Original Contribution

Atrial Fibrillation Known Before or Detected After Stroke Share Similar Risk of Ischemic Stroke Recurrence and Death

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Background and Purpose—We aim to compare the risk of 1-year ischemic stroke recurrence and death for atrial fibrillation diagnosed after stroke (AFDAS), atrial fibrillation known before stroke (KAF), and sinus rhythm (SR).

Methods—From June 2012 to January 2013, 19 604 patients with acute ischemic stroke were admitted to 219 urban hospitals in the China National Stroke Registry II. Based on heart rhythm assessed during admission, we classified patients as AFDAS, KAF, or SR. We explored the relationship between heart rhythm groups and 1-year ischemic stroke recurrence or death by using Cox regression adjusted for multiple covariates. Considering that death is a competing risk for stroke recurrence, we used the competing risks analysis of Fine and Gray and subdistribution Cox proportional hazards to test the association between heart rhythm and 1-year outcomes.

Results—Among 19 604 ischemic stroke patients, 17 727 had SR, 495 AFDAS, and 1382 KAF. At 1 year, 54 (10.9%) patients with AFDAS, 182 (13.2%) with KAF, and 1008 (5.7%) with SR had recurrent ischemic strokes ($P<0.0001$). Mortality was 22.0% in patients with AFDAS, 22.1% in patients with KAF, and 7.0% in patients with SR ($P<0.0001$). AFDAS-related ischemic stroke recurrence adjusted risk was higher than that of SR (adjusted subdistribution hazard ratios, 1.61; 95% CI, 1.29–2.01) but not different from that of KAF (adjusted subdistribution hazard ratio, 1.12; 95% CI, 0.87–1.45]). The adjusted risk of 1-year death for AFDAS was also higher than that of SR (hazard ratio, 1.70; 95% CI, 1.37–2.12) and not different from that of KAF (hazard ratio, 1.10; 95% CI, 0.86–1.41).

Conclusions—This study showed that AFDAS had similar risk of 1-year ischemic stroke recurrence and mortality when compared with KAF and higher risk when compared with SR. The potential risk of AFDAS should be given more emphasis, and appropriate treatment is needed to achieve reduction in the incidence of stroke recurrence and mortality. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.024176.)**

Key Words: atrial fibrillation ■ ischemic stroke ■ prognosis ■ risk ■ stroke

Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke as patients with AF are 5× more likely to experience a stroke event than those without AF.[1] With the availability of improved cardiac monitoring technologies, the detection of AF after ischemic stroke or transient ischemic attack (TIA) has improved substantially.[2,3] AF diagnosed in patients with stroke can be classified as (1) previously known AF (KAF), which is AF detected before stroke, or (2) AF detected after stroke (AFDAS).[4] Compared with KAF, which is presumed to be primarily cardiogenic with minimal or no participation of central neurogenic mechanisms, AFDAS may comprise a heterogeneous mix of AF phenotypes, possibly including cardiogenic and neurogenic types, as well as a combination of both.[5] Several studies have explored the underlying pathophysiologic mechanisms of AFDAS by comparing the cardiovascular risk factors as well as cardiac structure and function between KAF and AFDAS, though the results were not consistent.[6,7] According to a previous study, stroke patients with KAF and AFDAS share common cardiovascular risk factors,

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similar echocardiographic findings, and suffer equally severe strokes.[6] Another study showed that patients with AFDAS have a low frequency of underlying cardiac disease and a strikingly high proportion of concurrent strategic insular infarctions, which suggests that neurogenic mechanisms are responsible.[7] Recently, a study found that the AFDAS and sinus rhythm (SR) have similar 1-year ischemic stroke recurrence, suggesting that the underlying pathophysiology of AFDAS may differ from that of KAF.[8]

Considering the inconsistency of the previous studies, we aim to further characterize the clinical and prognostic features of AFDAS and compare them with those of KAF and SR in our study. Patients with AFDAS will comprise a mix of AFDAS phenotypes: neurogenic with potentially better outcomes and cardiogenic with worse outcomes. We aim to compare the prevalence of cardiovascular comorbidities and prognosis between AFDAS, KAF, and SR to further explore the pathophysiology of AFDAS.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Cohort

China National Stroke Registry II (CNSR II), launched in 2012 by the Ministry of Health of China, is a nationwide initiative to establish a reliable national stroke database for evaluating the delivery of stroke care in clinical practice.[9] The criteria for site selection in China National Stroke Registry I (CNSR I) have been published,[10] and in order for the hospital characteristics to be similar between CNSR I and CNSR II, the same criteria were used for selection. Patients were recruited consecutively from all 219 urban hospitals voluntarily participating in the China National Stroke Registry II from June 2012 to January 2013 if they met the following criteria: (1) age>18 years; (2) diagnosis within 7 days of the index event of ischemic stroke, TIA, spontaneous intracerebral hemorrhage, or subarachnoid hemorrhage; (3) direct hospital admission from a physician's clinic or emergency department; and (4) informed consent provided by the patient or a legally authorized representative.

The study was approved by the central Institutional Review Board at Beijing Tiantan Hospital. Every participant provided written informed consent before participation.

Data Collection and Management

Patient information including demographics, risk factors, comorbidities, medications, selected laboratory tests, discharge status, and hospital-level characteristics were systematically collected during hospitalization and at discharge by trained research coordinators at each participating hospital. The severity of stroke was assessed by the National Institutes of Health Stroke Scale.[11] Stroke risk was calculated at discharge using the CHA2DS2-VASc score (congestive heart failure, hypertension, age 65–74 years and age≥75 years, diabetes mellitus, prior stroke or TIA; vascular disease, and female sex).[12] Based on this definition, all patients had minimum CHA2DS2-VASc risk scores of 2 due to their index stroke.

Eligibility and Criteria

Patients underwent the 12-lead ECG or further ≥24-hour Holter cardiac rhythm recording/telemetry at the time of admission or during the hospitalization 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 according to a previous study[8]: (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) SR (no history of AF and no AF identified during admission).

Outcome Measures

The primary outcome of this study was the risk of a recurrent ischemic stroke and death at 1 year after discharge, which was ascertained by using a previously validated algorithm. Patients were contacted by telephone at 3, 6, and 12 months after stroke onset by trained research personnel who followed standard scripts to collect information on death, stroke recurrence, and disability. During the follow-up, stroke recurrences associated with rehospitalization were sourced to the corresponding hospitals to ensure reliable diagnosis. In case of a suspected recurrent cerebrovascular event without hospitalization, adjudication was performed by the research coordinators together with the principal investigator. The detailed follow-up procedure has been described previously.[13]

Statistical Analysis

Continuous variables are reported as mean with SD or median with interquartile ranges, and categorical variables are reported as frequencies with percentages. We adopted cumulative incidence function curves for recurrent ischemic stroke in each of the 3 heart rhythm groups, and comparison was conducted using the Fine and Gray test.[14] We estimated the association between each AF subgroup and recurrent ischemic stroke at 1 year after discharge by using subdistribution Cox proportional hazards. We developed 2 different models by using variables known to influence the risk of recurrent ischemic stroke. Model 1 was adjusted for age groups, sex, stroke severity, and prescription of anticoagulants at discharge. Model 2 was adjusted for age groups, sex, stroke severity, systemic hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral artery disease, myocardial infarction, prior history of stroke or TIA, and prescription of anticoagulants at discharge. We used the *Z*-test with 2-tailed probabilities for comparing proportions. All tests were 2-tailed with $P<0.05$ considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Among 19 604 ischemic stroke patients, 495 (2.5%) had AFDAS, 1382 (7.0%) had KAF, and 17 727 (90.4%) had SR (Table 1). At 1 year, 1244 (6.3%) patients had a recurrent ischemic stroke: 54 (10.9%) patients with AFDAS, 182 (13.2%) with KAF, and 1008 (5.7%) with SR had recurrent ischemic strokes ($P<0.0001$).

AFDAS Versus KAF and SR

When comparing characteristics between patients with KAF and AFDAS, fewer patients with AFDAS were female (41.1% versus 48.6%; $P=0.006$), had a previous stroke or TIA (32.5% versus 45.6%; $P<0.0001$), or were diagnosed with coronary heart disease (22.8% versus 31.8%; $P=0.0002$), heart failure, or myocardial infarction (6.9% versus 15.9%; $P<0.0001$). Compared with patients with SR, those with AFDAS had a significantly higher prevalence of coronary artery disease (22.8% versus 9.8%; $P<0.0001$), heart failure, or myocardial infarction (6.9% versus 3.3%; $P<0.0001$; Table I in the online-only Data Supplement).

Risk of Recurrent Ischemic Stroke at 1 Year

Accounting for the competing risk of death, the cumulative incidence of recurrent ischemic stroke within 1 year after discharge for patients with AFDAS was higher than that for participants with SR (Figure 1).

Table 1. Characteristics of Patients With KAF, AFDAS, and SR

	Total (N=19 604)	KAF (N=1382)	AFDAS (N=495)	SR (N=17 727)	*P* Value
Age, y	64.8±12.0	70.5±11.5	69.6±12.7	64.3±11.9	<0.0001
Age group					<0.0001
<65 y	9510 (48.5)	414 (30.0)	152 (30.7)	8944 (50.5)	
65–74 y	5373 (27.4)	375 (27.1)	137 (27.7)	4861 (27.4)	
≥75 y	4721 (24.1)	593 (42.9)	206 (41.6)	3922 (22.1)	
Female sex	7167 (36.6)	671 (48.6)	205 (41.4)	6291 (35.5)	<0.0001
NIHSS at admission	4.0 (2.0–7.0)	6.0 (3.0–12.0)	5.0(3.0–12.0)	4.0 (2.0–6.0)	<0.0001
NIHSS groups at admission					<0.0001
<8	15 182 (77.4)	799 (57.8)	297 (60.0)	14 086 (79.5)	
8–15	3282 (16.7)	339 (24.5)	119 (24.0)	2824 (15.9)	
≥16	1140 (5.8)	244 (17.7)	79 (16.0)	817 (4.6)	
NIHSS at discharge	2.0 (1.0–4.0)	3.0 (1.0–8.0)	3.0 (1.0–9.0)	2.0 (1.0–4.0)	<0.0001
NIHSS groups at discharge					<0.0001
<8	16 208 (86.9)	928 (73.8)	329 (70.9)	14 951 (88.4)	
8–15	1835 (9.8)	207 (16.5)	84 (18.1)	1544 (9.1)	
≥16	599 (3.2)	123 (9.8)	51 (11.0)	425 (2.5)	
Smoking	8672 (44.2)	455 (32.9)	192 (38.8)	8025 (45.3)	<0.0001
Previous stroke/TIA	6979 (35.6)	630 (45.6)	161 (32.5)	6188 (34.9)	<0.0001
Heart failure or MI	841 (4.3)	220 (15.9)	34 (6.9)	587 (3.3)	<0.0001
Coronary heart diseases	2294 (11.7)	440 (31.8)	113 (22.8)	1741 (9.8)	<0.0001
Hypertension	14 908 (76.0)	1012 (73.2)	372 (75.2)	13 524 (76.3)	0.0329
Diabetes mellitus	5171 (26.4)	346 (25.0)	119 (24.0)	4706 (26.5)	0.2305
Dyslipidemia	6867 (35.0)	424 (30.7)	150 (30.3)	6293 (35.5)	0.0001
Peripheral artery disease	948 (4.8)	223 (16.1)	17 (3.4)	708 (4.0)	<0.0001
CHA2DS2-VASC score	4.0 (3.0–5.0)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	<0.0001
Total cholesterol, mmol/L	4.7±1.1	4.5±1.1	4.4±1.1	4.7±1.1	<0.0001
Triglycerides, mmol/L	1.7±1.3	1.4±1.1	1.4±1.1	1.7±1.3	<0.0001
HDL, mmol/L	1.2±0.4	1.3±0.4	1.2±0.3	1.2±0.4	<0.0001
LDL, mmol/L	2.8±1.1	2.8±1.2	2.6±0.9	2.9±1.0	<0.0001
Glycated hemoglobin, %	6.6±1.8	6.5±1.6	6.2±1.4	6.6±1.8	0.0911
Antithrombotics before admission	3991 (20.4)	496 (35.9)	100 (20.2)	3395 (19.2)	<0.0001
Antithrombotics at discharge	17 312 (93.3)	1073 (89.0)	399 (89.3)	15 840 (93.7)	<0.0001
Antiplatelet agents	16 011 (81.7)	898 (65.0)	265 (53.5)	14 848 (83.8)	<0.0001
Anticoagulants	445 (2.3)	149 (10.8)	51 (10.3)	245 (1.4)	<0.0001
Anticoagulants at 1 y	200 (1.0%)	105 (7.6%)	31 (6.3%)	64 (0.4%)	<0.0001

Data are mean (SD), n (%), median (interquartile range), or n/N (%). AFDAS indicates atrial fibrillation detected after the index stroke; HDL, high density lipoprotein; IQR, interquartile range; KAF, atrial fibrillation known before the index stroke; LDL, low density lipoprotein; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; SR, sinus rhythm; and TIA, transient ischemic attack.

Both patients with KAF and patients with AFDAS had consistently higher risk of recurrent ischemic stroke at 1 year (adjusted subdistribution hazard ratios, 1.61; 95% CI, 1.29–2.01 and 1.61; 95% CI, 1.29–2.01], respectively) than those with SR in all the subdistribution Cox regression models (Table 2). The risk of recurrent ischemic stroke at 1 year in patients with AFDAS was not different from that of patients with KAF (adjusted subdistribution hazard ratio, 1.12; 95% CI, 0.87–1.45; Table 2).

Risk of Death at 1 Year

The adjusted cumulative incidence of death within 1 year after discharge for patients with AFDAS was higher than that of participants with SR (Figure 2).

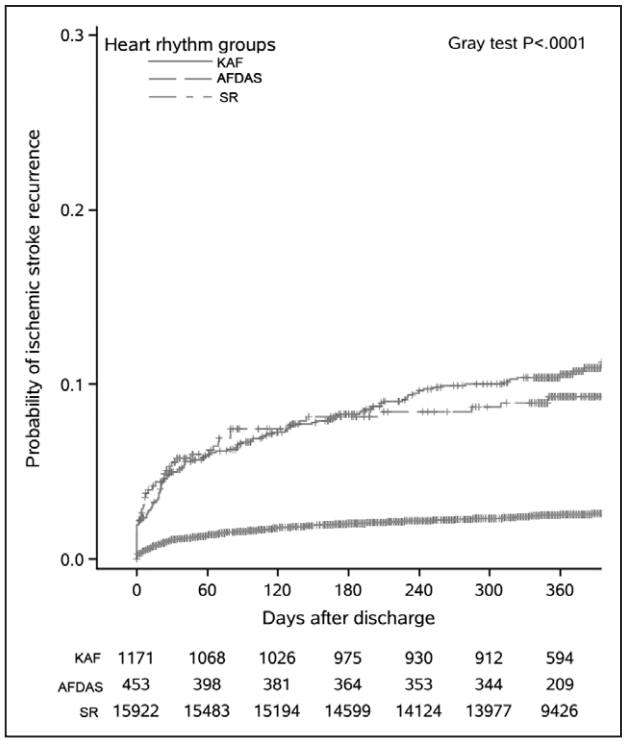

Figure 1. Cumulative incidence function curve for recurrent ischemic stroke in atrial fibrillation (AF) diagnosed after stroke (AFDAS), AF known before stroke (KAF), and sinus rhythm (SR).

Patients with KAF and patients with AFDAS both had a higher risk of death at 1 year (hazard ratio, 1.55; 95% CI, 1.32–1.82; and hazard ratio, 1.70; 95% CI, 1.37–2.12, respectively) than those with SR in all the cause-specific Cox regression models (Table 2). The risk of death at 1 year in patients with AFDAS was not different from that of patients with KAF (hazard ratio, 1.10; 95% CI, 0.86–1.41; Table 2).

Discussion

In our study of 18 222 ischemic stroke patients without a history of AF, AFDAS was identified in 495 patients. There are several potential explanations for the lower rate of AF among the ischemic stroke patients in our study. First, the stroke population in our study was younger than that in similar studies in Western countries,[15,16] and AF-associated stroke is associated with higher age. Furthermore, studies using prolonged noninvasive and invasive cardiac monitoring device[17,18] have shown increased detection of AF after ischemic stroke or TIA. In our study, however, AF was diagnosed at discharge according to the 12-lead ECG/24-hour Holter cardiac rhythm recording at the time of admission or during the hospitalization. As such, the detection rate of AF may have been underestimated.

We found a lower frequency of underlying cardiac disease, previous stroke, or TIA and lower CHA2DS2-VASc scores in patients with AFDAS compared with those with KAF, which were consistent with findings by Sposato et al.[8] These results support the hypothesis that AFDAS may comprise a wide spectrum of AF with cardiovascular risk factors that are dissimilar to those of KAF. However, this result was different from findings by Bisson et al,[19] which found that preexisting cardiovascular comorbidities underlie newly diagnosed poststroke AF. The discrepancy may be attributable to different definitions of AFDAS, KAF, and new AF in these 2 studies. In our study, patients with AFDAS were defined as those with no history of AF and had AF detected during their hospital stay after the index ischemic stroke. In the study by Bisson et al, a medical history of AF or AF recorded during the first 30 days of hospital stay was considered as KAF at baseline. Patients with AFDAS in our study were classified as having KAF in the study by Bisson et al. Furthermore, the definition of patients with new AF in the study by Bisson et al were those without AF at baseline and diagnosed as having incident AF during a subsequent hospitalization after a follow-up period of 7.9±11.5 months. In contrast, we did not have follow-up data for AF.

Considering the low rate of anticoagulant use in patients with AFDAS both at discharge and at 1-year follow-up, the rate of stroke recurrence in AFDAS patients may reflect the natural course of AF that was triggered by the stroke. At 1 year, patients with AFDAS had a higher risk of recurrent ischemic stroke and death than those with SR, even after adjusting for main confounders. When compared with KAF, patients with AFDAS had no difference in the risk of recurrent ischemic stroke or death at 1 year.

Our finding is in line with the study by Lip et al,[20] which found that among patients with an index stroke or TIA, patients with early AF (AF first diagnosed within 12 months before or within 7 days after the index stroke) had a higher hazard ratio for stroke recurrence within 1 year relative to patients without AF. They also observed that patients without oral anticoagulation prescribed at baseline and having AF first diagnosed >7 days poststroke (late AF) was highly associated with recurrent stroke/TIA. Although our study defined AFDAS as both AF detected within 7 days after index stroke and partial AF diagnosed between 7 days poststroke and discharge from the hospital, both of them were found to have higher stroke recurrence than patients without AF.

Other studies that explored the risk factors for stroke recurrence and mortality after ischemic stroke in patients with AF have found that age, National Institutes of Health Stroke Scale at admission, gender, and the absence of oral anticoagulation were associated with poor outcome or a higher rate of stroke recurrence and mortality.[21,22] In our study, we compared the baseline characteristics between patients with KAF and AFDAS, and we found that there were no differences in the risk factors mentioned above between the 2 groups.

However, our results were not consistent with a recent study by Sposato et al,[8] which found that compared with patients with SR, those with AFDAS had no difference in the risk of recurrent ischemic stroke at 1 year. They explained these results by hypothesizing that the presence of a given proportion of relatively benign neurogenic AFDAS phenotypes may dilute the overall AFDAS-associated risk of recurrent ischemic stroke. Indeed, several studies have found possible pathophysiologic mechanisms underlying neurogenic AFDAS such as the involvement of the insular cortex,[23–25] systemic inflammation,[26–28] and autonomic dysfunction.[29] The finding that patients with KAF have a higher prevalence of cardiovascular risk factors in our study was also compatible with the result by Sposato et al.[7] However,

Table 2. Risk of Recurrent Ischemic Stroke and Death at 1 Year for SR/KAF/AFDAS in Cox Regression Models

Outcome Measures	SR	KAF	AFDAS
Ischemic recurrence			
No (%)	1008 (5.7)	182 (13.2)	54 (10.9)
Adjusted sHR (95% CI)*	Reference	1.68 (1.35–2.09)	1.68 (1.35–2.09)
Adjusted sHR (95% CI)†	Reference	1.61 (1.29–2.01)	1.61 (1.29–2.01)
Adjusted sHR (95% CI)*	0.65 (0.55–0.76)	Reference	1.09 (0.85–1.40)
Adjusted sHR (95% CI)†	0.70 (0.59–0.82)	Reference	1.12 (0.87–1.45)
1-year death			
No (%)	1240 (7.0)	305 (22.1)	109 (22.0)
Adjusted HR (95% CI)*	Reference	1.64 (1.41–1.92)	1.76 (1.42–2.19)
Adjusted HR (95% CI)†	Reference	1.55 (1.32–1.82)	1.70 (1.37–2.12)
Adjusted HR (95% CI)*	0.61 (0.52–0.71)	Reference	1.07 (0.84–1.37)
Adjusted HR (95% CI)†	0.65 (0.55–0.76)	Reference	1.10 (0.86–1.41)

AFDAS indicates atrial fibrillation detected after the index stroke; HR, hazard ratio; KAF, atrial fibrillation known before the index stroke; sHR, subdistribution hazard ratio; and SR, sinus rhythm.

*Model 1, Model 1 was adjusted for age groups, sex, stroke severity, and prescription of anticoagulants at discharge.

†Model 2: Model 2 was adjusted for age groups, sex, stroke severity, systemic hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral artery disease, myocardial infarction, prior history of stroke or transient ischemic attack, and prescription of anticoagulants at discharge.

whether neurogenically triggered AFDAS is associated with a lower risk of recurrent stroke than cardiogenic AFDAS caused by underlying heart disease remains uncertain. We were unable to compare the proportion of neurogenic AFDAS between these 2 studies as neither of them can provide adequate distinction between the pathophysiologic mechanisms underlying AFDAS.

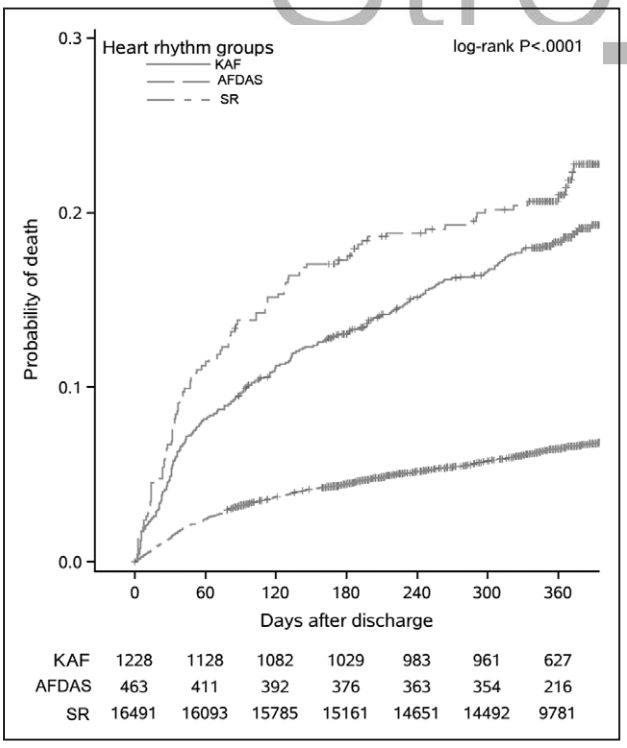

Figure 2. Cumulative incidence function curve for death in atrial fibrillation (AF) diagnosed after stroke (AFDAS), AF known before stroke (KAF), and sinus rhythm (SR).

There are several limitations in our study. First, some patients in the SR group may have had covert paroxysmal AF due to a lack of systematic evaluation of AFDAS, and the number of AFDAS patients may be underestimated in our study because of underdetection of AF. This could have weakly biased statistical comparisons of AFDAS and SR. Meanwhile, the lack of standardized use of cardiac monitoring and AF detection workup did not allow us to identify the proportion of patients with paroxysmal versus sustained AF in each group. Second, given the observational design, we could not provide the information of image data to analyze the effect of the locations of ischemic lesions on the development of AFDAS. Furthermore, because KAF was diagnosed according to self-report medical history or prior available medical records for patients in our study, we cannot rule out the possibility that patients with AFDAS may have actually had unknown AF before the stroke event. This may lead to misclassification of prior AF as AFDAS and result in biased comparisons between the KAF and AFDAS groups. It is also important to note that CNSR II did not record response rates during the screening stage, which may have led to response bias in our study. However, because the pilot study recorded a high response rate and registry studies do not modify the usual care provided by physicians, we believe that there is only minimal bias.

Considering the confounding factors, it is not enough to explore the underlying pathophysiology of AFDAS merely through the comparison of prognosis between AFDAS and SR. One ongoing study is trying to investigate the pathophysiology and risk of AFDAS through the experimental, clinical, and epidemiological streams.[30] Further research is needed to identify the specific features of neurogenic AFDAS to help identify more effective strategies for treatment.

Conclusions

Compared with SR, AFDAS has a higher risk of 1-year ischemic stroke recurrence and mortality but shares a similar level of risk with KAF. The potential risk of AFDAS should not be overlooked, and it is important to understand the underlying pathophysiology to help improve treatment in the future.

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Disclosures

None.

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