



# Atrial fibrillation predicts good functional outcome following intravenous tissue plasminogen activator in patients with severe stroke

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## ABSTRACT

**Objective:** Atrial fibrillation (AF) is associated with poor outcome after intravenous thrombolysis probably due to greater pretreatment stroke severity. We conducted this retrospective study to determine whether AF is an independent predictor for clinical outcome in patients stratified by initial stroke severity.

**Methods:** A total of 143 acute ischemic stroke patients who received intravenous thrombolysis within 3 h after onset were enrolled. The patients were categorized according to the baseline stroke severity by National Institute of Health Stroke Scale (NIHSS) score ( $\leq 10$  vs.  $>10$ ) and the presence of AF or not. Favorable 90-day outcome was defined as a modified Rankin Scale (mRS) score  $< 2$ .

**Results:** Among the 100 patients with severe stroke (NIHSS  $> 10$ ), those with AF ( $n = 52$ ) had a higher proportion of favorable 90-day outcome than those without AF (31% vs. 8%,  $P = 0.005$ ). After adjustment for age, baseline glucose level, and onset to treatment time, the difference remained significant (odds ratio 5.80, 95% confidence interval 1.63–20.68). In patients with mild stroke (NIHSS  $\leq 10$ ), no difference in clinical outcome was found between AF ( $n = 20$ ) and non-AF ( $n = 23$ ) groups.

**Conclusion:** Presence of AF was associated with favorable 90-day outcome following intravenous thrombolysis in patients with severe stroke at baseline, while the association did not exist in patients with mild stroke.

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## 1. Introduction

Atrial fibrillation (AF) is responsible for about 25% of all ischemic strokes [1], and the risk of stroke attributed to AF increases with age [2]. AF was associated with increased stroke severity, high frequency of complications, and poor outcome [3–5]. Thrombolytic therapy with intravenous tissue plasminogen activator (tPA) is of net benefit in patients with acute ischemic stroke regardless of stroke subtypes [6]. However, whether the benefits and harms of tPA are comparable among different stroke subtypes is incompletely understood.

Approximately 50–60% of ischemic strokes in patients with AF are definitely or probably cardioembolic in origin [7,8]. Patients with cardioembolic stroke may have more frequent, faster, and more complete early recanalization following intravenous tPA

therapy compared to those with other stroke subtypes, and thereby are more likely to have better 90-day outcome [9]. On the contrary, there were studies showing that AF was associated with a reduced recanalization rate [10,11]. A later study indicated that AF predicted poor clinical outcome after intravenous thrombolysis [12]. However, in this study, the imbalance of baseline stroke severity, measured by National Institute of Health Stroke Scale (NIHSS), between the AF (18.2% with NIHSS  $\leq 10$ ) and non-AF groups (48.8% with NIHSS  $\leq 10$ ) might have confounded the association. The worse 90-day outcome after intravenous tPA therapy in stroke patients with AF was probably due to more severe neurological deficits at baseline [13]. A recent study indicated that presence of AF has no independent impact on 90-day outcome after adjustment for age and baseline stroke severity [14]. Since the true mechanism of stroke among AF patients might be heterogeneous, those with non-cardioembolic stroke, particularly lacunar type, were less likely to have an initial NIHSS score over 10 [15]. We speculate that baseline stroke severity might modify the effect of AF on the outcome of thrombolytic therapy.

In this study, we sought to determine whether AF is an independent predictor for clinical outcome in thrombolized patients

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**Table 1**  
Characteristics of the study patients.

	Mild Stroke (NIHSS $\leq$ 10)		<i>P</i>	Severe Stroke (NIHSS > 10)		<i>P</i>
	AF ( <i>N</i> = 20)	Non-AF ( <i>N</i> = 23)		AF ( <i>N</i> = 52)	Non-AF ( <i>N</i> = 48)	
Age (years), mean $\pm$ SD	64 $\pm$ 13	66 $\pm$ 10	0.547	70 $\pm$ 12	64 $\pm$ 13	0.034
Male	12 (60%)	14 (61%)	0.954	30 (58%)	32 (67%)	0.356
Medical history						
Hypertension	14 (70%)	19 (83%)	0.329	43 (83%)	36 (75%)	0.345
Diabetes mellitus	10 (50%)	8 (35%)	0.313	10 (19%)	20 (42%)	0.014
Hyperlipidemia	8 (40%)	14 (61%)	0.172	29 (56%)	32 (67%)	0.264
Prior stroke/TIA	4 (20%)	3 (13%)	0.538	12 (23%)	8 (17%)	0.423
Current Smoking	7 (35%)	5 (22%)	0.334	6 (12%)	16 (33%)	0.009
Warfarin	2 (10%)	0 (0%)	–	1 (2%)	0 (0%)	–
Antiplatelets	8 (40%)	8 (35%)	0.724	19 (37%)	9 (19%)	0.048
Baseline NIHSS score, median (IQR)	9 (8–10)	7 (7–9)	0.087	21 (17–23)	18 (15–23)	0.089
Mean arterial pressure (mmHg), mean $\pm$ SD	118 $\pm$ 18	115 $\pm$ 20	0.584	109 $\pm$ 19	107 $\pm$ 18	0.593
Glucose (mg/dL), mean $\pm$ SD	186 $\pm$ 97	137 $\pm$ 64	0.054	147 $\pm$ 53	163 $\pm$ 70	0.180
OTT (min), median (IQR)	132 (118–156)	116 (95–140)	0.108	106 (90–137)	121 (94–144)	0.236
Cardioembolic stroke	12 (60%)	1 (4%)	<0.001 <sup>a</sup>	40 (77%)	8 (17%)	<0.001

AF, atrial fibrillation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OTT, onset to treatment time; SD, standard deviation; TIA, transient ischemic attack.

<sup>a</sup> Fisher's exact test.

stratified by baseline stroke severity. We hypothesized that severe stroke patients with AF benefit more from intravenous tPA treatment than those without AF.

## 2. Materials and methods

Data were from two phases of registry. The first phase took place from 1998 to 2007 and data of stroke patients treated with intravenous tPA in the study hospital were retrospectively collected [16]. The second phase of the registry has been conducted since 2007 and followed the design of the nationwide Taiwan Stroke Registry [17], which prospectively registered all stroke patients presenting within 10 days of symptom onset. Our institution is a 1000-bed community hospital serving a city and its adjoining rural area of around 500,000 inhabitants. The study was approved by the hospital's Institutional Review Board.

All thrombolized patients underwent computed tomography or magnetic resonance imaging between 24 and 36 h after thrombolysis and additional scans in case of clinical deterioration. Symptomatic intracerebral hemorrhage (SICH) was defined as a parenchymal hematoma associated with a neurological deterioration of 4 or more points on the NIHSS [18]. Extracranial carotid and vertebral ultrasound, transcranial color-coded sonography, magnetic resonance angiography, and/or transthoracic echocardiography were performed to identify potential mechanisms of cerebral infarction. We classified patients as having cardioembolic stroke or not using the Trial of ORG 10172 in Acute Stroke Treatment criteria [19]. Functional status was measured with modified Rankin Scale (mRS) at discharge, and at 90 days from the medical records of clinic visits or through telephone interview by the study nurse. We conformed to the clinical guidelines developed by the Taiwan Stroke Society [20,21], including within a 3-h time window after stroke onset.

Because low baseline stroke severity (NIHSS  $\leq$  10) was an independent predictor of favorable outcome in thrombolized patients [22], we classified patients as having mild (NIHSS  $\leq$  10) or severe stroke (NIHSS > 10) according to their NIHSS scores at presentation. Each group was further divided by the presence or absence of AF. The presence of AF had to be documented by the electrocardiograms on admission or during the whole hospital stay, including both paroxysmal and persistent forms.

### 2.1. Outcome measures

Primary outcome was the mRS at 90 days. An mRS score of 0 to 1 was considered to indicate a favorable functional outcome. Secondary outcome measures included all-cause mortality at discharge and SICH within 36 h of thrombolysis.

### 2.2. Statistical analysis

Chi-square tests or Fisher's exact tests were used to compare categorical variables; *t*-tests or Mann–Whitney *U* tests were used for continuous variables. Multivariable logistic regression analysis was used to explore the association of AF with outcomes of interest in patients with severe stroke. We considered *P* value < 0.05 statistically significant. All analyses were performed using STATA version 10 (StataCorp LP, College Station, TX).

## 3. Results

A total of 143 stroke patients who received intravenous tPA from 2003 to 2011 were included in the study: 100 patients had severe stroke (52 with AF, 48 non-AF) and 43 patients with minor stroke (20 with AF, 23 non-AF). Baseline characteristics were summarized in Table 1. In patients with severe stroke, AF was associated with older age, less diabetes mellitus, less smokers, and more users of antiplatelet agents compared with non-AF. The NIHSS scores appeared higher in patients with AF, although the difference was non-significance. In patients with mild stroke, characteristics between AF and non-AF groups were similar. Of all AF patients regardless of NIHSS score (*n* = 72), 52 (72%) were classified as having cardioembolic stroke and AF was evident on electrocardiography at presentation in 64 (89%) patients (80% in mild stroke and 92% in severe stroke).

Overall, 45 (31%) patients achieved a favorable 90-day functional outcome: 25 (58%) in mild strokes and 20 (20%) in severe strokes. In patients with severe stroke, those with AF, despite being older, had a significantly favorable 90-day functional outcome and a trend toward lower in-hospital mortality or SICH. In patients with mild stroke, all outcomes were comparable between AF and non-AF (Table 2). In multivariable analysis, adjusted for age, glucose on admission, and onset to treatment time, AF remained significantly associated with favorable outcome at 90 days in patients with severe stroke (Table 3). Fig. 1 shows the distribution of mRS scores at 90 days.

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