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Outcome, Recurrence and Mortality after Non-Valvular Atrial Fibrillation Stroke: Long-Term Follow-Up Study

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Abstract

Objective—Non-valvular atrial fibrillation (NVAF) is a major risk factor for ischemic stroke (IS) and a powerful predictor of mortality. This study investigates early and long-term outcome among patients with IS secondary to NVAF and identify the main factors associated with poor outcome, recurrence, and death.

Methods—We analyzed the data from our consecutive NVAF acute IS database, over a period of 23 years. The endpoints were bad outcome (Modified Rankin Score ≥3), recurrence, and mortality at discharge, after 6 months, 12 months, and final follow-up. Multivariate Cox and Kaplan–Meier analysis were used to estimate the probability of death.

Results—129 consecutive acute IS patients were included (77 [59.7%] females, mean age 70.2 ± 10.1 years). Discharge, 6 and 12 months bad outcome was 62%, 63%, and 61%, respectively. After a median follow-up of 17 months (IQR 6–54.5), 35.6% patients had bad outcome, 21.7% had recurrence and 36.4% died. The recurrence and death annual rates were 19.1% and 6.32%. The absence of oral anticoagulation (OAC) and NIHSS score > 12 were the strongest predictors of mortality.

Conclusions—IS secondary to NVAF has a high rate of stroke recurrence and mortality in our population, with the absence of OAC and major stroke as the main risk factors.

Keywords

ischemic stroke; cardioembolic stroke; non-valvular atrial fibrillation; prognosis; stroke outcome; oral anticoagulation

INTRODUCTION

Atrial fibrillation (AF) is the most frequent persistent cardiac arrhythmia [1] and it is a major risk factor for stroke [2–4]. Several studies reported higher case fatality and morbidity after ischemic stroke (IS) in patients with AF versus patients with sinus rhythm [5–7]. The underlying cause of this high case fatality is unclear. Possible factors include a higher frequency of large cortical infarcts, the presence of concomitant ischemic heart disease and a high frequency of early recurrent stroke [6,7]. However, the influence of AF on long-term follow-up outcome remains to be explored. A better understanding of the determinants of poor prognosis in AF stroke patients may help identify approaches to reduce stroke recurrence and mortality and improve outcome. To address these issues, we characterized IS patients with non-valvular atrial fibrillation (NVAF) and report their natural history in a long-term follow-up. We also described factors associated with stroke severity, mortality, recurrence, and disability in the long-term follow-up.

PATIENTS AND METHODS

For the current study, we retrospectively analyzed patients with confirmed diagnosis of IS secondary to NVAF treated at the National Institute of Neurology (a tertiary University research hospital of neurologic patients referred from across the country) in Mexico City over a period of time of 23 years (January 1990–

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December 2013). Detailed clinical data on all patients were systematically collected in our stroke database. Patients' data including demographics, vascular risk factors, clinical findings, laboratory results as well as complications and functional outcomes after discharged and at the outpatient clinic were registered on each case. We also recorded history of previous vascular or neurological events and the imaging results from computed tomography (CT) scan or magnetic resonance imaging (MRI). All cases were studied during the first week of the stroke and treated in the general neurological department. We used the TOAST classification to determine cerebral infarct etiology [8]. The following defined causes of IS were excluded: (a) large-vessel atherosclerosis (≥50% of vessel stenosis or occlusion of the affected vessel); (b) lacunar infarction of at least 15 mm diameter in patients with traditional clinical lacunar syndromes; (c) other potential cardioembolic sources such as a valvular atrial fibrillation, inactive rheumatic heart disease, mechanical valve prosthesis, sick sinus syndrome, recent myocardial infarction, atrial mixoma, akinetic left ventricular segment and dilated cardiomyopathy, as well as possible causes such as patent foramen ovale, atrial septal aneurysm or mitral valve prolapse; and (d) other defined causes, such as arterial dissection, muscle fibrodysplasia, coagulopathies or antiphospholipid syndrome.

Definition and classification of cerebral infarction

We defined IS as the presence of an acute neurological deficit lasting longer than 24 hours and the presence of ischemia confirmed by either CT or MRI. In all cases, NVAF was corroborated by electrocardiogram (ECG), 24 hours rhythm telemetry and/or echocardiogram. We also investigated history of chronic AF supported by a past ECG and positive ECG for arrhythmia during hospitalization, or past medical history supported by positive ECG. The clinical characteristics of IS were defined by the Oxfordshire Community stroke classification into [9]: total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), lacunar infarct (LICA), and posterior circulation infarction (POCI).

The risk of thrombotic events were assessed by CHA2DS2-VASc score [10], divided into low (0–1 points), moderate (2–3 points) and high risk (≥4 points) categories, whereas, the risk of hemorrhagic complications were evaluated by the HAS-BLED score [11]. In some patients, both scores were retrospectively calculated with data from the database, as it was not present at the first medical examination.

Clinical assessment at the stroke onset and discharge was made through NIHSS, stratified in patients lower than 12 points and upper this value. In some cases, this score was calculated retrospectively from medical records.

Data collection

For each patient, the clinical, laboratory, and imaging data were reviewed by at least two neurologists. In the first week after stroke, a 12-lead ECG, 24h rhythm telemetry, echocardiogram, and at least one of the following procedures were performed: CT angiogram or magnetic resonance angiogram of extra cranial arteries along with carotid ultrasound. The decision to perform additional test was considered on a patient-by-patient basis.

Because of the lack of treatment influence, the study was exempt from informed consent. However, patients, or family members if the patient was neurologically impaired, verbally agreed to participate in the project. This study was approved by the Institutional Ethics Committee.

Treatment

Patients were treated according to the recommendations of treatment in acute and long-term prevention settings from institutional guidelines. The first line treatment was oral anticoagulants, but depending on the functional outcome, the risk of hemorrhagic complications, and the difficult to access to the hospital for monitoring the INR and adjust medication, some patients were treated only with aspirin. In all cases, treatment decision was taken based on a patient's individual preference. However, in our population there is no financial or medical insurance support, which can be related to the low utilization of anticoagulants.

Follow-up

We followed all patients by personal clinical assessment with interval periods from discharge, after 6 months, 12 months, and at the end of the follow-up period. Specific questions concerning remaining symptoms, disability, recurrent vascular events, treatment, and compliance were evaluated.

The recurrence was defined as a new neurological deficit lasting more than 24 hours in a different territory or location; compared with baseline stroke, worsening of an already known deficit; both corroborated by CT or MRI with extension of the previous lesions or the presence of new ischemic lesions.

Outcome and recurrence were analyzed for the entire period and for discharge, at 6, 12 months, and at the end

of follow-up. Functional outcome was assessed by modified Rankin scale (mRs). The mRs between 0 and 2 was considered as a favorable outcome.

Statistical analysis

Statistical analysis was performed using the statistical package Statistical Package for the Social Sciences (SPSS, version 20.0, IBM Inc., Armonk, NY). Continuous variables were expressed, with mean and standard deviation or median and interquartile range when necessary, while categorical variables as counts and percentages. The influence of risk factors in the incidence of recurrent event or complications was analyzed by the use of bivariate analysis through two-tailed chi square for categorical variables, or a two-tailed student *t*test for continuous variables, expressed with adjusted odds ratios (OR) and confidence intervals (CI) of 95%. Factor risk variables were analyzed in a logistic regression model, in order to measure the association between them and the functional outcome. Adjusted hazard ratios (HRs) were calculated from a Cox proportional hazard regression model with CI of 95% and covariate adjustment; a *p*value under 0.05 was considered significant for all results. Median survival after the initial stroke for the entire population and oral anticoagulation (OAC) condition was examined with unadjusted Kaplan–Meier curve; Log-rank test was used to compare the survival of stroke patients and it comparator.

The annual recurrence rate was calculated according to the following: (1−[1−*P*] 1/*n*) where *P*is the accumulate event rates in *N*years of follow-up.

RESULTS

Patient characteristics

During the study period 3365 consecutive IS patients were admitted with acute IS, of which 757 (22.5%) were from cardioembolic source. From cardioembolic stroke, we excluded 628 cases (193 valvular AF, 140 valvulophaties without rhythm disturbances, 19 other arrhythmias, 48 with previous acute myocardial infarction, 31 with hypokinetic segment, 19 with dilated myocardiopathy, 14 with sick sinus syndromes, and 164 with other cardiac conditions), for a final sample of 129 (17.1%) NVAF patients, (77 [59.7%] females, mean age of 70.2 ± 10.1 years); 71 patients (55%) had 70 years old and above (Figure 1).

Baseline characteristics of patients are presented in Table 1. The most common risk factors were hypertension 85 (65.9%), cigarette smoking 27 (20.9%), diabetes

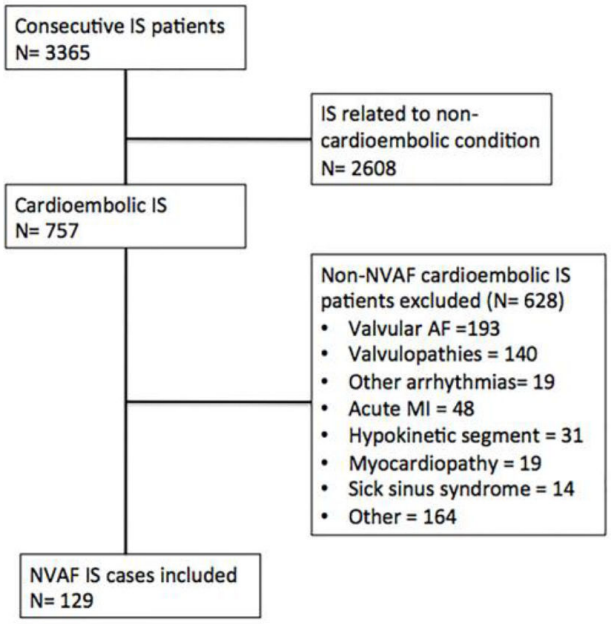

Figure 1. Patients' flowchart.

mellitus 25 (19.4%), dyslipidemia 17 (13.2%), and history of transient ischemic attack 4 (3.1%).

CT scan was carried out in all cases: in 77 (59.7%) patients, MRI was also performed. NVAF diagnosis was confirmed with ECG and echocardiogram in 84 (65.2%) cases, by history of chronic AF supported by past ECG in 38 (29.4%) cases and 24-hours rhythm telemetry in 7 (5.4%).

From all the patients, by the OCSC clinical assessment at first medical evaluation, 69 (53.5%) were PACI, 31 (24%) were TACI, 25 (19.4%) were POCI, and 4 patients (3.1%) behave like LACI (but infarctions were larger than 1.5 cm to be classified as lacunar).

Patients with CHA2DS2-VASc severe score (>3 points) were 112 (86.4%). A total of 75 (58.1%) patients presented HAS-BLED score between 2 and 3 points; the rest had a high-risk score (>3 points); no bad outcome significance was achieved on univariate or multivariate analysis on the evaluation periods for both scales. The median total NIHSS at first evaluation was 12 (interquartile range 6-16), and at discharge was 7 points (interquartile range 2–12).

OAC was used as secondary prevention treatment in 77 (59.7%) patients, and the rest of them were treated with aspirin with a standardized dose of 100 mg. The main reason for not using OAC was the difficulty to access to

Table 1. Demographic baseline patients' characteristics

	Total N = 129 (%)	Female N = 77 (%)	Male N = 52 (%)	*p* *
Age, years (SD)	70.2 ± 10.1	67.2 ± 10.3	72.3 ± 9.6	0.13
≥70 years old	71 (55)	49 (69)	22 (31)	0.17
Hypertension	85 (65.9)	56 (72.7)	29 (55.8)	0.06
Diabetes mellitus	25 (19.4)	17 (22.1)	8 (15.4)	0.24
Dyslipidemia	17 (13.2)	13 (16.9)	4 (7.7)	0.13
Ischemic cardiac disease	20 (15.5)	9 (11.7)	11 (21.2)	0.14
Transient ischemic attack	4 (3.1)	2 (2.6)	2 (3.84)	0.23
Cigarette smoking	24 (18.6)	4 (5.2)	20 (38.5)	<0.001
Alcohol	22 (17.1)	5 (6.5)	17 (32.7)	<0.001
CHA2DS2-VASc score				0.001
Moderate (2–3)	17 (13.2)	4 (5.2)	13 (25)	
Severe (>3)	112 (86.8)	73 (94.8)	39 (75)	
HAS-BLED score				0.933
2–3	75 (58.1)	45 (58.4)	57.7)	
>3	54 (41.9)	32 (41.6)	22 (42.3)	

SD: standard deviation.

* *T*-Student test.

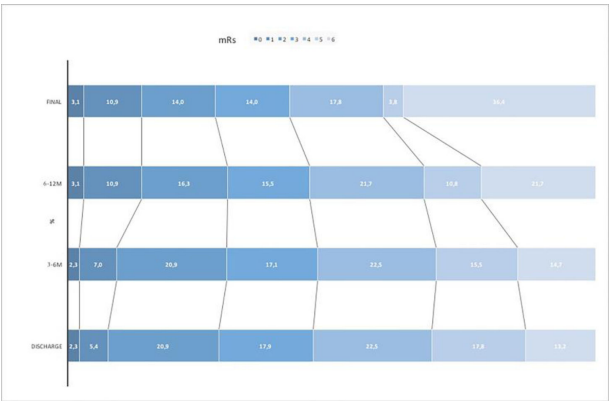

Figure 2. Distribution of modified Rankin score (mRs) over time, during the first year follow-up until final evaluation.

the hospital for monitoring the INR and adjust medication.

A total of 28 (21.7%) patients with OAC and 9 (7%) with aspirin had good prognosis at discharge (OR 0.37; 95% CI 0.15–0.86; *p*= 0.02). At the end of the follow-up period, 31 (24%) patients with OAC had good prognosis versus 9 (7%) on aspirin treatment (OR 0.31; CI 95% 0.13–0.73; *p*= 0.006).

Evolution and recurrence

At discharge, 73 (62%) patients had an mRs between 3 and 5 points, and there were 17 (13.2%) deaths during the acute phase. At 6 months follow-up, 80 (63%) patients had an mRs between 3–5 points, and 2 (2%) more deaths were registered. At 6 months follow-up, 72 (61%) had an mRs between 3 and 5 and 9 (8%) more deaths were registered; 19 (13%) patients died beyond this first-year follow-up period (Figure 2). The causes of mortality were recurrent stroke in 29 (61.7%) patients, acute myocardial infarction in one patient (2.1%), other medical conditions (complicated infections, metabolic conditions, bleeding) in 14 (29.8%) patients, and unknown causes (6.4%) in 3 patients. Only one patient had a major cerebral hemorrhagic complication, which made necessary surgical decompression.

At the end of the follow-up (median of 17 months, IQR 6–54.5), 47 (36.4%) patients died, 28 (21.7%) had a recurrent stroke, and 46 (35.6%) patients had an mRs between 3 and 5 points. Annual recurrence rate was 6.32% per year. Patients under OAC with recurrence were 19 (24.7%), whereas 9 (17.3%) had only antiplatelet therapy (OR 0.64, 95% CI 0.26–1.55; *p*= 0.32). The mean individual time of death and stroke recurrence were 12.4 and 13.5 months, respectively (see Table 2).

Survival analysis

Independent predictors for specific causes of bad outcome and death by multivariate analysis are reported in Table 3. The main independent predictors of bad outcome were the absence of OAC at discharge (HR 0.52; 95% CI 0.33–0.82; *p*= 0.005), 6 months (HR 0.51; 95% CI 0.32–0.81; *p*= 0.004) and 12 months (HR 0.47; 95% CI 0.30–1.71; *p*= 0.001), and also NIHSS >12 points at discharge (HR 0.12; 95% CI 0.41–0.36; *p*= 0.001), 6 months (HR 0.10; 95% CI 0.03–0.29; *p*= 0.001), and 12 months (HR 0.73; 95% CI 0.22–0.24; *p*= 0.001). The strongest predictor factors for total mortality at the end of the follow-up period were also the absence of OAC (HR 0.29; 95% CI 0.15–0.57; *p*= 0.0001), and NIHSS > 12 points (HR 1.6; 95% CI 0.68–2.7; *p*= 0.003).

No significant evidence of association was found between bad outcome and the other risk factors (sex, age, hypertension, diabetes mellitus, current cigarette

Table 2. Clinical and functional outcome from NAVF stroke patients

	Total N = 129 (%)	Female*N*= 77 (%)	Male*N*= 52 (%)	*p*
NIHSS score at discharge				
0–5	27 (21.1)	16 (21.1)	11 (21.2)	0.90
6–11	28 (21.7)	18 (23.4)	10 (19.2)	0.57
≥12	74 (57.4)	43 (55.8)	31 (59.6)	0.67
Bad outcome (mRs ≥3)				
Discharge	92 (71.4)	59 (76.6)	33 (63.5)	0.10
6 months	90 (69.8)	57 (74)	33 (63.5)	0.20
12 months	89 (69.7)	57 (74)	32 (61.5)	0.13
Oral Anticoagulation	77 (59.7)	43 (55.8)	34 (65.4)	0.28
Recurrence	28 (21.7)	16 (20.8)	12 (23.1)	0.46
Mortality (end of period)	47 (36.4)	31 (40.3)	16 (30.8)	0.18

mRs: modified Rankin score.

Table 3. Multivariate Cox proportional hazard analysis on risk factors for bad clinical outcome (mRs = 3–6) and total mortality

	Discharge (mRs 3–6)		6 months (mRs 3–6)		12 months (mRs 3–6)		Total mortality	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Female	0.61 (0.25–1.48)	0.63	1.12 (0.66–1.90)	0.66	1.17 (0.69–1.99	0.56	1.21 (0.56–2.40)	0.69
Age > 70y	0.89 (0.56–1.43)	0.65	0.38 (0.52–1.31)	0.44	0.84 (0.52–1.35)	0.47	0.75 (0.33–1.67)	0.65
Hypertension	1.15 (0.73–1.83)	0.54	1.17 (0.74–1.86)	0.5	1.21 (0.75–1.93)	0.44	0.88 (0.47–1.65)	0.69
Diabetes Mellitus	0.69 (0.39–1.24)	0.22	0.66 (0.37–1.19)	0.16	0.68 (0.38–1.22)	0.2	0.61 (0.26–1.44)	0.26
Cigarette Smoking	0.60 (0.31–1.17)	0.13	0.63 (0.33–1.22)	0.17	0.69 (0.36–1.33)	0.27	0.37 (0.13–1.11)	0.07
Ischemic cardiac disease	0.87 (0.45–1.68)	0.68	0.86 (0.45–1.67)	0.66	0.88 (0.46–1.71)	0.72	0.71 (0.09–5.48)	0.74
Non-OAC	0.52 (0.33–0.82)	**0.005**	0.51 (0.32–0.81)	**0.004**	0.47 (0.3–1.71)	**0.001**	0.29 (0.15–0.57)	**0.001**
CHA2DS2-VASc > 3	1.46 (0.23–9.30)	0.69	1.04 (0.13–8.55)	0.97	1.78 (0.26–11.95)	0.55	0.97 (0.16–5.94)	0.975
NIHSS > 12	0.12 (0.41-0.36)	**0.001**	0.10 (0.03–0.29)	**0.001**	0.73 (0.22–0.24)	**0.001**	1.6 (0.68–2.7)	**0.003**

mRs: modified Rankin score; CI: confidence interval; HR: hazard ratio; non-OAC: non-oral anticoagulation.

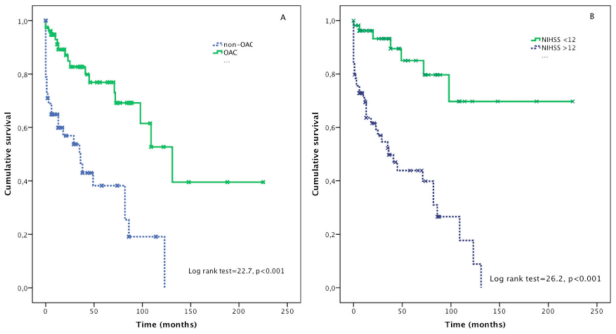

Figure 3. Kaplan–Meier cumulative survival curves after IS in NVAF. (A) Survival comparison of patients with post-stroke NVAF patients matched between OAC versus non-OAC users. (B) Survival comparison of patients with post-stroke NVAF patients matched between NIHSS score ≥ 12 versus < 12 points.

smoking) in both bivariate and multivariate analyses. Kaplan–Meier curve at 20-year estimates for death were significantly worst for non-OAC users (long rank test 22.7, $p< 0.001$) and NIHSS >12 (log rank test 26.2, $p< 0.001$) (see Figure 3).

DISCUSSION

Our study investigates the long-term outcome of IS related to NVAF in a long-term follow-up model, with the analysis of the main risk factors reported in previous studies, associated with a bad outcome [12–15]. We found a high number of large strokes (NIHSS >12) in 57.4% of our population, with significant bad outcome at discharge, 6 and 12 months, and higher mortality rates (HR 1.6, CI 95% 0.68–2.7; $p= 0.003$); these findings are similar to descriptions from previous studies [13–15]. As previously stated, possible factors that have been described for high mortality in NVAF include a higher frequency of large cortical infarcts, the presence of concomitant ischemic heart disease and a high frequency of early recurrent stroke [6,7]. In our patients, high scores in NIHSS (>12) correlate with large infarctions, therefore this association was positive for higher bad outcomes and mortality rates.

OAC was prescribed in 77 (59.7%) of our patients. The main reason reported for not starting OAC therapy in our group is related to the difficulty to access to the hospital for monitoring the INR and adjust medication; this condition is one of the main issues reported in previous studies [15–18], which becomes more common in Latin-American countries with restriction and limited control to OAC [19]. Not only the access to medical services, but the adequate level of anticoagulation is an issue in patients with NVAF, especially after IS. Our study showed a total recurrence of 21.7%, with an annual rate of 6.32 during the long-term follow-up; 19 cases (67.8%) were under OAC, which means that therapeutic

INR targets were not achieved. The good quality of OAC therapy showed a good prognosis with a OR of 0.31 (CI 95% 0.13–0.73; p= 0.006), and on the other hand, the absence of OAC showed a significant bad prognostic condition at the same evaluation periods, as in total mortality (HR 0.29, CI 95% 0.15–0.57; p= 0.0001); such findings are best seen on Kaplan–Meier curves. Some of these findings were previously reported in a Mexican population study [20], which showed that the use of antiplatelet drugs, living in rural area, and an mRs ≥ 3 on admission are factors suggesting a poor prognosis in the clinical control at 5 years follow-up. According to these results, novel oral anticoagulants could have some advantages as an alternative in this clinical setting, when INR monitoring could be problematic due to accessibility issues; cost-benefit analysis therefore should be critical in this scenario.

Our study showed a fatality progression from 13.2% at discharge to 36.4% at the final follow-up period. The main cause of death was related to recurrent stroke (61.7%), which again is strongly associated with the lack of OAC in the entire population, and possibly not therapeutic INR in those patients under OAC; populations with an optimal OAC therapy in the setting of NVAF, majority of deaths are not related to recurrent stroke [14].

From the European Community Stroke Project, 32.8% patients with AF compared with 19% non-AF patients were dead at 3-month follow-up (mean age of 71.8 ± 12.6 years) [15]; age of presentation of first-ever IS was a strong predictor for poor outcome, over stroke subtype and any other risk factor; probably because of the high incidence of morbidities in this group of age that predispose to futile outcomes, but in our case we could not find this association. It has been previously described that the prevalence of AF increases with age and that the most important single cause of stroke in people over 70 years old is AF [21].

Common risk factors (diabetes mellitus, hypertension, hypercholesterolemia, and cigarette smoking) had no significant influence as independent factors for bad outcomes and mortality in our study. Even though these factors have been strongly associated with NVAF, no significance was found among them; therefore, NVAF could be treated as intrinsic bad prognostic condition according to our data analysis.

Our study has several strengths, including prospective data collection on a large consecutive series of patients and the use of a standard protocol for diagnosis, treatment, and follow-up. This is the first long-term study in NVAF and related stroke in Mexican population, which highlights the importance of OAC and current limitation to medical access in such population. In addition, we included an unselected population, probably with a higher risk of recurrence, and poorly represented in clinical trials.

Certain limitations in our study need to be acknowledged. First, our population treated under OAC therapy was limited by conditions related to accessibility to medical services, which is a very important factor to prevent stroke recurrence, and therefore, improve the long-term good outcome. Also, in our model we used a prospectively collected cohort, and the decision of treatment and long-term follow-up was made from a retrospective fashion. Hence, the study holds all the drawbacks of an observational design.

CONCLUSION

According to our results, the main factors related to bad outcome and mortality in NVAF-related IS are high NIHSS score (>12) and the absence of OAC. Considering the prevalence of NVAF, reducing the burden of stroke in this population with local health actions to improve access to OAC therapy and optimal therapeutic ranges for those patients under medical therapy should be some of the main goals in national health services across the country.

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