stroke setting to prevent neurogenic AFDAS. Before this, we should be able to identify markers of neurogenic AFDAS to clinically recognize patients at risk. Identifying specific clinical features, plasma proteins, neuroimaging findings, echocardiographic results, or autonomic profiles of neurogenic AFDAS may help to implement more effective and personalized secondary prevention strategies in the future. Also, disentangling the neurogenic mechanisms of AFDAS could result in a better understanding of other AF pathophysiologic aspects that have been less frequently investigated thus far.

Disclaimers

This study was supported by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions and statements expressed in the material are those of the authors, and not necessarily those of the Canadian Institute for Health Information. This observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Author contributions

Luciano A. Sposato: study concept and design, data interpretation, manuscript drafting, study supervision. Joshua O. Cerasuolo: study design, manuscript drafting. Lauren E. Cipriano: data interpretation, critical revision of manuscript for intellectual content. Jiming Fang: data analysis and interpretation. Sebastian Fridman: data interpretation, critical

revision of manuscript for intellectual content. Maryse Paquet: critical revision of manuscript for intellectual content. Gustavo Saposnik: study concept and design, data interpretation, critical revision of manuscript for intellectual content, study supervision.

Study funding

Dr. Sposato is supported by the Kathleen & Dr. Henry Barnett Research Chair in Stroke Research (Western University, London, Canada); the Edward and Alma Saraydar Neurosciences Fund (London Health Sciences Foundation, London, Canada); and the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO) (Canada). Dr. Saposnik is supported by the Heart and Stroke Foundation Career Award following an open, peer-reviewed advertisement.

Disclosure

L.A. Sposato: speaker honoraria from Boehringer Ingelheim and Pfizer; research grants from Boehringer Ingelheim and Medtronic. Dr. Saposnik is supported by the Heart and Stroke Foundation Scientist Award following an open and peer reviewed competition. Dr. Saposnik is the Section Editor of Emerging Therapies for STROKE journal. J.O. Cerasuolo, L.E. Cipriano, J. Fang, S. Fridman, and M. Paquet report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received September 6, 2017. Accepted in final form November 29, 2017.

References

1. Cerasuolo JO, Cipriano LE, Sposato LA. The complexity of atrial fibrillation newly diagnosed after ischemic stroke and TIA: advances and uncertainties. Curr Opin Neurol 2017;30:28–37.
2. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377–387.
3. Frontzek K, Fluri F, Siemerkus J, et al. Isolated insular strokes and plasma MR-proANP levels are associated with newly diagnosed atrial fibrillation: a pilot study. PLoS One 2014;9:e92421.
4. Scheitz JF, Erdur H, Haeusler KG, et al. Insular cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. Stroke 2015;46:1196–1201.
5. Abboud H, Berroir S, Labreuche J, Orjuela K, Amarenco P. Insular involvement in brain infarction increases risk for cardiac arrhythmia and death. Ann Neurol 2006;59:691–699.
6. Sposato LA, Riccio PM, Hachinski V. Poststroke atrial fibrillation: cause or consequence? Critical review of current views. Neurology 2014;82:1180–1186.
7. Sposato LA, Cipriano LE, Riccio PM, Hachinski V, Saposnik G. Very short paroxysms account for more than half of the cases of atrial fibrillation detected after stroke and TIA: a systematic review and meta-analysis. Int J Stroke 2015;10:801–807.
8. Paquet M, Cerasuolo JO, Thorburn V, et al. Pathophysiology and risk of atrial fibrillation detected after ischemic stroke (PARADISE): a translational, integrated, and transdisciplinary approach. J Stroke Cerebrovasc Dis Epub 2017 Nov 13.
9. Tsai JP, Rochon PA, Raptis S, Bronskill SE, Bell CM, Saposnik G. A prescription at discharge improves long-term adherence for secondary stroke prevention. J Stroke Cerebrovasc Dis 2014;23:2308–2315.
10. Sposato LA, Kapral MK, Wu J, et al. Declining incidence of stroke and dementia: coincidence or prevention opportunity? JAMA Neurol 2015;72:1529–1531.
11. O'Donnell M, Oczkowski W, Fang J, et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol 2006;5:749–754.
12. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–609.
13. Gonzalez Toledo ME, Klein FR, Riccio PM, et al. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. J Stroke Cerebrovasc Dis 2013;22:e486–e491.
14. Lip GY, Hunter TD, Quiroz ME, Ziegler PD, Turakhia MP. Atrial fibrillation diagnosis timing, ambulatory ECG monitoring utilization, and risk of recurrent stroke. Circ Cardiovasc Qual Outcomes 2017;10:e002864.
15. Edwards JD, Kapral MK, Fang J, Saposnik G, Gladstone DJ; Investigators of the Registry of the Canadian Stroke Network. Underutilization of ambulatory ECG monitoring after stroke and transient ischemic attack: missed Opportunities for atrial fibrillation detection. Stroke 2016;47:1982–1989.
16. Esenwa CC, Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. Nat Rev Neurol 2016;12:594–604.
17. Agarwal SK, Norby FL, Whitsel EA, et al. Cardiac autonomic dysfunction and incidence of atrial fibrillation: results from 20 years follow-up. J Am Coll Cardiol 2017;69:291–299.

FULL-LENGTH ARTICLE NPub.org/1e72ig

Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence

Luciano A. Sposato, MD, MBA, FRCPC, Joshua O. Cerasuolo, MSc, Lauren E. Cipriano, PhD, Jiming Fang, PhD, Sebastian Fridman, MD, MPH, Maryse Paquet, MSc, PhD, and Gustavo Saposnik, MD, MSc, FRCPC, On behalf of the PARADISE Study Group

Correspondence
Dr. Sposato
lsposato@uwo.ca

Cite as: *Neurology*® 2018;90:e924-e931. doi:10.1212/WNL.0000000000005126

Study questions

Does the risk of ischemic stroke differ among patients with sinus rhythm and those with atrial fibrillation (AF) diagnosed after stroke (AFDAS)? Are cardiac comorbidities less frequent in patients with AFDAS than in those with AF known before the stroke (KAF)?

Summary answer

After adjusting for multiple confounders, the risk of ischemic stroke recurrence 1 year after stroke was similar in patients with sinus rhythm and AFDAS. The prevalence of all cardiac comorbidities was lower in patients with AFDAS than in those with KAF.

What is known and what this paper adds

This study suggests that AFDAS is different from KAF, at least in its lower risk if ischemic stroke recurrence. This may be due to different pathophysiologic mechanisms in neurogenic AFDAS, a subtype of AF triggered by brain damage in stroke patients with healthier hearts.

Participants and setting

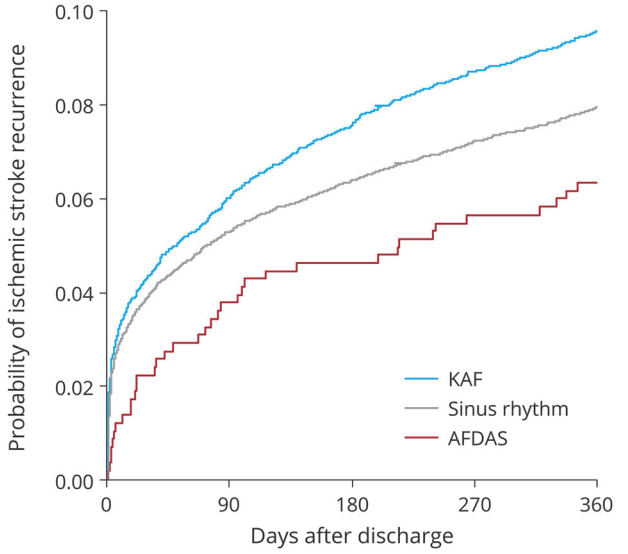
Patients with acute ischemic stroke who had been admitted to 11 participating institutions of the Ontario Stroke Registry were classified into 3 groups of heart rhythm including sinus rhythm, AFDAS, and KAF.

Design, size, and duration

This is a retrospective cohort study, which included 23,376 ischemic stroke patients with ischemic stroke admitted from July 1, 2003 to March 31, 2013: 15,885 with sinus rhythm, 587 with AFDAS, and 6,904 with KAF. The association between each AF subgroup and recurrent ischemic stroke was analyzed using Cox proportional hazard models. The prevalence of cardiovascular comorbidities was compared among the 3 groups to evaluate the hypothesis of neurogenic vs cardiogenic AFDAS.

Main results and the role of chance

In all, 1,969 patients experienced ischemic stroke recurrence at 1 year: 1,269 (8.0%) with sinus rhythm, 39 (6.6%) with AFDAS, and 661 (9.6%) with KAF. The risk of recurrent ischemic stroke at 1 year in all Cox regression models did not differ between patients with AFDAS and those with sinus rhythm (HR: 0.90 [95% CI: 0.63–1.30]; $p = 0.57$), while this risk was higher in patients with KAF than in those with sinus rhythm (hazard ratio [HR]: 1.25 [95% CI: 1.12–1.39]; $p = 0.001$). Patients with AFDAS had a lower prevalence of cardiac comorbidities than those with KAF.



Bias, confounding, and other reasons for caution

This study did not evaluate the mechanism of incident or recurrent ischemic strokes or the topography of brain infarcts, which may have helped to explain the study findings.

Generalizability to other populations

The findings are applicable to the population of ischemic stroke patients admitted to Ontario stroke centers but require further validation in other cohorts.

Study funding/potential competing interests

This study was supported by the Kathleen and Dr. Henry Barnett Research Chair in Stroke Research and the Edward and Alma Saraydar Neurosciences Fund. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

