Unfavorable Outcome of Thrombolysis in Chinese Patients with Cardioembolic Stroke: a Prospective Cohort Study

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Keywords

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SUMMARY

Background: Thrombolysis with alteplase is an effective and safe treatment for acute ischemic stroke (AIS). It is controversial whether the outcome of thrombolysis in cardioembolic stroke is different from that of other stroke subtypes. This study compares the outcomes at 3 months postthrombolysis in Chinese patients with AIS secondary to cardioembolism (CE) to the outcomes of those with large-artery atherosclerosis (LAA). **Methods:** Using the Thrombolysis Implementation and Monitoring of Acute Ischemic Stroke in China (TIMS-China) cohort, we prospectively followed 827 patients treated within 4.5 h of onset symptoms with alteplase as an intravenous thrombolytic agent. CE and LAA were defined according to TOAST criteria. We compared symptomatic intracerebral hemorrhage (SICH), mortality, and functional outcome at 3 months using multivariable logistic regression analysis. **Results:** In this cohort, 221 (19.6%) had CE and 606 (53.7%) had LAA. Approximately 2/3 of patients with CE had atrial fibrillation. Symptoms at onset were more severe in patients with CE than in those with LAA (NIHSS, 15.0 vs. 11.0; $P < 0.0001$); increased rate of SICH (5.9% vs. 0.8%; $P < 0.0001$); higher mortality (18.6% vs. 10.3%; $P = 0.0015$); and reduced functional independence (43.6% vs. 55.9%; $P = 0.0018$) at 3-month follow-up. After adjustment for baseline variables, the clinical outcome of patients with CE was worse than that of patients with LAA (OR, 0.62; 95% CI, 0.39 to 0.97, $P = 0.0378$). **Conclusions:** Patients with cardioembolic stroke had more SICH after thrombolysis, and worse clinical outcome at 3-month follow-up compared with those with LAA. This emphasizes the importance of preventing cardioembolism.

Introduction

Cardioembolic stroke accounts for 20% of all ischemic stroke [1] and is associated with high morbidity and mortality. Several factors contribute to the poor outcome including large infarction volume, lack of collateral blood supply, and a high risk of hemorrhage transformation [2–4]. Since 1995, intravenous thrombolysis with recombination tissue plasminogen activator (rtPA) has been used as the most effective therapeutic intervention for acute ischemic stroke (AIS) [5,6]. The National Institute of Neurological Disorders and Stroke (NINDS) team initially reported consistent efficacy of functional outcome across all stroke subtypes [7]. Hsia et al. confirmed the result and suggested intravenous

thrombolysis in the hyperacute stage of stroke should not be delayed by the need for investigations to distinguish the causes of stroke [8]. However, subsequent clinical data and research showed that the outcome may differ according to the different stroke subtypes [9].

The effectiveness of thrombolysis is based on early re-canalization, which may vary according to size, composition, and origin of thrombus. Theoretically, cardioembolic clots, rich in fibrin and red blood cells, are more lysable compared to the more organized platelet-rich atherosclerotic clot. Limited studies to date have showed conflicting results [10,11]. Molina et al. reported early and more complete proximal middle cerebral artery (MCA) recanalization after rtPA in patients with cardioembolic stroke

compared with other stroke subtypes [10]. However, Nam *et al.* found that cardioembolism was an independent predictive factor for poor thrombolysis outcome at 3 months [11].

Few thrombolysis trials, including those from China, compared outcomes following intravenous rtPA by stroke subtypes [6,12]. This study aims to compare the stroke outcomes of cardioembolism (CE) and large-artery atherosclerosis (LAA) at 3 months post-rtPA thrombolysis, using the Thrombolysis Implementation and Monitoring of Acute Ischemic Stroke in China (TIMS-China) database.

Materials and Methods

Patients and Study Design

We screened consecutive patients registered in TIMS-China, a nationwide prospective stroke registry of intravenous rtPA treated patients with AIS from 67 major stroke centers across China [12]. The inclusion criteria were as follows: (1) age 18–80 years; (2) clinical diagnosis of ischemic stroke; (3) computed tomography (CT) or magnetic resonance imaging (MRI) scan confirming AIS; (4) no contraindication for thrombolysis therapy; and (5) thrombolized within 4.5 h of onset of symptoms. All patients (or their next of kin when appropriate) gave written consent. The study protocol was approved by the Ethics Committee of Beijing Tiantan Hospital and followed by all participating centers.

The baseline data, including sex, age, vascular risk factors such as hypertension, diabetes, hyperlipidemia, smoking habit, and current medication (including anticoagulant/antiplatelet), were recorded. Clinical assessments and outcome measures, including National Institutes of Health Stroke Scale (NIHSS) on admission; symptomatic intracerebral hemorrhage (SICH) on CT or MRI at 24 to 36 h; modified Rankin scale (mRS) on day 90; and death by day 90, were also prospectively collected.

TOAST criteria [13] were used to classify the subtype of stroke, based on medical and radiological data. We carried out 24 h ambulatory electrocardiogram, ambulatory blood pressure monitor, transthoracic/transesophageal echocardiogram, carotid duplex ultrasound, and transcranial Doppler (TCD). Some cases had additional CT angiography, MR angiography, or digital subtraction angiography. The diagnosis of LAA was based on clinical and imaging evidence of either significant (>50%) stenosis or occlusion of a major brain artery. The diagnosis of cardioembolic stroke was made based on evidence of atrial fibrillation, cardiac conditions that predispose to emboli formation such as postinfarction akinetic left cardiac ventricular wall and dilated cardiomyopathy, and/or stroke involving multiple arterial territories on imaging. The final evaluation and diagnosis of stroke subtypes were made by experienced stroke physicians.

Clinical Outcomes

Clinical outcomes at 3 months were measured by mRS at clinic follow-ups or telephone interview. The definition of self-independence was mRS ≤ 2. Hemorrhagic transformations were assessed by CT or MRI at 24–36 h after thrombolysis or whenever clinical deterioration was suspected. SICH was defined according to the

Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [14].

Statistical Analysis

The chi-square (χ^2) test was used to compare categorical variables. The t-test or Mann–Whitney *U*-test was used to compare means or medians for continuous variables. Univariable and multivariable logistic regression were used to analyze 95% confidence intervals (CI) and odds ratios (OR) of clinical outcome comparisons between CE and LAA groups. Variables with significant differences in all univariable analysis were included in the multivariable model to calculate adjusted OR. All analyses were performed with SAS software version 9.1.3. Difference significance was defined with a two-sided alpha level of 5%.

Results

Baseline Characteristics of Study Patients

Between May 2007 and April 2012, there were 1440 consecutive patients of AIS who received thrombolysis, registered in TIMS-China. Of those, 322 patients were excluded because of incomplete data ($n = 15$) or because they had been thrombolized outside the 4.5 h time window ($n = 307$). Based on TOAST criteria, a further 291 patients were excluded: 117 of small vessel disease and 174 had other/undetermined etiology. Finally, a total of 827 patients were included in the study: 221 (19.6%) with CE and 606 (53.7%) with LAA (Figure 1).

The demographic and baseline clinical characteristics of patients in the study are shown in Table 1. Compared with the LAA group, there were more females in the CE group. Patients in the CE group were older and had a higher prevalence of atrial fibrillation (65.6% vs. 6.6%; $P < 0.0001$). In the LAA group, patients with atrial fibrillation had severe atherosclerotic disease (>70% stenosis or occlusion) corresponding to the location of cerebral lesion; and

Figure 1 Numbers of Eligible Patients.

Table 1 Demographic and baseline characteristics of the patients

Variables	LAA (N = 606)	CE (N = 221)	P- value
Mean age (years)	63.6 ± 10.8	67.2 ± 10.2	<0.0001
Sex female (%)	208 (34.3)	120 (54.3)	<0.0001
Medical history (%)			
Independence (mRS 0–1) prior to stroke	569 (94.2)	213 (96.8)	0.13
Atrial fibrillation	40 (6.6)	145 (65.6)	<0.0001
TIA	60 (9.9)	12 (5.43)	0.04
Hypertension	374 (61.7)	130 (58.8)	0.45
Diabetes mellitus	131 (21.6)	28 (12.7)	<0.01
Hyperlipidemia	48 (7.9)	12 (5.4)	0.22
Previous stroke	126 (20.8)	46 (20.8)	0.99
Current smoking	234 (38.6)	38 (17.2)	<0.0001
Previous smoking	272 (44.9)	50 (22.6)	<0.0001
Mean blood glucose (mmol/L)	8.00 ± 3.40	7.43 ± 2.34	0.26
Receiving antiplatelet drug in 24 h prior to thrombolysis (%)	87 (14.4)	44 (19.9)	0.05
Receiving anticoagulants in 24 h prior to thrombolysis (%)	6 (1.0)	8 (3.6)	0.02
Systolic blood pressure (mmHg)	150 ± 21	145 ± 22	<0.01
Diastolic blood pressure (mmHg)	86 ± 12	86 ± 14	0.70
Median NIHSS score (IQR)	11 (8–16)	15 (10–19)	<0.0001
Median stroke onset to treatment time (IQR) (min)	170 (140–192)	170 (140–206)	0.48
INR prior to thrombolysis	1.01 ± 0.12	1.03 ± 0.12	0.01
Patients with standard dosage of rtPA (%)	413 (68.2)	154 (69.7)	0.67
Mean rtPA dose (mg)	56.8 ± 10.7	54.8 ± 12.4	<0.01
Mean weight (kg)	67.0 ± 11.2	64.2 ± 13.2	<0.001

Variables are mean ± standard deviation or number (%). IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; TIA, transient ischemic attack. LAA, large-artery atherosclerosis; CE, cardioembolism.

a recent history of TIA involving the same territory prior to stroke, supporting the diagnosis of LAA. Patients with LAA were more likely to be ex- or current smoker and had a higher prevalence of diabetes (21.6% vs. 12.7%; $P < 0.01$) and previous TIA prior to the stroke (9.9% vs. 5.4%; $P = 0.04$). More patients in the CE group had been taking antiplatelets or anticoagulants, but not both, 24 h prior to thrombolysis. NIHSS scores on admission were significantly higher in the CE group compared to those in the LAA group (15.0 vs. 11.0; $P < 0.0001$). Of note, there was no significant difference in time to treat, from onset to thrombolysis. In addition, in both groups, an equivalent proportion of patients was treated with standard full dosage of rtPA (69.7% in CE vs. 68.2% in LAA; $P = 0.67$).

Symptomatic Intracerebral Hemorrhage (SICH)

Patients with CE have a higher SICH rate at 24–36 h postthrombolysis (5.9% vs. 0.8%; $P < 0.0001$). After multivariable adjustment, patients with CE were nearly 11 times more likely to suffer from SICH (OR, 10.67; 95% CI 2.94 to 38.81; $P = 0.0003$).

Clinical Outcome

The clinical outcomes at 3 months are shown in Figure 2. The functional independence rate (mRS 0–2) at 3 months was significantly lower in the CE group compared with that of LAA group (43.6% vs. 55.9%; $P = 0.002$). After adjusted for all confounding variables (age, sex, vascular risk factors, medicine, blood pressure,

Figure 2 Distribution of scores on the modified Rankin Scale in patients with cardioembolism and large-artery atherosclerosis.

NIHSS at admission, and body weight), the proportion of patients with good functional outcome was significantly lower in the CE group compared to that in the LAA group (OR, 0.62; 95% CI 0.39 to 0.97; $P = 0.0378$).

In total, 102 patients died within 3 months of thrombolysis (Table 2). Of these, 41 (18.6%) were in the CE group and 61 (10.3%) in the LAA group. After adjusting for multivariables, the CE group showed a trend toward a higher mortality rate, but this was not statistically significant (OR, 1.78; 95% CI 0.96 to 3.26; $P = 0.0657$).

Discussion

This prospective study using the TIMS-China registry showed an unfavorable outcome following thrombolysis in stroke patients

Table 2 Safety and functional outcome

Outcome	LAA n/N (%)	CE n/N (%)	Unadjusted OR (95% CI)	P-value	Adjusted OR* (95% CI)	P-value
SICH (SITS-MOST definition)	5/606 (0.8)	13/221 (5.9)	7.51 (2.65–21.33)	0.0002	10.67 (2.94–38.81)	0.0003
Mortality at 3 months	61/592 (10.3)	41/220 (18.6)	1.99 (1.30–3.07)	0.0017	1.77 (0.96–3.26)	0.0657
mRS 0–2 at 3 months	330/590 (55.9)	96/220 (43.6)	0.61 (0.45–0.83)	0.0019	0.62 (0.39–0.97)	0.0378

SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; mRS, modified Rankin Scale; LAA, large-artery atherosclerosis; CE, cardioembolism. *Adjusted for age, sex, atrial fibrillation, TIA, diabetes mellitus, current and previous smoking, prior medication (antiplatelet, anticoagulation therapy), systolic blood pressure, admission NIHSS score, INR prior to thrombolysis, body weight.

with CE compared to those with LAA. Patients with CE had a higher risk of postthrombotic SICH, were less likely to be functional independent (mRS 0–2 43.6% vs. 55.9%; $P = 0.0378$), and showed a trend of higher mortality rate (18.6% vs. 10.3%; $P = 0.0657$) at 3 months. These findings are consistent with the results of Korean study by Kim et al. [15].

Meta-analysis showed that recanalization is associated with a good clinical outcome in patients with AIS [16]. Intravenous thrombolysis with rtPA is currently the most effective therapy for recanalization. Successful recanalization depends on the site of the artery occlusion and the lytic susceptibility of the clots.

Saqqur et al., using early TCD, demonstrated that proximal artery occlusion (e.g., distal internal carotid artery) was least likely to respond to thrombolysis and was associated with poor long-term outcomes [17]. Sato et al. showed that emboli from the left atrium might be three times larger than atherothrombotic emboli [18], resulting in a greater likelihood of a sudden larger vessel occlusion in CE. Large vessel occlusion secondary to LAA usually occurs over time with the development of collateral perfusion, resulting in production of smaller infarct. In their cohort stroke study of patients with CE or non-CE, Nam et al. found that overall initial recanalization rates were similar, but the recanalization in patients with CE was less likely to be complete (19% vs. 39%; $P = 0.011$) [11], resulting in a higher rate of re-occlusion and poor outcome [10,19].

In our study, we did not have data on the site of occlusion before thrombolysis or early recanalization. However, high NIHSS on admission in patients with CE indirectly suggested more proximal occlusion and larger ischemic volume.

Besides location, the actual structure of thrombi may also attribute to their lytic susceptibility. It is assumed that cardiogenic emboli are rich in fibrin and red cells, whereas atherosclerotic plaques are platelet-rich and well organized, but to date there is little histological data. A single *in vitro* study showed that clots rich in fibrin and red cells were more susceptible to thrombolytic agents than platelet-rich well-organized thrombi [20]. However, Marder et al. studied the thrombi retrieved from cerebral arteries in patients with acute stroke and showed similar histological components, whether derived from cardiac or arterial sources, suggesting it was the size of the thrombi that determined the outcome [21]. Molina et al. studied early MCA recanalization by TCD and showed that CE had faster and more complete recanalization compared with other stroke subtypes, resulting in a better outcome [10]. This differs from the results of our study. However, this can be partially explained when the sites of occlusion are taken into account, that is proximal occlusion as explained above, and also that the composition of cardioembolic may not all be as

previously suggested. Indeed, Urbach et al. showed significantly less recanalization in patients with confirmed cardiac emboli detected by transesophageal echocardiogram [22].

Patients with CE have relatively higher risk of hemorrhagic transformation [23,24]. In this study, the rate of postthrombolysis SICH was higher in patients with CE. SICH may offset the benefits of thrombolysis. Similar results were reported by Strbian [25] and Goldstein [26]. Some patients with CE in our study were on antiplatelet or oral anticoagulant therapy prior to thrombolysis. However, studies have showed that aspirin and warfarin (if INR ≤ 1.7) did not increase the risk of hemorrhage [15,27]. Therefore, the high incidence of SICH may be due to large-artery occlusion. Nam and Saqqur had shown that SICH transformation is usually related to persistent blood vessel occlusion or incomplete recanalization [11,28].

Although this is a large, prospective cohort study, there are some possible limitations. Firstly, we used TOAST criteria for classification of stroke subtypes. TOAST criteria are widely used, but are limited in that coexisting vascular conditions are not reflected (e.g., evidence of small vessel disease in the presence of severe large vessel obstructions) [29]. Secondly, most patients did not have early recanalization data available. Thirdly, TIMS-China registry included patients received lower dosage of rtPA (0.6 mg/kg), and our previous study showed that the standard dosage of intravenous rtPA for stroke is better than the lower dosage [30]. However, in our current study, a similar percentage of patients in CE and LAA received the standard dosage of rtPA (Table 1), so this did not affect the statistical results.

In conclusion, using TIMS-China cohort data, this prospective cohort study found poor outcome at 3 months postthrombolysis in patients with cardioembolic stroke compared with those with large-artery atherosclerotic disease. Our study emphasized the need of further thrombolytic studies in patients with CE to optimize rtPA dosage and the route of thrombolysis. In addition, monitoring of recanalization during and immediately after thrombolysis treatment is essential, as timely intraarterial thrombolysis or mechanical clot retrieval therapies could be applied if intravenous thrombolysis fails to obtain early complete recanalization [31,32]. Finally, because of the unfavorable outcome for patients with cardioembolic stroke, prevention of CE using anticoagulation or other appropriate therapies is most important.

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Conflict of Interest

The authors declare no conflict of interests.

References

- Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2011;**42**:227–276.
- Broderick JP, Phillips SJ, O'Fallon WM, et al. Relationship of cardiac disease to stroke occurrence, recurrence, and mortality. *Stroke* 1992;**23**:1250–1256.
- Jorgensen HS, Nakayama H, Reith J, et al. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke* 1996;**27**:1765–1769.
- Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996;**27**:1760–1764.
- Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;**363**:768–774.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;**359**:1317–1329.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–1587.
- Hsia AW, Sachdev HS, Tomlinson J, et al. Efficacy of IV tissue plasminogen activator in acute stroke: Does stroke subtype really matter? *Neurology* 2003;**61**:71–75.
- Mustanoja S, Meretoja A, Putaala J, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: Descriptive subtype analysis. *Stroke* 2011;**42**:102–106.
- Molina CA, Montaner J, Arenillas JF, et al. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke* 2004;**35**:486–490.
- Nam HS, Lee KY, Kim YD, et al. Failure of complete recanalization is associated with poor outcome after cardioembolic stroke. *Eur J Neurol* 2011;**18**:1171–1178.
- Liao XL, Wang CX, Wang YL, et al. Implementation and outcome of thrombolysis with alteplase 3 to 4.5 h after acute stroke in Chinese patients. *CNS Neurosci Ther* 2013;**19**:43–47.
- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41.
- Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): An observational study. *Lancet* 2007;**369**:275–282.
- Kim YD, Lee JH, Jung YH, et al. Safety and outcome after thrombolytic treatment in ischemic stroke patients with high-risk cardioembolic sources and prior subtherapeutic warfarin use. *J Neurol Sci* 2010;**298**:101–105.
- Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: A meta-analysis. *Stroke* 2007;**38**:967–973.
- Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007;**38**:948–954.
- Sato Y, Ishibashi-Ueda H, Iwakiri T, et al. Thrombus components in cardioembolic and atherothrombotic strokes. *Thromb Res* 2012;**130**:278–280.
- Heo JH, Lee KY, Kim SH, et al. Immediate reocclusion following a successful thrombolysis in acute stroke: A pilot study. *Neurology* 2003;**60**:1684–1687.
- Blinic A, Planinsic G, Keber D, et al. Dependence of blood clot lysis on the mode of transport of urokinase into the clot—a magnetic resonance imaging study in vitro. *Thromb Haemost* 1991;**65**:549–552.
- Marder VJ, Chute DJ, Starkman S, et al. Analysis of thrombi retrieved from cerebral arteries of patients with acute ischemic stroke. *Stroke* 2006;**37**:2086–2093.
- Urbach H, Hartmann A, Pohl C, et al. Local intra-arterial thrombolysis in the carotid territory: Does recanalization depend on the thromboembolus type? *Neuroradiology* 2002;**44**:695–699.
- Terruso V, D'Amelio M, Di Benedetto N, et al. Frequency and determinants for hemorrhagic transformation of cerebral infarction. *Neuroepidemiology* 2009;**33**:261–265.
- Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: Results of a prospective multicenter study. *Stroke* 2008;**39**:2249–2256.
- Strbian D, Sairanen T, Meretoja A, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology* 2011;**77**:341–348.
- Goldstein JN, Marrero M, Masur S, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol* 2010;**67**:965–969.
- The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997;**28**:2109–2118.
- Saqqur M, Tsvigoulis G, Molina CA, et al. Symptomatic intracerebral hemorrhage and recanalization after IV rt-PA: A multicenter study. *Neurology* 2008;**71**:1304–1312.
- Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici G. Classification of stroke subtypes. *Cerebrovasc Dis* 2009;**27**:493–501.
- Liao XL, Wang YL, Pan YS, et al. Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. *Stroke* 2014;**45**:2354–2358.
- Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. *Stroke* 2005;**36**:1432–1438.
- Ims II. Trial Investigators. The Interventional Management of Stroke (IMS) II Study. *Stroke* 2007;**38**:2127–2135.