Clinical Outcomes of Valvular versus Nonvalvular Atrial Fibrillation in Acute Anterior Circulation Occlusive Stroke Undergoing Endovascular Treatment

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Background: Thrombectomy is the first choice for cardioembolism due to atrial fibrillation (AF), however, whether valvular AF and nonvalvular AF had different safety and functional outcomes has not been reported yet. We aimed to investigate the differences between patients with valvular AF and patients with nonvalvular AF on safety and functional outcomes in acute large artery occlusion undergoing thrombectomy. *Methods:* Valvular AF refers to patients with mitral stenosis or artificial heart valves and valve repair. Rate of symptomatic intracerebral hemorrhage [sICH], modified Rankin Scale Score (mRS), and death at 90 days were compared between valvular AF and nonvalvular AF groups. Univariate and multivariable logistic regression was performed to identify the predictors for unfavorable functional outcome (mRS 3-6). *Results:* 18.8% (51/271) of AF were valvular AF. The valvular AF group had significantly higher proportion of mRS 0-2 (49% [25/51] versus 33.3% [73/219], $P = .04$) and less death (21.6% [11/51] versus 38.4% [84/219], $P = .02$) comparing with nonvalvular AF group. The rates of sICH between both groups were nonsignificantly different (21.5% [47/219] for nonvalvular AF versus 13.7% [7/51] for valvular AF, $P = .46$). Valvular AF was not an independent predictor for unfavorable functional outcome (odds ratio .67, 95% confidence interval: .24-1.84) with age, collateral flow, chronic heart failure, NIHSS at admission, recanalization status, glucose at admission, occlusion site, ASPECTS, and ICH as covariates. *Conclusions:* Valvular AF and nonvalvular AF have similar safety and functional outcomes in patients with acute anterior circulation large artery occlusion undergoing thrombectomy.

Key Words: Atrial fibrillation—stroke—endovascular treatment—thrombectomy—valvular atrial fibrillation.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and confers a high risk for cardioembolic stroke. Valvular AF, which refers to patients with mitral stenosis or artificial heart valves, may have different mechanism with nonvalvular AF for causing stroke.[1] Previous study showed that the stroke risk in valvular AF patients had approximately 15 times stroke risk in

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patients without AF, and the relatively risk is around 6 times in patients with nonvalvular AF.[2] And patients with valvular AF with cardioembolic stroke have the highest rate of stroke recurrence in AF patients.

Currently, thrombectomy using stent-retrieval devices was considered the first-line treatment for cardioembolic stroke due to large artery occlusion.[3] Whether valvular AF and nonvalvular AF had different safety and functional outcomes has not been reported yet.

Through analyzing a multicenter clinical registry on acute stroke due to large artery occlusion, we aimed to investigate the differences between patients with valvular AF and patients with nonvalvular AF on safety (rate of symptomatic intracerebral hemorrhage [sICH]) and functional outcomes (modified Rankin Scale Score [mRS] and death at 90 days). We hypothesized that valvular AF patients may have significantly higher rates of poor functional outcome, death, and sICH than nonvalvular AF patients.

Methods

Study Population

Subjects were included from a multicenter retrospective registry—the Endovascular Treatment For Acute Anterior Circulation Ischemic Stroke Registry (ACTUAL). Detail of the ACTUAL study was previously published.[4] For the current study, we included patients who fulfilled the following inclusion criteria: (1) adult patients (age $\geq$ 18 years), (2) anterior circulation large vessel occlusion (internal carotid artery [ICA], middle cerebral artery [MCA] M1 and M2) confirmed by CT angiography, magnetic resonance angiography, or digital subtracted angiography, (3) thrombectomy using retrievable stents device, and (4) AF patients. The ACTUAL registry was approved by the central institutional review board at Nanjing Jinling Hospital and the ethics committee of each participating center.

Data Collection and Measurements

Patients' demographic data, clinical history (hypertension, hyperlipidemia, diabetes, AF, coronary heart diseases, chronic heart failure, etc.), laboratory tests (triglyceride, low-density lipoprotein, high-density lipoprotein, total cholesterol, and glucose at admission) and stroke severity (NIHSS score at admission) were recorded. In addition to thrombectomy, rescue therapy including intra-arterial rt-PA or urokinase and tirofiban were also recorded.

AF was documented as valvular AF and nonvalvular AF according to the medical records. Valvular AF refers to patients with moderate to severe mitral stenosis or artificial heart valves and valve repair.[1] Valvular heart diseases, such as mitral regurgitation, aortic stenosis, and aortic insufficiency, which do not result in conditions of low flow in the left atrium, and do not apparently increase the risk of thromboembolism brought by AF. They were documented as nonvalvular AF.

ASPECTS was evaluated on noncontrast head CT. Collateral status was assessed by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading on digital subtracted angiography, with grade 0 representing no collaterals, grade 1 poor collaterals, grade 2 moderate, grade 3 good, and grade 4 excellent.[5] Successful recanalization was defined as a modified Thrombolysis in Cerebral Ischemia (mTICI) score of 2b-3 after the complement of endovascular treatment (EVT.) sICH was defined by the criteria of the Heidelberg Bleeding Classification.[6] All images were reviewed by 2 physicians who were blinded to the clinical outcomes in the core laboratory in Jinling Hospital, in case of disagreement, a third physician was invited for a final decision.

The mRS at 90 days after endovascular treatment was usually assessed by a clinical visit and telephone follow-up. mRS 0-2 and mRS 3-6 were considered as good and poor functional outcome, respectively.

Statistical Analysis

Student *t* tests or Mann-Whitney U tests for continuous variables and χ^2 tests or trend tests for categorical variables were used to identify the differences on demographics, clinical history, laboratory tests, and imaging variables (ASPECTS, mTICI, collateral flow) between valvular AF and nonvalvular AF. Univariate analyses were performed to detect the significant different variables between patients with mRS 0-2 and mRS 3-6 groups. Those statistically significant variables with $P < .10$ were further put into a multivariable logistic regression model with unfavorable functional outcome (mRS 3-6) as dependent variable to determine whether valvular AF was an independent predictor for unfavorable functional outcome. Statistical analysis was performed using the SPSS version 22 software package (SPSS Inc, Chicago, IL), $P < .05$ was considered to be statistically significant.

Results

Characteristics of Valvular and Nonvalvular AF Patients

In total, 271 patients had AF, 219 (80.8%) of them were nonvalvular AF, and 51 (18.8%) of them were valvular AF, 1 (0.4%) patient cannot be categorized due to missing data on valvular disease. The comparisons of demographics, clinical history, and laboratory tests were summarized in Table 1. Comparing with nonvalvular AF, the valvular AF patients were significantly younger, higher proportions of female and congestive heart failure, less coronary heart disease, lower proportion of hypertension and diabetes, lower low-density lipoprotein, glucose at admission, and higher international normalised ratio (INR) (Table 1).

Table 1. *Comparisons of clinical characteristics between nonvalvular AF and valvular AF*

Variables	Nonvalvular AF N = 219	Valvular AF N = 51	*P*
Age, mean ± SD, years	70.8 ± 9.1	61.4 ± 11.6	<.001
Male, n (%)	100 (45.7%)	15 (29.4%)	.04
Coronary heart diseases, n (%)	93 (42.5%)	7 (13.7%)	<.001
Hypertension, n (%)	162 (74.0%)	13 (25.5%)	<.001
Hyperlipidemia, n (%)	16 (7.3%)	3 (5.9%)	1.00
Diabetes, n (%)	51 (23.3%)	3 (5.9%)	.005
Chronic heart failure, n (%)	22 (10%)	14 (27.5%)	.001
History of transient ischemic attack, n (%)	2 (0.9%)	1 (2.0%)	.47
History of stroke, n (%)	40 (18.3%)	8 (15.7%)	.66
History of intracranial hemorrhage, n (%)	3 (1.4%)	0 (0%)	1
Systolic blood pressure, mean ± SD, mm Hg	147 ± 24	132 ± 25	<.001
Diastolic blood pressure, median (IQR),mmHg	85 ± 15	81 ± 15	.12
Total cholesterol, mean ± SD, mmol/L	4.13 ± 1.03	3.94 ± .92	.25
High-density lipoprotein, mean ± SD, mmol/L	1.26 ± .40	1.23 ± .40	.64
Low-density lipoprotein, mean ± SD, mmol/L	2.47 ± .80	2.17 ± .80	.03
Triglyceride, median (IQR), mmol/L	.97 (.70-1.45)	.98 ± .52	.08
Glucose at admission, n (%)			.003
≤5.73	30 (14.6%)	13 (26.5%)	
5.74-6.72	52 (25.2%)	16 (32.7%)	
6.73-8.60	57 (27.7%)	13 (26.5%)	
>8.60	67 (32.5%)	7 (14.3%)	
Anticoagulation drugs	136 (63.6%)	37 (72.5%)	.22
INR > 1.5	19 (8.7%)	12 (23.5%)	.003
Onset to groin puncture, mean ± SD, mins	273.34 ± 110.04	261.18 ± 110.65	.48
Onset to revascularization, mean ± SD, mins	386.53 ± 130.67	382.16 ± 124.25	.83
Anesthesia, n (%)			.43
General anesthesia	37 (16.9%)	11 (21.6%)	
Conscious sedation	182 (83.1%)	40 (78.4%)	
Occlusion sites, n (%)			.06
Internal carotid artery	98 (44.7%)	20 (39.2%)	
Middle cerebral artery, M1	113 (51.6%)	25 (49.0%)	
Middle cerebral artery, M2	8 (3.7%)	6 (11.8%)	
Collateral flow by ASITN/SIR, n (%)			.81
0	57 (26.1%)	12 (23.5%)	
1	75 (34.4%)	17 (33.3%)	
2	55 (25.2%)	12 (23.5%)	
3	31 (14.2%)	10 (19.6%)	
ASPECTS, n (%)			.95
0-8	88 (41.5%)	21 (42%)	
9-10	124 (58.5%)	29 (58%)	
NIHSS, n (%)			.47
≤10	19 (8.7%)	6 (11.8%)	
11-20	123 (56.2%)	29 (56.9%)	
≥21	77 (35.2%)	16 (31.4%)	
Operation methods, n (%)			.18
Thrombectomy alone	126 (57.5%)	24 (47.1%)	
Thrombectomy plus rescue therapy*	93 (42.5%)	27 (52.9%)	
Thrombectomy times, n (%)			0.61
≤3	178 (81.3%)	43 (84.3%)	
>3	41 (18.7%)	8 (15.7%)	

Rescue therapy included intra-arterial rt-PA or urokinase and tirofiban.

Regarding procedural-related variables, the valvular AF group had higher proportion of MCA M2 segment but with borderline significance, whereas the nonvalvular AF seems to have more ICA and MCA M1 segment occlusion. Other variables including NIHSS, ASPECTS, collateral flow, time points, and

Table 2. *Comparisons of outcomes between nonvalvular AF and valvular AF*

Variables	Nonvalvular AF N = 219	Valvular AF N = 51	*P*
mTICI, n (%)			.36
0-2a	42 (19.2%)	7 (14.3%)	
2b-3	177 (80.1%)	44 (86.3%)	
mRS			.04
0-2	73 (33.3%)	25 (49.0%)	
3-6	146 (66.7%)	26 (51.0%)	
ICH			.46
No	96 (42.7%)	24 (47.1%)	
Symptomatic	47 (21.5%)	7 (13.7%)	
Asymptomatic	76 (34.7%)	20 (39.2%)	
Death	84 (38.4%)	11 (21.6%)	.02

thrombectomy times were balanced between the 2 groups (Table 1).

Recanalization and Functional Outcome of Valvular and Nonvalvular AF Patients

Table 2 summarizes the outcomes between nonvalvular and valvular AF groups. There was no significant difference on recanalization rates in nonvalvular AF (80.1% [177/219]) and valvular AF (86.3% [44/51], $P = .36$), respectively. The valvular AF group had significantly higher proportion of mRS 0-2 (49% [25/51] versus 33.3% [73/219, $P = .04$]) and less death (21.6% [11/51] versus 38.4% [84/219], $P = .02$) comparing with nonvalvular AF group. Figure 1 shows the mRS distributions of nonvalvular AF and valvular AF groups. The rates of ICH between both groups were nonsignificantly different (21.5% [47/219] for nonvalvular AF versus 13.7% [7/51] for valvular AF, $P = .46$).

Predictors for Functional Outcome in the Whole AF Patients

Table 3 shows the univariate result for predictors of unfavorable functional outcomes. Age, valvular AF, chronic heart failure, collateral flow, recanalization status, ASPECTS, NIHSS at admission, glucose at admission, and ICH were significantly different between mRS 0-2 and mRS 3-6 groups ($P < .10$). The subsequent multivariable logistic regression model with enter method revealed that valvular AF was not an independent predictor for unfavorable functional outcome (odds ratio [OR] .67, 95% confidence interval [CI]: .24-1.84), age, collateral flow, NIHSS at admission, recanalization status, occlusion site, ASPECTS,

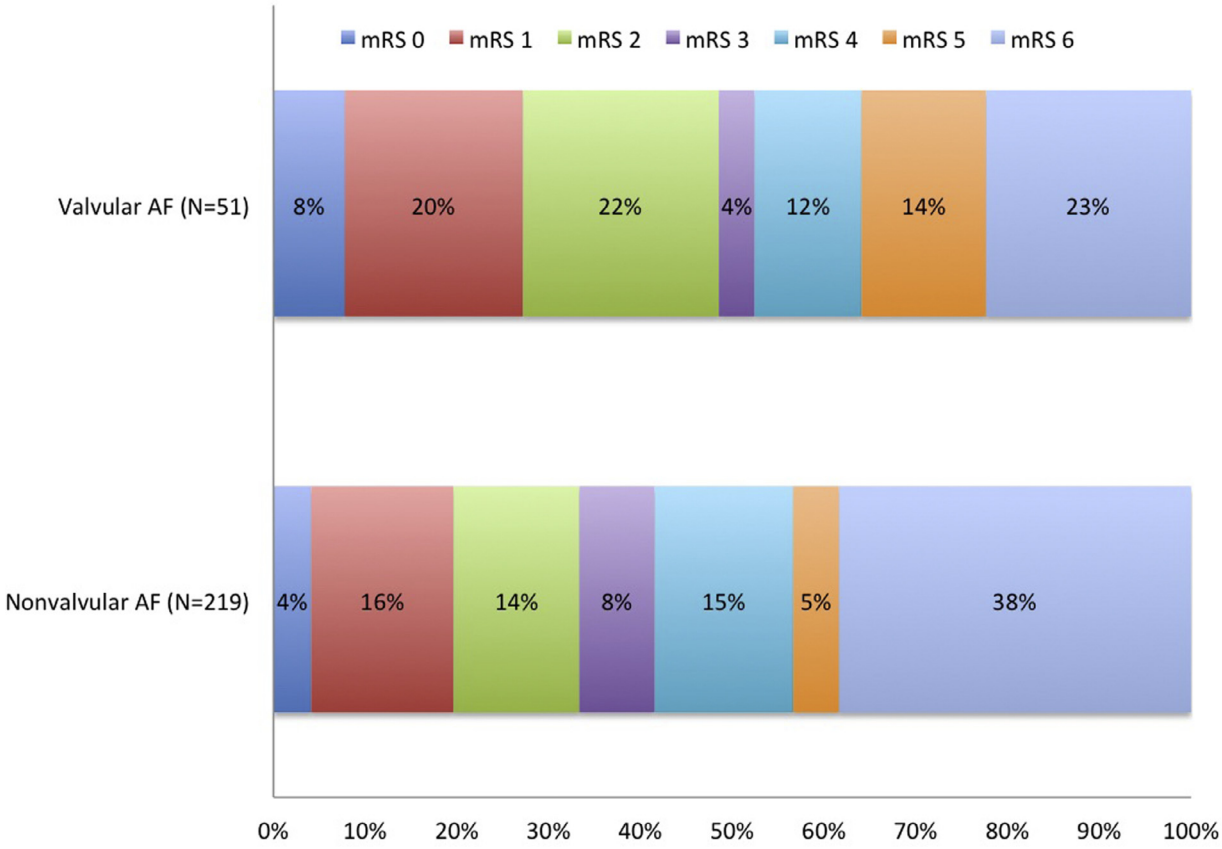

Figure 1. *The mRS distributions of nonvalvular and valvular AF groups.*

Table 3. *Univariate results for poor functional outcome*

Variables	mRS 0-2	mRS 3-6	*P*
	N = 98	N = 173	
Age, mean ± SD, years	64.8 ± 11.3	71.36 ± 8.9	<.001
Male, n (%)	37 (37.8%)	78 (45.1%)	.24
Coronary heart diseases, n (%)	36 (36.7%)	64 (37.0%)	.97
Hypertension, n (%)	56 (57.1%)	119 (68.8%)	.05
Hyperlipidemia, n (%)	8 (8.2%)	11 (6.4%)	.58
Diabetes, n (%)	21 (21.4%)	33 (19.1%)	.64
Chronic heart failure, n (%)	8 (8.2%)	28 (16.2%)	.06
Valvular AF*	25 (25.5%)	26 (15.1%)	.04
Glucose at admission, n (%)†			.06
≤5.73	21 (22.6%)	22 (13.5%)	
5.74-6.72	28 (30.1%)	40 (24.5%)	
6.73-8.60	25 (26.9%)	46 (28.2%)	
>8.60	19 (20.4%)	55 (33.7%)	
Anticoagulation drugs	61 (34.7%)	115 (66.5%)	.48
INR > 1.5	6 (6.7%)	6 (3.7%)	.36
Onset to groin puncture, mean ± SD, mins	267.57 ± 107.00	273.21 ± 111.71	.69
Onset to revascularization, mean ± SD, mins	372.83 ± 120.32	392.81 ± 133.59	.21
Occlusion sites, n (%)			.02
Internal carotid artery	30 (30.6%)	89 (51.4%)	
Middle cerebral artery, M1	64 (65.3%)	74 (42.8%)	
Middle cerebral artery, M2	4 (4.1%)	10 (5.8%)	
Collateral flow by ASITN/SIR, n (%)‡			<.001
0	12 (12.3%)	57 (33.1%)	
1	29 (29.6%)	63 (36.6%)	
2	35 (35.7%)	33 (19.2%)	
3	22 (22.4%)	19 (11.0%)	
ASPECTS, n (%)§			.004
0-8	28 (30.1%)	82 (48.2%)	
9-10	65 (69.9%)	88 (51.8%)	
NIHSS, n (%)			<.001
≤10	19 (19.4%)	6 (3.5%)	
11-20	59 (60.2%)	94 (54.3%)	
≥21	20 (20.4%)	73 (42.2%)	
ICH			<.001
No	60 (61.2%)	60 (34.7%)	
Symptomatic	2 (2%)	52 (30.1%)	
Asymptomatic	36 (36.7%)	61 (35.3%)	
mTICI			<.001
0-2a	6 (6.1%)	43 (24.9%)	
2b-3	92 (93.9%)	130 (75.1%)	

*1 missing value.
†15 missing values.
‡1missing value.
§10 missing values.

and ICH were independent predictors, and chronic heart failure had borderline significance (OR 2.99, 95% CI: .89-10.01; Table 4).

Discussion

Using a multicenter clinical registry, we identified that valvular AF and nonvalvular AF had similar rates of poor functional outcome, death, and sICH. Age and chronic heart failure are 2 independent predictors for poor functional outcome and death at 90 days.

It is unexpected to us that both valvular AF and nonvalvular AF had no significant differences on the outcomes at 90 days in acute stroke due to large artery occlusion undergoing thrombectomy. The valvular AF confers higher risk for embolic stroke, due to its low flow occurring in the left atrium, which leads to thrombosis. In our initial point of view, the thrombus in valvular AF patients may be hard with intense thrombus load, which

Table 4. *Predictors for unfavorable functional outcomes in AF patients*

	P	OR	95% CI
Age	.001	1.07	1.03-1.11
Valvular AF	.43	.67	.24-1.84
Chronic heart failure	.08	2.99	.89-10.01
Glucose at admission			
5.74-6.72 vs. ≤5.73	.96	1.03	.36-2.91
6.73-8.60 vs. ≤5.73	.84	.89	.30-2.66
≥8.60 vs. ≤5.73	.67	1.28	.42-3.87
Occlusion site			
MCA, M1 vs. ICA	.92	.94	.27-3.31
MCA, M2 vs. ICA	.04	8.45	1.17-61.08
ASPECTS 9-10	.33	.70	.34-1.44
NIHSS at admission			
11-20 vs. ≤10	.03	4.76	1.14-19.90
≥21 vs. ≤10	.005	8.72	1.92-39.63
mTICI 2b-3	.02	.25	.08-.81
Collateral flow (ASITN_SIR)			
1 vs. 0	.40	.65	.24-1.78
2 vs. 0	.04	.36	.13-.98
3 vs. 0	.04	.28	.08-.97
ICH			
Symptomatic vs. no	<.001	44.18	5.26-370.84
Asymptomatic vs. no	.26	1.53	.74-3.18

may cause lower recanalization rate, more thrombectomy times, higher risk for intracerebral hemorrhage, and poor functional outcome. However, it seems that valvular AF patients have higher probability of small thrombus which consequently occluded the MCA M2 segment, whereas nonvalvular AF patients had more ICA occlusion. After endovascular treatments, the recanalization rate in valvular AF patients was even numerically higher than that in nonvalvular AF patients but not reach statistical significance. Although patients were treated with Warfarin, most of the valvular AF patients did not reach the treatment effect with low INR values. And thrombectomy times were similar among both groups, as well as collateral flow, mTICI score, and sICH. These core variables are the most important determinants for functional outcomes, which explain why there is no difference between nonvalvular AF and valvular AF on functional outcomes.

In consistent with previous studies, the collateral flow,[7] NIHSS at admission, recanalization status, and symptomatic ICH were independent predictors for unfavorable functional outcomes.[8] The chronic heart failure had a borderline significance for unfavorable functional outcome in AF patients with acute large artery occlusion undergoing thrombectomy. Patients with chronic heart failure confer 3 times the risk for poor functional outcome than the risk in patients without chronic heart failure. And the OR is almost 4 times for death. Heart failure is a clinical symptom that may be caused by various heart diseases.[9] AF is the most common arrhythmia in heart failure irrespective of concomitant left ventricular heart failure.[10] Our finding is consistent with previous studies in heart diseases which also found that patients with chronic heart failure and permanent AF have a worse outcome than those in sinus rhythm, and this is largely explained by more advanced age and heart failure severity.[11,12]

The strength of our study lies on multicenter setting and a relatively large sample size with thrombectomy and AF. Certain limitations should be paid into attention. First, the retrospective nature of this study may cause information bias. Second, the valvular AF was recorded according to medical records, lacking of detailed continuous severity of the mitral stenosis, the dosage and duration of Warfarin use. Third, the ejection fraction value is lacking, and detailed treatments of chronic heart failure have not been recorded in our study. Further studies specifically evaluation of the chronic heart failure may be needed. Fourth, no information on the pathological findings of thrombi, future studies are warranted to include the pathological findings in order to fully understand the difference between the nonvalvular AF and valvular AF.

Conclusion

Valvular AF and nonvalvular AF have similar safety and functional outcomes in patients with acute large artery occlusion undergoing thrombectomy.

Disclosure

None.

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