The Impact of Atrial Fibrillation on the Outcome of Ischemic Stroke Treated With Thrombolysis or Endovascular Therapy

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Abstract

Background: The purpose of this study was to assess the impact of atrial fibrillation (AF) on stroke outcome in acute ischemic stroke (AIS) treated with thrombolysis or endovascular therapy (EVT).

Method: Consecutive AIS treated at five stroke centers over 15 years was evaluated. Using multiple logistic regressions, we compared adjusted odds ratio (OR) with 95% confidence interval (CI) of symptomatic intracranial hemorrhage (sICH), thrombolysis in cerebral infarction (TICI), poor discharge disposition (hospice/skilled nursing facility), in-hospital mortality, and disability (modified Rankin Scale (mRS)) and death at 90 days. Patients were classified according to AF and treatment plans, including tissue plasminogen activator (tPA) or EVT.

Results: We identified 720 patients treated in the study period (196 +AF, aged 78.2 ± 12.5 years and 524 -AF, aged 66.9 ± 15.2 years). In adjusted logistic regression, there was no difference in the rate of sICH (OR: 1.18, 95% CI: 0.44 - 3.17), TICI (OR: 1.19, 95% CI: 0.29 - 4.84), poor discharge disposition to hospice/skilled nursing facility (OR: 0.96, 95% CI: 0.56 - 1.63) or in-hospital mortality (OR: 0.95, 95% CI: 0.46 - 1.97). There was no significant difference in a 90-day mRS in those with and without AF. Likewise, there were no between group differences in sICH, discharge outcome, or 90-day mRS in the six groups based on the presence of AF and treatment plans (tPA, EVT, or both).

Conclusions: AF did not significantly impact sICH, discharge outcome, or 90-day mRS in AIS patients treated with thrombolysis, EVT, or both. Age and baseline National Institutes of Health Stroke Scale (NIHSS) were significant predictors of outcome in this sample.

Keywords: Ischemic stroke; Atrial fibrillation; Endovascular treatment; Tissue plasminogen activator; Symptomatic intracranial hemorrhage

Introduction

Atrial fibrillation (AF) is a major risk factor of vascular disease with a 4-5-fold increased risk of acute ischemic stroke (AIS) [1]. The attributable risk of stroke to AF in patients aged 50 - 59 years is 1.5%, increasing to nearly 25% for those aged ≥ 80 years [1, 2]. Despite the significant role of AF in stroke risk, the impact of AF on stroke outcome of those receiving tissue plasminogen activator (tPA) and/or endovascular therapy (EVT) is still unclear. In one study of AIS patients with severe stroke, those with AF had a higher proportion of favorable 90-day outcomes than those without AF (odds ratio (OR): 5.80, 95% confidence interval (CI): 1.63 - 20.68). This was not observed in patients with mild stroke [3]. Other studies have shown that AF is an independent predictor of no recanalization after thrombolysis [4]. Tu et al suggested that the worse stroke outcome in AF may be explained by more severe hypoperfusion, infarct growth, and hemorrhagic transformation [5]. However, a study using the Virtual International Stroke Trials Archive (VISTA; n = 7,091 patients) database did not find a significant association between AF and stroke outcome [6]. Previous embolic ischemic stroke animal models, which combined recombinant tPA (r-tPA) with an antiplatelet agent or statin revealed decrease in worse outcomes and increase in treatment window to 6 h [7, 8].

The role of AF in stroke outcome and response to acute therapy is still unclear. This study aimed to assess the impact of AF on short-term stroke outcome in AIS patients treated with tPA or EVT, or both.
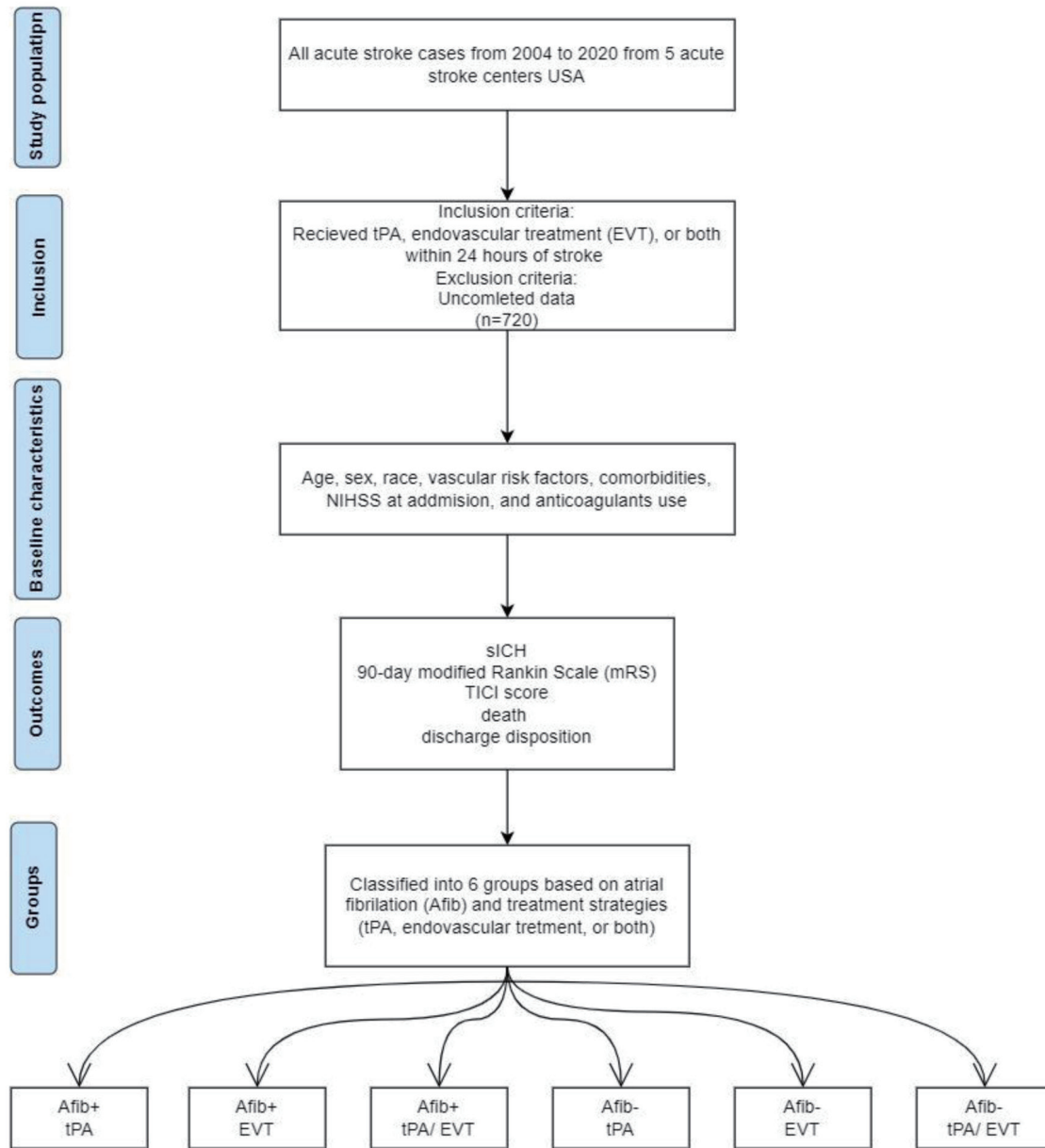
Figure 1. The algorithm of study design.

Materials and Methods

Study population

We retrospectively reviewed prospectively collected data from an IRB-approved registry (USCD; IRB# 800900). We included all consecutive stroke code activations between January 2004 and June 2020 from five acute stroke centers (three comprehensive stroke centers and two primary stroke centers) in San Diego, California, that a single provider group staff. Patients were included if they were treated with tPA, EVT, or both within 24 h of stroke onset based on current stroke treatment guidelines. Cases with AF (AF+) were identified based on the previous recorded history or patient/family discussion at any time in the past or diagnosed during hospitalization. Patients were stratified into six groups depending on their history of AF and whether or not they received treatment (tPA, EVT, or both) (Fig. 1).

Outcome measures

Baseline characteristics were prospectively collected. Socio-

demographic, baseline vascular risk factors, comorbidities, and radiological information were assessed. The National Institutes of Health Stroke Scale (NIHSS) measured admission severity at admission [9]. We defined symptomatic intracranial hemorrhage (sICH) based on the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria [10]. Contrast extravasation versus sICH was determined based on clinical exam and magnetic resonance imaging findings. We defined discharge disposition as good (discharge to home or acute rehabilitation facility and poor discharge) vs. poor (discharge to a skilled nursing facility, hospice, or in-hospital death). Stroke outcome was assessed by a 90-day modified Rankin Scale (mRS) with a good outcome defined as mRS 0 - 2 [11]. Thrombolysis in cerebral infarction (TICI) score was used to assess successful revascularization after EVT [12]. Poor recanalization was defined as TICI score < 2b (2a, 1, and 0) [13].

Statistical analysis

Baseline demographics were compared between groups using Pearson's Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables. We used Brown-Mood median test to compare the median baseline NIHSS score by the group. To compare any differences in functional outcome (90-day mRS) between groups, we performed a pairwise Wilcoxon rank test followed by adjusted multinomial regression. We used multiple logistic regressions to compare the adjusted OR with 95% CI of 90-day mRS, discharge disposition, and sICH between baseline AF- and AF+ subjects. A similar analysis was performed among six groups of patients according to the presence or absence of AF and treatment plans (tPA, EVT, or both) and within the six groups (AF + receiving only thrombolysis as the reference group). Data were adjusted for baseline NIHSS, age, sex, baseline systolic blood pressure, pre-stroke mRS, smoking status, glucose, anticoagulant use, and congestive heart failure (CHF) at admission. All analyses used an alpha of 0.05, and a P-value ≤ 0.05 was considered significant.

Results

We identified 720 AIS patients who received tPA or EVT or both, including 196 AF+ (55.6% women) and 524 AF- (43.3% women). Those with AF were older (78.2 ± 12.5 vs. 66.9 ± 15.2; P < 0.0001) and had a higher rate of CHF (21.4% vs. 9.5%; P = 0.0001) and a lower rate of smoking (3.1% vs. 16%; P < 0.0001). In addition, AF+ had a more severe stroke at admission as measured by NIHSS > 5 (77.4% vs. 64.4%; P = 0.0014) (Table 1). A majority of AF patients were white (n = 583; 28.5%), followed by Hispanic/Latino (n = 146; 26%) and African Americans (n = 60; 3.7%). Details of groups based on their treatment plans are summarized in Tables 2 and 3.

Outcome variables

Twenty-four cases had sICH (nine cases with AF and 15 with-

out AF). The rate of sICH did not have a significant difference between cases with and without AF (OR: 1.18, 95% CI: 0.44 - 3.17, P = 0.74). We compared TICI scores in those treated with EVT. Six cases with AF and 11 without AF had TICI < 2b (P = 0.89). In adjusted regression analysis, the rate of TICI < 2b was not significantly different among patients with and without AF (OR: 1.19, CI: 0.29 - 4.84, P = 0.81) (Table 2). We classified poor short-term outcomes into in-hospital death (18 (9.2%) of AF+ vs. 35 (6.7%) of AF-; P = 0.3), discharge to hospice or skilled nursing facility (47 (14.1%) of AF+ vs. 74 (23.9%) of AF-; P < 0.0001) and composite rate of hospital death with discharge to hospice and skilled nursing facility (65 (33.2%) of AF+ vs. 109 (20.8%) of AF-; P < 0.0001). In adjusted analysis, there was no significant difference in the rate of in-hospital death (OR: 0.95, 95% CI: 0.46 - 1.97, P = 0.89), discharge to hospice or skilled nursing facility only (OR: 0.96, 95% CI: 0.56 - 1.63, P = 0.87) and a combined rate of death and hospice/skilled nursing facility (OR: 1, 95% CI: 0.63 - 1.59, P = 0.99) (Table 3).

All cases discharged from the hospital were success assessed at 90 days post-stroke (n = 667). Three models were run for the 90-day mRS analysis (score of 0 - 2 was a good outcome), one with poor outcome as both moderate and severe disability as well as death (mRS score of 3 - 6; OR: 0.73, 95% CI: 0.48 - 1.11, P = 0.14), moderate and severe disability only (score of 3 - 5; OR: 0.75, 95% CI: 0.47 - 1.20, P = 0.23) and death only (score of 6; OR: 0.67, 95% CI: 0.37 - 1.21, P = 0.19). We did not find any significant difference based on the presence of AF. Results for the three models are shown in Table 3. Likewise, in the subgroup analysis based on stroke etiology and treatment plan as compared to the reference group, there were no significant differences in the adjusted odds of TICI, sICH, discharge disposition (including hospice/skilled nursing facility, and composite rate of discharge to hospice/skilled nursing facility and death) and post-stroke disability in cases with AF (Supplementary Materials 1, 2 and 3, www.neurores.org).

Discussion

Our study has important clinical implications. Among 720 cases with AIS, AF was not a determinant of poor outcome in patients treated with thrombolytic therapy, EVT, or both. In adjusted analysis, stroke disability, discharge disposition, symptomatic hemorrhage, and TICI score were not different according to AF etiology and treatment arms.

The overall rate of AF has increased significantly with more cases of stroke attributed to AF [14]. Despite the importance of AF in stroke, available data about the role of AF in stroke outcomes are controversial. A meta-analysis by Yue et al emphasized that AF may increase the risk of adverse outcomes for AIS undergoing thrombolysis due to an increase in the rate of sICH and death [15]. Another meta-analysis of 18 studies reported worse outcomes in AF versus non-AF cases of ischemic stroke treated with thrombolysis and higher incidence of sICH in patients with AF treated with thrombolysis compared to the other therapies [16]. On the other hand, Tong

Table 1. Demographic Data, Vascular Risk Factors and Baseline Assessments: Patient Classification According to Those With and Without Atrial Fibrillation

Variables	AF- (n = 524)	AF+ (n = 196)	P value
Age[a]	66.9 (15.2)	78.2 (12.5)	< 0.0001
Sex (female)	227 (43.3%)	109 (55.6%)	0.004
White	417 (82.7%)	166 (88.8%)	0.03
Asian	28 (5.6%)	10 (5.3%)	
Black/African American	53 (10.5%)	7 (3.7%)	
Native American	2 (0.4%)	3 (1.6%)	
Pacific Islander	1 (0.2%)	1 (0.5%)	
Not Hispanic/Latino	412 (78.6%)	155 (79.1%)	0.79
Hispanic/Latino	108 (20.6%)	38 (19.4%)	
Current smoker	84 (16%)	6 (3.1%)	< 0.0001
Hypertension	348 (66.4%)	146 (74.5%)	0.10
Diabetes	128 (24.4%)	42 (21.4%)	0.46
Coronary artery disease	94 (17.9%)	46 (23.5%)	0.18
Congestive heart failure	50 (9.5%)	42 (21.4%)	0.0001
Stroke/TIA	122 (23.3%)	46 (23.5%)	0.57
Anticoagulants	4 (0.8%)	6 (3.1%)	0.05
Baseline SBP[a]	150.7 (25.6)	150.6 (26)	0.93
Baseline glucose[a]	133 (46.6)	141.3 (64.8)	0.11
NIHSS > 5 at baseline	338 (64.6%)	151 (77.4%)	0.001
Baseline mRS > 2	46 (9%)	39 (20.3%)	< 0.0001
EVT	61 (11.6%)	39 (19.9%)	0.006
Thrombolysis	435 (83%)	140 (71.4%)	0.0008
Thrombolysis and EVT	28 (5.3%)	17 (8.7%)	0.14

[a]Measure is continuous (results are mean and standard deviation). AF: atrial fibrillation; AF-: without atrial fibrillation; AF+: with atrial fibrillation; EVT: endovascular therapy; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; TIA: transient ischemic attack.

Table 2. A Comparison Between the Rate of Successful Recanalization and Hemorrhagic Transformation in Cases With and Without Atrial Fibrillation: The Result of Adjusted Logistics Regression

Variables	TICI < 2b		sICH	
	OR (CI)	P	OR (CI)	P
Age	0.96 (0.9 - 1.02)	0.1637	1.02 (0.99 - 1.06)	0.1909
Sex[a]	0.19 (0.04 - 0.92)	0.0392	0.65 (0.26 - 1.64)	0.365
SBP	1.03 (1 - 1.06)	0.0429	1.01 (0.99 - 1.02)	0.515
Smokers[b]	0.22 (0.02 - 3.01)	0.2587	2.04 (0.52 - 7.93)	0.3059
Glucose	1 (0.99 - 1.02)	0.5451	1 (1 - 1.01)	0.3189
Severity[c]	4.71 (0.44 - 50.88)	0.2015	2.99 (0.84 - 10.61)	0.0899
Disability[d]	0.91 (0.14 - 6.06)	0.9217	0.39 (0.08 - 1.81)	0.2285
CHF	1.97 (0.26 - 14.96)	0.5138	1.78 (0.61 - 5.26)	0.294
Anticoagulants	0.64 (0.05 - 7.9)	0.7306	0 (0 - Inf)	0.9878
AF+	1.19 (0.29 - 4.84)	0.8097	1.18 (0.44 - 3.17)	0.7433

[a]Female. [b]Never smoked or ex-smoker. [c]Severity was defined as baseline NIHSS > 5. [d]Disability was defined as baseline modified Rankin Scale > 2. P-values less than 0.0001 are reported as zero. TICI: thrombolysis in cerebral infarction; sICH: symptomatic intracranial hemorrhage; CHF: congestive heart failure; OR: odds ratio; CI: confidence interval; SBP: systolic blood pressure; AF+: with atrial fibrillation.

Table 3. A Comparison Between Discharge Disposition and Poststroke Disability in Cases With and Without Atrial Fibrillation: The Result of Adjusted Logistics Regression

Variables	Discharge disposition						Modified Rankin Scale					
	Hospice/SNF/death		In-hospital death		Hospice/SNF		0 – 2 vs. 3 – 6		0 – 2 vs. 3 – 5		0 – 2 vs. 6 (death)	
	OR (CI)	P	OR (CI)	P	OR (CI)	P	OR (CI)	P	OR (CI)	P	OR (CI)	P
Age	1.04 (1.02 - 1.06)	0	1.04 (1.01 - 1.06)	0.0117	1.04 (1.02 - 1.07)	0	0.97 (0.96 - 0.98)	0	0.98 (0.96 - 0.99)	0.0029	0.95 (0.93 - 0.97)	0
Sex[a]	1.03 (0.67 - 1.57)	0.8913	1.15 (0.59 - 2.22)	0.6846	1.03 (0.63 - 1.68)	0.9026	1.02 (0.71 - 1.46)	0.9315	1.05 (0.71 - 1.55)	0.8098	0.81 (0.46 - 1.42)	0.4615
SBP	1.01 (1.01 - 1.02)	0.0015	1.01 (1 - 1.02)	0.1129	1.02 (1.01 - 1.03)	0.0016	1 (0.99 - 1)	0.2487	1 (0.99 - 1)	0.3718	1 (0.98 - 1.01)	0.4421
Smokers[b]	1.1 (0.55 - 2.19)	0.7904	0.4 (0.09 - 1.84)	0.2382	1.49 (0.7 - 3.16)	0.2982	0.85 (0.5 - 1.46)	0.5569	0.77 (0.44 - 1.36)	0.3645	1.53 (0.56 - 4.18)	0.4086
Glucose	1 (1 - 1)	0.3601	1 (1 - 1.01)	0.1462	1 (1 - 1)	0.7929	1 (1 - 1)	0.3204	1 (1 - 1)	0.4	1 (1 - 1)	0.8785
Severity[c]	6.61 (3.68 - 11.87)	0	6.73 (2.51 - 18.05)	0.0002	7.06 (3.52 - 14.13)	0	0.22 (0.15 - 0.33)	0	0.28 (0.18 - 0.43)	0	0.12 (0.05 - 0.26)	0
Disability[d]	1.24 (0.7 - 2.19)	0.4639	0.9 (0.36 - 2.26)	0.8298	1.41 (0.75 - 2.64)	0.2819	0.13 (0.06 - 0.28)	0	0.15 (0.07 - 0.35)	0	0.11 (0.04 - 0.27)	0
CHF	1.87 (1.05 - 3.32)	0.033	1.68 (0.71 - 3.98)	0.2395	2.04 (1.07 - 3.9)	0.0308	0.7 (0.41 - 1.2)	0.1997	0.67 (0.37 - 1.21)	0.1864	0.66 (0.3 - 1.43)	0.2923
Anticoagulants	3.7 (0.75 - 18.27)	0.1079	4.77 (0.4 - 56.63)	0.2154	3.85 (0.66 - 22.53)	0.1354	1.25 (0.31 - 5.11)	0.7521	1.82 (0.34 - 9.74)	0.4839	1.36 (0.14 - 12.84)	0.7906
AF+	1 (0.63 - 1.59)	0.9998	0.95 (0.46 - 1.97)	0.8932	0.96 (0.56 - 1.63)	0.8693	0.73 (0.48 - 1.11)	0.1403	0.75 (0.47 - 1.2)	0.2284	0.67 (0.37 - 1.21)	0.1853

aFemale. bNever smoked or ex-smoker. cSeverity was defined as baseline NIHSS > 5. dDisability was defined as baseline modified Rankin Scale > 2. P-values less than 0.0001 are reported as zero. SBP: systolic blood pressure; AF+: with atrial fibrillation; CHF: congestive heart failure; OR: odds ratio; CI: confidence interval; SNF: skilled nursing facility; TICI: thrombolysis in cerebral infarction.

et al reported no significant differences in the mRS score, successful recanalization, sICH and mortality between patients with and without AF after EVT [17]. In contrast, Zhang et al found that patients with stroke and AF may benefit from tPA in terms of 90-day follow-up [18]. A nationwide cohort study in Taiwan reported although a higher risk of ICH according to the National Institute of Neurological Disorders and Stroke standard (NINDS) in the AF group treated with alteplase but no differences in sICH according to SITS-MOST standards, favorable 90-day outcome, and mortality in comparison with the non-AF group [19]. Among 143 AIS patients who received intravenous thrombolysis, AF was associated with a favorable 90-day outcome in patients with severe stroke at baseline (NIHSS > 10). However, this association did not exist in patients with mild stroke and AF [20]. Our study is novel as we have added information regarding thrombolysis or EVT. In our study, AF was not associated with poor outcomes as defined by discharge disposition, in-hospital death, and a 3-month poststroke disability. While some studies found a higher rate of hemorrhagic transformation after thrombolysis [21], we did not find this trend in our cases.

There is also controversy about the rate of recanalization after thrombolysis in AF patients. Some studies have found similar [11], lower [4], or even higher recanalization rates in the AF population compared to non-AF [22]. Differences in clot organization and collagen composite can affect responses to medical or mechanical reperfusion therapy [18, 23]. In our cases, AF did not impact the degree of recanalization as evidenced by the TICI score after EVT.

It is important to assess the effect of age on all AF studies. AF is more prevalent in older adults, with a steady increase in its prevalence by aging from 0.12% to 0.16% in those aged < 49 years to 10-17% in those aged > 80 years [24]. In our study, cases with AF were significantly older than those without AF. In the VISTA study, 29% of the variability of outcome in AF patients was accounted for by age and baseline NIHSS. After adjustment for these variables, AF was not associated with the 90-day outcomes [6]. Likewise, Saposnik et al found a correlation between AF with older age and higher baseline NIHSS. Patients with AF had higher mortality and rates of sICH [25]. Another study reported a higher rate of unfavorable outcomes in patients with AF aged ≥ 80 versus the rest after EVT in AIS [26]. Our study is important as we adjusted our data not only for age and sex but also for baseline NIHSS and pre-stroke mRS. Our patients had a more severe stroke (according to their baseline NIHSS), comorbidities (such as CHF), and pre-stroke disability (according to baseline mRS). We did not observe a significant difference in cases with AF treated with thrombolysis, EVT, or both compared to other groups. Therefore, some previous reports of worse outcomes in patients with AF in clinical practice may be due to the aging effect, baseline disability, limitation for thrombolytic therapy, and more severe strokes in cases with AF.

Our study has some limitations. First, this is a retrospective study that may have an inherent bias due to the convenience sampling method. Second, we did not have access to the type of AF (i.e., paroxysmal or chronic) that can influence the outcomes. Third, we followed our case for 3 months, and we cannot comment on the long-term outcome of our cases. Fourth, we did not measure the effect of the door-to-needle

times in thrombolysis and door-to-device times in endovascular treatment on patients' outcomes. Major strengths of our study include access to detailed clinical and radiological information on cases with AF treated with tPA, EVT, or both. In the next phase of the study, we are planning to evaluate imaging variables, including infarct size, reperfusion rate, infarct core growth rate, and collaterals, to identify differences in cases with AF as compared to other groups. We will also try to increase our sample size to perform a detailed analysis based on different subgroups, particularly for those with AF and EVT.

Conclusion

In this study, AF did not significantly impact the outcome in AIS patients treated with thrombolysis, EVT, or both. Patients with AF are older and have had more severe strokes and baseline disability. A close clinical follow-up during their admissions. Further studies with larger sample sizes that include rigorous radiographic, clot morphology, and collateral flow factors are needed to optimize the acute treatment of stroke patients with AF.

Learning points

AF is a leading cause of ischemic stroke.

Those with AF are older and have more disability/comorbidities at baseline.

Differences in the clinical outcome of AF cases are likely due to stroke severity, older age, and comorbidities rather than AF alone.

Supplementary Material

Suppl 1. Demographic data, vascular risk factors and baseline assessments: patient classification according to those with and without atrial fibrillation and treatment plans.

Suppl 2. A comparison between the rate of successful recanalization and hemorrhagic transformation in cases with and without atrial fibrillation according to treatment plans: the result of adjusted logistics regression.

Suppl 3. A comparison between discharge disposition and poststroke disability in cases with and without atrial fibrillation according to treatment plans: the result of adjusted logistics regression.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Reza Bavarsad Shahripour: study design, writing the first draft, and data analysis. Datis Azarpazhooh: writing the first draft, data analysis, and revision of the manuscript. Benjamin Shifflett: data analysis and revision of the paper. Sima Osouli: revision of the draft. Brett C. Meyer: data gathering and revision of the paper. Dawn Meyer: study design, revision of the final draft, and study supervisor.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

AF: atrial fibrillation; tPA: tissue plasminogen activator; EVT: endovascular therapy; AIS: acute ischemic stroke; VISTA: Virtual International Stroke Trials Archive; NIHSS: National Institutes of Health Stroke Scale; sICH: symptomatic intracranial hemorrhage; SITS-MOST: The Safe Implementation of Thrombolysis in Stroke-Monitoring Study; mRS: modified Rankin Scale; TICI: thrombolysis in cerebral infarction; OR: odds ratio; CI: confidence interval; CHF: congestive heart failure; NINDS: National Institute of Neurological Disorders and Stroke standard

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