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ORIGINAL ARTICLE

Factors Associated with Thrombolysis Outcome in Ischemic Stroke Patients with Atrial Fibrillation

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Abstract The outcome of early intravenous thrombolysis for ischemic stroke in patients with atrial fibrillation (AF) is worse than that without thrombosis. How to increase the efficacy of intravenous thrombolysis for AF-related ischemic stroke remains largely unknown. In this study, we investigated factors that influence the effect of intravenous thrombolysis in these patients. Our results showed that thrombolysis was independently associated with a favorable outcome ($P < 0.001$) and did not influence the mortality of AF-related ischemic stroke, although it increased the risk of hemorrhage within 24 h after treatment. Risk factors for a poor outcome at admission were: heart failure ($P = 0.045$); high systolic pressure ($P = 0.039$); high blood glucose ($P = 0.030$); and a high National Institutes of Health Stroke Scale (NIHSS) score ($P < 0.001$). Moreover, high systolic pressure at admission ($P = 0.007$), high blood glucose ($P = 0.027$), and a high NIHSS score ($P < 0.001$) were independent risk factors for

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mortality at 3 months. Besides thrombolysis, a high NIHSS score ($P = 0.006$) and warfarin taken within 48 h before stroke onset ($P = 0.032$) were also independent risk factors for symptomatic hemorrhage within 24 h after treatment. Ischemic stroke patients with AF benefited from intravenous thrombolysis with recombinant tissue plasminogen activator within 4.5 h after stroke.

Keywords Ischemic stroke · Atrial fibrillation · Intravenous recombinant tissue plasminogen activator · Intravenous thrombolysis · Favorable outcome · Risk factors

Introduction

Atrial fibrillation (AF)-related ischemic stroke is often severe and has a poor prognosis [1, 2]. AF contributes to a poor outcome in ischemic stroke patients and is an independent predictor of high mortality [3]. Intravenous thrombolysis within 4.5 h can significantly improve the prognosis of ischemic stroke patients [4, 5] and an increasing number of retrospective studies have demonstrated that AF-related stroke patients also benefit from intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) compared to those without rt-PA [3, 6]. A recent prospective study enrolling 734 ischemic stroke patients, including 155 with AF, supported the use of rt-PA intravenous thrombolysis for acute cases [7]; however, ischemic stroke patients with AF benefited less than those without AF [6, 8–10]. Compared to non-AF patients, stroke patients with AF had worse outcomes after rt-PA intravenous thrombolysis, including higher mortality and disability rates and lower recanalization due to the resistance of previous thrombi to rt-PA in patients with AF [8, 11].

Previous studies on the independent prognostic factors of intravenous rt-PA thrombolysis in AF-induced stroke patients are limited. In this study, 267 AF-related ischemic stroke patients were enrolled from 15 hospitals in Jiangsu Province, China; 151 received rt-PA thrombolytic therapy and all received follow-up examinations at 3 months. The aim was to determine whether intravenous rt-PA thrombolytic therapy is an independent beneficial factor for AF-related acute stroke patients. Meanwhile, potential factors influencing the outcome in thrombolytic patients were also investigated. The results will help physicians to determine appropriate individual thrombolysis therapy for AF-related ischemic stroke patients.

Methods

Patients and Materials

This was an open-label, multicenter, retrospective study approved by the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School, China. Patients with acute ischemic stroke were selected from the 15 hospitals of the Jiangsu Stroke Research Collaborative Group between November 2009 and July 2013. AF-related ischemic stroke patients who were eligible for thrombolysis were included. All patients gave written informed consent.

Inclusion criteria: (1) >18 years old; (2) clinical diagnosis of ischemic stroke causing a significant neurological deficit; (3) time from symptom onset to initiation of rt-PA or other treatment <4.5 h; (4) computed tomography (CT) or magnetic resonance imaging (MRI) indicating no intracranial hemorrhage; (5) AF on admission or diagnosed before onset; and (6) signed informed consent.

Exclusion criteria: (1) NIHSS (National Institutes of Health Stroke Scale) score <4 or rapidly improving symptoms or signs; (2) NIHSS >20 and baseline MRI or CT showing extensive infarction; (3) history of intracranial hemorrhage (ICH) or symptoms suggestive of symptomatic intracranial hemorrhage (SICH); (4) myocardial infarction, stroke, or serious head trauma in the previous 3 months; (5) urinary tract, lung, or gastrointestinal hemorrhage within the 21 previous days; (6) serious trauma or major surgery within the previous 14 days; (7) lumbar or arterial puncture at a non-compressible site within 7 days; (8) received heparin within 48 h, resulting in an activated partial thromboplastin time greater than the upper limit of normal; (9) systolic pressure >185 mmHg or diastolic pressure >110 mmHg; (10) blood glucose <50 or >400 mg/dL; (11) current use of anticoagulants with an International Normalized Ratio >1.7 or prothrombin time >15 s; (12) platelet count <100,000/mm^3; (13) pregnant; (14) serious heart, lung, kidney or other organ dysfunction; and (15) allergy to active ingredients of rt-PA.

AF was diagnosed using a 12-lead electrocardiogram at admission or diagnosed before admission. Rt-PA was administered by experienced neurologists; all information was systematically and rigorously recorded. The attending physician collected detailed information by inviting the patients to our department for follow-up or by telephone if they could not come, including details of the modified Rankin Scale (mRS) score and survival rate. Qualified, experienced observers completed the CT/MRI scanning

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and reading; and professional statisticians completed the follow-up analyses.

We reviewed the medical records of enrolled patients to obtain information about the demographics, baseline hemodynamics, medical history, vascular risk factors, stroke severity, and mRS score at 3 months. Hypertension was defined as a blood pressure >140/90 mmHg or the use of anti-hypertensive drugs. Diabetes mellitus was defined as the use of hypoglycemic drugs or insulin therapy. The criteria for a diagnosis of diabetes mellitus were symptoms of diabetes and casual plasma glucose ≥11.1 mmol/L (200 mg/dl), fasting plasma glucose ≥7.0 mmol/L (126 mg/dl), or 2-h postprandial blood glucose ≥11.1 mmol/L. Heart failure was defined as New York Heart Association functional class III to IV. Drinking was defined as a history of drinking alcohol.

To evaluate the efficacy of thrombolysis in ischemic stroke patients with AF, the enrolled patients were divided into the thrombolysis group and the control group according to whether or not they received rt-PA. In the thrombolysis group, 0.9 mg/kg rt-PA (maximum of 90 mg; 10% bolus with the remainder over 1 h) was administered. Patients who rejected thrombolysis received pharmaceutical treatment.

Measurement of Outcome

NIHSS and mRS scores were used to assess patients at admission, after rt-PA treatment, at discharge, and at 90 days by each patient's attending physician. A favorable outcome was defined as an mRS score of 0–1 at 3 months, while a score >1 was defined as an unfavorable outcome. We also recorded the mortality within 3 months, as well as total ICH and SICH within 24 h after treatment (SICH was defined as the appearance of a new hemorrhage on imaging with neurologic deterioration ≥4 points on the NIHSS at 24 h after treatment). One patient in the thrombolysis group was lost to follow-up.

Statistical Analysis

To compare the categorical variables of the clinical features, χ^2 tests were used and the Mann-Whitney U-test or Student's *t*-test was used to compare continuous variables of clinical characteristics. Univariate logistic regression analysis was used to identify potential factors influencing outcomes. Univariate predictors at a level of $P < 0.10$ were considered significant and were entered into a multivariate logistic regression model. All tests were two-tailed. $P < 0.05$ was considered to be statistically significant, but $P < 0.01$ was considered to suggest statistical significance in subgroup analysis to minimize the probability of Type I errors. All statistical analyses were performed using SPSS ver.16.0 (Chicago, IL) and Stata ver. 12.0 (StataCorp LP, College Station, TX) softwares.

Results

Baseline Information on Patients

A total of 267 ischemic stroke patients with AF (116 male, mean age 72.25 ± 9.10 years) were involved in this study. Baseline characteristics are summarized in Table 1. A total of 189 patients had hypertension and 81 suffered from heart failure. One patient did not receive follow-up.

Independent Predictors of Outcome for Ischemic Stroke Patients with AF

Heart failure, systolic pressure at admission, blood glucose at admission, and a high NIHSS score were independent risk factors for a favorable outcome in AF-related ischemic stroke patients. However, thrombolysis was an independent predictor of a favorable outcome (adjusted OR: 5.73, 95%CI[2.40, 13.69], adjusted $P < 0.001$) (Table 2).

Inpatients with AF-related ischemic stroke, high systolic pressure at admission (adjusted OR: 1.03, 95%CI[1.01, 1.04], adjusted $P = 0.007$), high blood glucose (adjusted OR: 1.16, 95%CI[1.02, 1.31], adjusted $P = 0.027$), and high NIHSS score (adjusted OR: 1.16, 95%CI[1.10, 1.22], adjusted $P < 0.001$) were independent risk factors for mortality at 3 months (Table 3). Thrombolysis (adjusted OR: 9.49, 95%CI[2.09, 43.06], adjusted $P = 0.004$), high NIHSS score (adjusted OR: 1.10, 95%CI[1.03, 1.17], adjusted $P = 0.006$), and warfarin taken within 48 h before stroke onset (adjusted OR: 6.31, 95%CI[1.18, 33.87], adjusted $P = 0.032$) were independent predictors for ICH in ischemic stroke patients with AF (Table 4).

Efficacy and Safety of Thrombolysis in AF-Related Ischemic Stroke Patients

The baseline characteristics of the 151 patients in the thrombolysis group and 116 in the control group are summarized in Table 5. The mean NIHSS score was 15.06 ± 6.76 in the rt-PA group and 13.89 ± 8.75 in the control group ($P = 0.054$). The control group had fewer smokers than the thrombolysis group ($P < 0.001$). There were no significant differences between the two groups in the other baseline characteristics (Table 5).

The distribution of mRS scores in the thrombolysis and control groups is summarized in Fig. 1. At 3 months, 54 patients (36.0%) in the thrombolysis group had a favorable outcome compared with 28 patients (24.1%) in the control group, representing an absolute improvement of 11.9% ($P = 0.038$) though there was no significant difference in neurological function between the two groups at discharge (data not shown). Mortality within 3 months in rt-PA patients was not significantly different from that in the

Table 1 Demographic and clinical features of stroke patients with atrial fibrillation.

	Overall patients ($n = 267$) (%)
Gender, male	116 (43.45%)
Age, mean±SD	72.25±9.10
Smoking	56 (20.97%)
Drinking	34 (12.73%)
Hypertension	189 (70.79%)
Diabetes mellitus	46 (17.23%)
Hyperlipidemia	40 (14.98%)
Heart failure	81 (30.34%)
History of stroke	83 (31.09%)
Warfarin taken within 48 h	12 (4.49%)
Time from stroke onset to treatment (min), mean±SD	171.62±57.34
Systolic pressure at admission (mmHg), mean±SD	148.13±20.59
Diastolic pressure at admission (mmHg), mean±SD	85.60±13.43
Blood glucose at admission (mmol/L), mean±SD	7.61±2.58
NIHSS score at admission, mean±SD	14.55±7.69
Thrombolysis treatment	151 (56.6%)

Table 2 Univariate and multivariate logistic regression to predict primary outcome (mRS 0-1) of stroke patients with AF.

	Univariate		Multivariate	
	OR[95%CI]	Unadjusted *P* value	OR[95%CI]	Adjusted *P* value
Gender, male	0.44[0.26–0.74]	0.002	0.68[0.30–1.51]	0.338
Age	0.98[0.95–1.01]	0.122		
Smoking	2.04[1.11–3.77]	0.022	1.13[0.39–3.29]	0.826
Drinking	1.94[0.93–4.05]	0.076	0.77[0.25–2.37]	0.643
Hypertension	1.30[0.73–2.34]	0.375		
Diabetes mellitus	0.86[0.43–1.74]	0.679		
Hyperlipidemia	0.96[0.46–1.99]	0.902		
Heart failure	0.44[0.24–0.83]	0.011	0.44[0.19–0.98]	0.045
History of stroke	0.69[0.39–1.24]	0.220		
Warfarin taken within 48h	1.13[0.33–3.85]	0.848		
Time from stroke onset to treatment (min)	1.00[0.99–1.01]	0.413		
Systolic pressure at admission (mmHg)	0.98[0.97–0.99]	0.023	0.98[0.96–0.99]	0.039
Diastolic pressure at admission (mmHg)	0.99[0.98–1.01]	0.534		
Blood glucose at admission (mmol/L)	0.85[0.75–0.97]	0.012	0.83[0.70–0.98]	0.030
NIHSS score at admission	0.81[0.76–0.86]	<0.001	0.76[0.70–0.82]	<0.001
Thrombolysis	1.77[1.03–3.04]	0.039	5.73[2.40–13.69]	<0.001

NIHSS National Institutes of Health Stroke Scale.

control group ($P = 0.730$). Forty patients (26.5%) suffered from ICH within 24 h after rt-PA treatment, compared with only 2 patients (1.7%) in the control group ($P < 0.001$). Similarly, patients with rt-PA had a higher risk of SICH within 24 h after treatment than those in the control group (13.9% *vs* 1.7%, $P < 0.001$) (Table 5).

Subgroup analyses assessing the efficacy of thrombolysis in high-risk stroke patients with AF demonstrated that thrombolysis had an independent effect on a favorable outcome in patients with heart failure (adjusted OR: 73.66, 99%CI[1.89, 2872.75], $P = 0.003$); hypertension (adjusted OR: 3.66, 99%CI[1.01, 13.27], $P = 0.009$); and an NIHSS score of 11–20 ($P < 0.001$). There were no benefits for patients with blood glucose ≥7.8 mmol/L ($P = 0.245$) and an NIHSS score >20 ($P = 0.261$) at admission (Fig. 2).

Table 3 Univariate and multivariate logistic regression to predict death at 3 months for stroke patients with AF.

	Univariate		Multivariate	
	OR[95%CI]	Unadjusted *P* value	OR[95%CI]	Adjusted *P* value
Gender, male	1.51[0.84–2.69]	0.166		
Age	1.05[1.02–1.09]	0.004	1.02[0.98–1.06]	0.349
Smoking	0.63[0.30–1.34]	0.632		
Drinking	0.65[0.26–1.64]	0.358		
Hypertension	1.32[0.70–2.50]	0.396		
Diabetes mellitus	0.99[0.47–2.10]	0.996		
Hyperlipidemia	0.14[0.03–0.60]	0.140		
Heart failure	1.84[1.02–3.31]	0.042	1.73[0.83–3.60]	0.145
History of stroke	1.22[0.67–2.21]	0.515		
Warfarin taken within 48h	2.37[0.73–7.75]	0.153		
Time from stroke onset to treatment (min)	1.00[0.99–1.01]	0.867		
Systolic pressure at admission (mmHg)	1.02[1.01–1.04]	0.003	1.03[1.01–1.04]	0.007
Diastolic pressure at admission (mmHg)	1.01[0.99–1.03]	0.579		
Blood glucose at admission (mmol/L)	1.21[1.09–1.35]	<0.001	1.16[1.02–1.31]	0.027
NIHSS score at admission	1.17[1.11–1.22]	<0.001	1.16[1.10–1.22]	<0.001
Thrombolysis	0.91[0.51–1.59]	0.730		

AF atrial fibrillation, *NIHSS* National Institutes of Health Stroke Scale.

Table 4 Univariate and multivariate logistic regression to predict symptomatic intracranial hemorrhage at 24 h after treatment in stroke patients with AF.

	Univariate		Multivariate	
	OR[95%CI]	Unadjusted *P* value	OR[95%CI]	Adjusted *P* value
Thrombolysis	9.21[2.11–40.13]	0.003	9.49[2.09–43.06]	0.004
Gender, male	1.22[0.51–2.91]	0.663		
Age	1.01[0.96–1.06]	0.679		
Smoking	1.37[0.51–3.65]	0.530		
Drinking	0.29[0.04–2.23]	0.235		
Hypertension	0.94[0.37–2.38]	0.893		
Diabetes mellitus	0.70[0.20–2.47]	0.580		
Hyperlipidemia	0.52[0.12–2.29]	0.385		
Heart failure	1.54[0.64–3.71]	0.340		
History of stroke	0.97[0.38–2.45]	0.944		
Warfarin taken within 48h	3.92[0.98–15.63]	0.053	6.31[1.18–33.87]	0.032
Time from stroke onset to treatment (min)	0.99[0.986–1.001]	0.994		
Systolic pressure at admission (mmHg)	1.01[0.99–1.04]	0.217		
Diastolic pressure at admission (mmHg)	0.99[0.96–1.02]	0.374		
Blood glucose at admission (mmol/L)	1.13[0.98–1.30]	0.086	1.09[0.93–1.28]	0.295
NIHSS score at admission	1.08[1.02–1.14]	0.006	1.10[1.03–1.17]	0.006

AF atrial fibrillation, *NIHSS* National Institutes of Health Stroke Scale.

Discussion

In this study, we found that (1) rt-PA thrombolysis within 4.5 h was an independent effect factor for AF-related ischemic stroke; (2) risk factors associated with death at 3 months after thrombolysis in AF-related ischemic stroke were high systolic pressure, high blood glucose, and a high NIHSS score at admission; (3) predictors for symptomatic ICH within 24 h after thrombolysis were warfarin-use within 48 h before thrombolysis and a high NIHSS score at admission; (4) AF-related stroke patients with heart failure, hypertension, and an NIHSS score between 11 and 20 at

Table 5 Demographics, baseline characteristics, and outcomes of patients in the thrombolysis and control groups.

Baseline characteristics	Thrombolysis (n = 151) (%)	Control (n = 116) (%)	P value
Gender, male	66 (43.7%)	50 (43.1%)	0.921
Age, mean±SD	71.32±7.77	73.47±10.05	0.066
Smoking	44 (29.1%)	12 (10.3%)	<0.001
Drinking	19 (12.6%)	15 (12.9%)	0.933
Hypertension	111 (73.5%)	78 (67.2%)	0.264
Diabetes mellitus	24 (15.9%)	22 (19.0%)	0.510
Hyperlipidemia	26 (17.2%)	14 (12.1%)	0.243
Heart failure	44 (29.1%)	37 (31.9%)	0.627
History of stroke	43 (28.5%)	40 (34.5%)	0.293
Warfarin taken within 48h	6 (4.0%)	6 (5.2%)	0.639
Time from stroke onset to treatment (min), mean±SD	165.70±54.50	179.28±60.20	0.055
Systolic pressure at admission (mmHg), mean±SD	148.07±20.94	148.21±20.20	0.958
Diastolic pressure at admission (mmHg), mean±SD	85.83±13.69	85.29±13.14	0.748
Blood glucose at admission (mmol/L), mean±SD	7.81±2.53	7.32±2.64	0.139
NIHSS score at admission, mean±SD	15.06±6.76	13.89±8.75	0.054
Median (min, max)	15 (4–38)	12 (4–36)	
Clinical outcomes			
Favorable outcome(mRS 0–1) at 3 months	54 (36.0%)	28 (24.1%)	0.038
Death at 3 months	35 (23.2%)	29 (25.0%)	0.730
ICH within 24 h after treatment	40 (26.5%)	2 (1.7%)	<0.001
SICH within 24 h after treatment	21 (13.9%)	2 (1.7%)	<0.001

ICH intracranial hemorrhage, *NIHSS* National Institutes of Health Stroke Scale, *SICH* symptomatic intracranial hemorrhage.

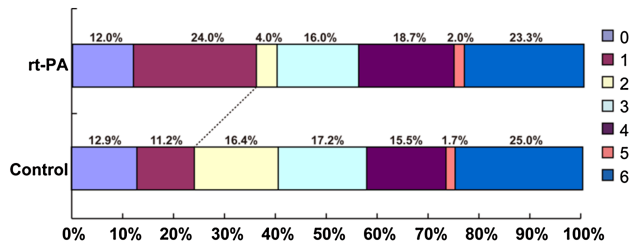

Fig. 1 Outcome at 3 months: modified Rankin Scale (mRS) distribution in treatment and control groups.

admission had more favorable outcomes with rt-PA thrombolysis than those without thrombolysis; and (5) no benefits of thrombolysis were found in AF-related ischemic stroke patients with blood glucose ≥7.8 mmol/L and an NIHSS score >20 at admission.

The efficacy of rt-PA in patients with stroke has been confirmed; however, results for the AF subgroup have not been well explored. A few large, randomized, controlled trials regarding the effectiveness of rt-PA treatment in AF patients have been conducted, but with apparently conflicting conclusions. In 1997, a National Institute of Neurological Disorders and Stroke trial found no difference in outcome, with or without thrombolysis treatment [12]. In the European Cooperative Acute Stroke Study III, no significant difference in response to rt-PA was found among patients with AF compared with the placebo group [13]. In 2012, the Third International Stroke Trial 3, which likely contained the largest number of AF cases, demonstrated a trend toward improved outcome in its rt-PA-treated group [14]. In the Virtual International Stroke Trials Archive, which documented results involving 1631 AF stroke patients, a similar magnitude of benefit with rt-PA compared with placebo for patients with AF and without AF was reported [6] and it was demonstrated that the presence of AF had no independent influence on stroke outcome relative to the untreated comparators. Similarly, Visnja *et al.* recently reported a prospective study of 734 ischemic stroke patients (including 155 with AF) who received rt-PA thrombolysis. The results indicated a trend that ischemic stroke patients with AF treated intravenously with rt-PA had worse outcomes because they were older and had more serious dysfunction at baseline; AF was not an independent predictor of a bad outcome or death [7]. Later, in 2013 [3], a study also supported a similar trend for a favorable outcome after rt-PA among stroke patients with AF,

In the present study, the rt-PA treatment group had a better outcome at 3 months and, as shown by logistic

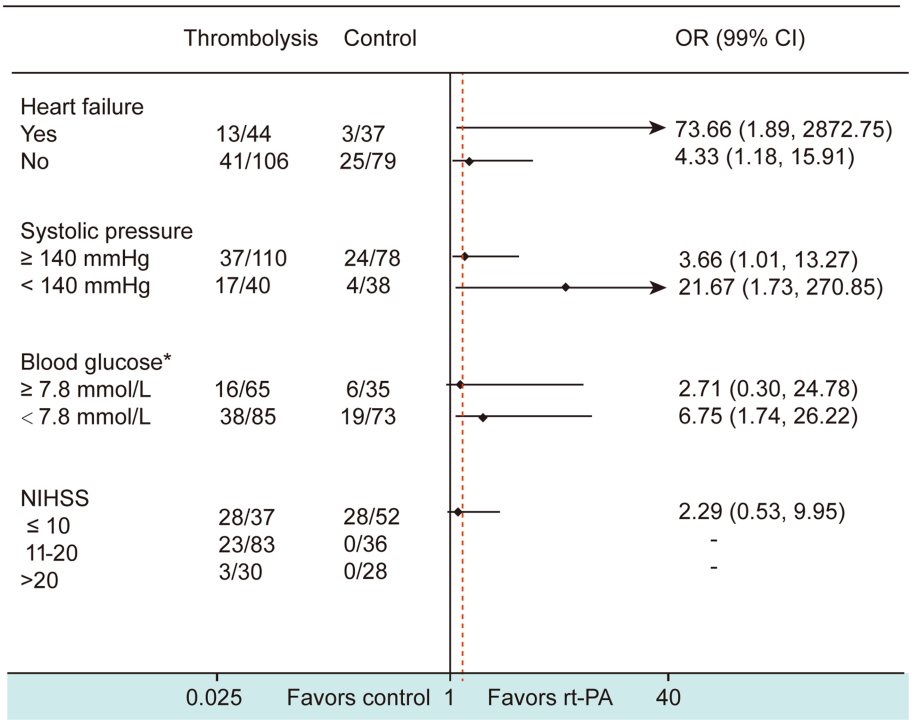

Fig. 2 Effect of thrombolysis on a favorable outcome (mRS 0–1 at 3 months) in stroke patients with atrial fibrillation. Data on the *left* represent the number of patients with mRS 0–1 at 3 months/total number of patients in each subgroup divided according to the variables heart failure, systolic pressure, blood glucose, and NIHSS score. *Asterisk* eight patients lacked blood glucose data at admission. The treatment OR in each subgroup has been adjusted for gender, smoking, drinking, and other key variables (heart failure, systolic pressure, blood glucose, and NIHSS score at admission). *Diamonds* represent the OR value. *Lines without arrows* indicate the range of 99%CI. *Lines with arrows* mean that the OR or 99%CI exceeds the upper limit of the scale (40) shown at the *bottom*. The *red dash line* shows the location of total OR of the effect of rt-PA therapy versus conventional therapy on favorable outcome.

regression analysis, intravenous thrombolysis was independently associated with a better outcome (mRS 0–1). We again showed that intravenous thrombolysis was beneficial for cerebral infarction patients with AF. Heart failure, high systolic blood pressure, high blood glucose, and a high NIHSS score at admission were the risk factors for a poor prognosis. Congestive heart failure is known to increase mortality at 3 months in AF-related stroke patients [15, 16]. However, based on our subgroup analysis, AF-related ischemic stroke patients with heart failure still benefited from intravenous rt-PA thrombolysis.

Moreover, data from our study suggested that thrombolysis is beneficial for AF-related ischemic stroke patients with heart failure, high BP, or an NIHSS score of 11–20. This finding may guide physicians to administer rt-PA sooner and more aggressively to this type of patient.

In the baseline characteristics of this study, more smoking patients appeared in the rt-PA treatment group than those without. Anna *et al.* found that smoking is probably independently associated with recanalization and reperfusion in rt-PA therapy [17]. However, this study did not have sufficient weight to support this assumption (OR 0.63, 95%CI 0.30–1.34, $P = 0.632$) by univariate and multivariate logistic regression analyses. Similar to previous studies [12, 13, 18–20], we found a higher rate of ICH (26.5% *vs* 1.7%) and SICH (13.9% *vs* 1.7%) in AF-related ischemic stroke with thrombolysis than without, which could result in a higher mortality in AF-related ischemic stroke patients with rt-PA treatment. However, the AF ischemic stroke patients with rt-PA who were alive and independent (mRS 0–1) at 3 months were increased (36% *vs* 24.1%) in contrast to previous reports. This may be due to early arterial recanalization, which is recognized as a marker of a favorable prognosis after thrombolysis with rt-PA [21–23].

The current study has some limitations: (1) it was a small-scale and non-randomized study so it may be difficult to evaluate the real efficacy of rt-PA in every patient; (2) no classification of AF types and related response differences was carried out (one study found a relationship between patients with chronic AF and risk of poor prognosis compared with other types of AF [24]); (3) the follow-up time was short and did not provide data on longer-term prognosis; long-term survival (e.g., 2 years) may be a better predictor of response to intravenous thrombolysis with rt-PA; (4) no analysis of other factors that may

influence prognosis, such as intracranial infarct size, biochemical indicators, the region of stroke, and history of other diseases, was carried out; and (5) basic differences between enrolled patients that may affect prognosis could not be excluded (for instance, different smoking patterns between the two groups). Additional studies are needed to clarify these problems.

We conclude that intravenous rt-PA thrombolysis is beneficial for ischemic stroke patients with AF, including those with heart failure, high systolic blood pressure, and a high NIHSS score at admission.

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