Intravenous Thrombolysis Is Safe and Effective for the Cryptogenic Stroke in China: Data From the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China)

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Background: The intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) therapy is safe and efficient during the treatment of acute ischemic stroke. Nonetheless, the different outcomes among various stroke subgroups have limited data with regard to the safety and efficacy of cryptogenic stroke (CS). The present study compared the safety and efficacy when IVT with rt-PA was used for the treatment of CS and the other stroke subtypes. *Methods:* This study classified the IVT with rt-PA patients within 4.5 hours after stroke onset, based on the trial of ORG 10172 in acute stroke treatment criteria in terms of diagnostic evaluation. The data were obtained from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China database, a large multicenter prospective registry. A multivariable logistic regression model was employed to compare the differences between the subtypes in symptomatic intracerebral hemorrhage (sICH) within 7 days and studied the mortality and the outcome during 90 days. *Results:* In total, 1118 patients were recruited; of these, 131 (11.7%) suffered from CS and 987 (88.3%) with the other etiology. In the CS group, patients were younger than those in the other etiology groups ($P < .001$). Moreover, it had a lower prevalence of previous stroke ($P = .0117$), receiving antiplatelet drug in 24 hours prior to thrombolysis ($P = .0017$), and functional independence (mRS > 1 before stroke, $P = .003$). The CS group had lower blood pressure (systolic blood pressure $P = .0001$; diastolic blood pressure; $P = .0212$) before thrombolysis, atrial fibrillation ($P < .001$), and diabetes mellitus ($P = .0005$). Transient ischemic attack, hypertension, hyperlipidemia, blood glucose, receiving anticoagulants in 24 hours prior to thrombolysis, and standard dosage of rt-PA were equally distributed in both groups. After the adjustment of confounders between the CS and the other subgroups, no obvious differences were observed in sICH rate and mortality ($P > .05$) The CS patients exhibited excellent recovery (mRS, 0-1; 63.78%) and functional independence (mRS, 0-2; 74.8%) than the large artery atherosclerosis patients. *Conclusions:* IVT with rt-PA is a safe and effective method for the treatment of CS patients.

Key Words: Cryptogenic stroke—intravenous thrombolysis—outcome—Acute ischemic stroke

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Introduction

Cryptogenic stroke (CS) is a symptomatic cerebral infarct. The sufficient diagnostic evaluation cannot identify the potential causes. The cryptogenic mechanisms underlying all ischemic strokes were 10%-40%.[1] Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) is yet a therapeutic method with efficacy and safety for acute ischemic stroke (AIS). Nonetheless, whether different outcomes exist among various stroke subgroups remain unclear, especially due to the limited data on the safety and efficacy of CS. The trial by National Institute of Neurological Disorders and Stroke (NINDS) found that IVT with rt-PA results in a favorable outcome despite the stroke subtype that is diagnosed at the baseline; however, it does not include CS in the analysis.[2] As reported by the European Cooperative Acute Stroke Study (ECASS) I, II, and III, a study on the benefit based on the etiologic subgroups is yet lacking.[3-5] As the largest stroke thrombolysis registry, Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) includes 228 stroke patients with unknown etiology; it does not analyze the impact of stroke etiology on the therapeutic effect of IVT with rt-PA on patients.[6] Few thrombolysis trials have compared the outcomes of IVT with rt-PA by stroke subtypes. The data were obtained from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) database, a large multicenter prospective registry and used for comparing the differences of IVT with rt-PA between CS and the other stroke subtypes with respect to safety and efficacy.

Methods

Population

The present study enrolled patients in TIMS-China, which is a national prospective stroke registry related to IVT with rt-PA and records the subjects, suffering from AIS at 67 main Chinese stroke centers.[7] The Ethics Committee of Beijing Tiantan Hospital approved the research protocol in compliance with the Helsinki Declaration. There are 2 organizations independently responsible for this registry: the Quality Monitoring Committee of TIMS-China and the Contract Research Organization. The informed consent was signed by the subjects or their legal representatives prior to IVT. The National Institutes of Health Stroke Scale (NIHSS) was measured at different time points: baseline, 2 hours, 24 hours, and 7 days. The modified Rankin scale (mRS) was measured at 7 days and 90 days. Only the neurologists, who had been trained and were qualified for using NIHSS and mRS, recorded the scores. The brain imaging computed tomography (CT) and magnetic resonance (MR) were performed at baseline, 24 hours, and 7 days (or at discharge). The imaging findings were interpreted by at least 2 experienced radiologists at each of the participating centers. This analysis included all patients who received IVT with rt-PA within 4.5 hours in the database of TIMS-China. The criteria of Trial of Org 10172 in Acute Stroke Treatment were used for the classification of the stroke subtypes[8]: large artery atherosclerosis (LAA), small artery occlusion (SAO), cardioembolism (CE), stroke of other determined cause, and stroke of undetermined cause CS. The etiological subtype of the stroke was based on the clinical characteristics and diagnostic test outcomes after standard evaluation, such as brain imaging on CT or MRI, and cerebral artery on computed tomographic angiography, magnetic resonance angiography, echocardiography, electrocardiography, and laboratory test.

Safety and Efficacy Outcomes

The safety outcomes included symptomatic intracranial hemorrhage (sICH) after the treatment of IVT with rt-PA, and mortality within 7 days and 90 days. sICH was defined by the following 3 criteria: (1) SITS-MOST protocol[6] was local or remote parenchymal hemorrhage type 2 within 22-36 hours after treatment. It combined a neurological deterioration of ≥4 points on NIHSS from baseline or the lowest NIHSS value between baseline and 24 hours or led to death. (2) NINDS study[2]: No hemorrhage on CT scan was observed previously. Then, a suspicion of hemorrhage or the decrease in neurological status might appear. (3) ECASS II study,[4] any intracranial bleeding or clinical worsening presents NIHSS score ≥4. The efficacy outcomes included excellent recovery (mRS, 0-1) and functional independence (mRS, 0-2) at 90 days.[9]

Statistical Analysis

This study compared the data at baseline of the CS group and the other stroke subtype groups. The continuous variables and medians were analyzed using the one-way ANOVA and Kruskal-Wallis H test. The χ^2 method was used for the calculation of significant differences among the proportions. For comparing the outcomes after IVT with rt-PA between the groups, the univariate and multivariate logistic regression models calculated the odds ratios (ORs) in 95% confidence intervals (CIs) and adjusted the ORs in 95% CIs. The baseline variables showed possible associations among the confounding factors with the consequences from univariate analysis ($P < .05$) that were entered into the multivariate model. Statistical significance was defined as $P < .05$. SAS statistical software was employed for all analyses (version 9.3, SAS Institute Inc., Cary, NC).

Results

From May 2007 to April 2012, the TIMS-China database enrolled 1440 consecutive subjects who gained rt-PA. Due to the lack of data, 15 subjects were excluded, while 307 patients were excluded as the IVT exceeded the 4.5 hours window. Finally, based on the criteria of Trial of Org 10172 in Acute Stroke Treatment, 1118 participants were recruited in this study, among which 606 (54.2%) suffering from LAA, 221 (19.8%) suffered from cardioembolism, 131 (11.7%) suffering from CS, 117 (10.5%) suffered small vessel disease, and 43 (3.8%) suffered from other determined etiology (Fig 1).

Baseline Characteristics

Table 1 demonstrated the clinical information at baseline of subjects in this study. In the CS group, patients were younger than those in the other etiology groups (59.73 ± 12.7 years, $P < .001$). Moreover, it had a lower prevalence of previous stroke (9.16%; $P = .0117$), receiving antiplatelet drug in 24 hours prior to thrombolysis (4.58%; $P = .0017$), and functional independence (mRS > 1 before stroke, 0%; $P = .003$). Significant differences were observed between CS and other etiology groups regarding the major risk factors for stroke such as atrial fibrillation (4.58%; $P < .001$) and diabetes mellitus (8.4%; $P = .0005$). The CS group had lower blood pressure (systolic blood pressure 142.01 ± 20.3; $P = .0001$; diastolic blood pressure 83.11 ± 12.74; $P = .0212$) before thrombolysis. Patients in the CE group were less male (45.7%; $P < .001$), significantly lower smoking (current smoking 17.19; $P < .001$; previous smoking 22.62%; $P < .001$), lighter weight (64.15 ± 13.21; $P = .0125$), and higher NIHSS scores (15; $P < .001$) at the time of admission than others. Because of lighter weight, the dose of rt-PA was also less in patients suffered from CE. In the CS and SAO, groups had shorter stroke onset to treatment time (2.73 hours; 2.75 hours; $P = .0013$). However, there were no obvious differences in the other baseline variables (e.g., transient ischemic attack, hypertension, hyperlipidemia, blood glucose, receiving anticoagulants in 24 hours prior to thrombolysis, standard dosage of rt-PA) in all subgroups ($P > .05$).

Safety and Efficacy Outcomes

Table 2 demonstrated the safety and efficacy consequences. In all etiology subgroups, mRS scores at 90 days were compared in Figure 2. Twenty-three patients (2.1%) were lost to follow-up at 90 days. In the SAO group, there was no sICH which was significant according to the SITS-MOST, NINDS, and ECASS II criteria. Based on the adjustment of the distinct variables in the univariable analysis (age, gender, independence before stroke, atrial fibrillation, diabetes mellitus, previous stroke, smoking, receiving antiplatelet drug in 24 hours prior to thrombolysis, blood pressure, NIHSS score, INR prior to thrombolysis, rt-PA dose, and weight), no obvious differences were noted in sICH rate in the LAA, CS, and other determined cause groups despite the evaluation by SITS-MOST, NINDS, or ECASS II criteria ($P > .05$). After multivariable adjustment, patients with CE had a higher SICH rate according to the 3 criteria, respectively. Based on the excellent recovery (mRS, 0-1) at 90 days, the CS group was approximately 1.6-fold better than that of the LAA group (63.78% versus 44.41%; OR 1.664, 95% CI: 1.069-2.589, $P = .0241$) after adjusting the significant baseline variables. Furthermore, no difference was noted in the mortality at either 7 days or 90 days. The rate of functional independence demonstrated remarkable differences

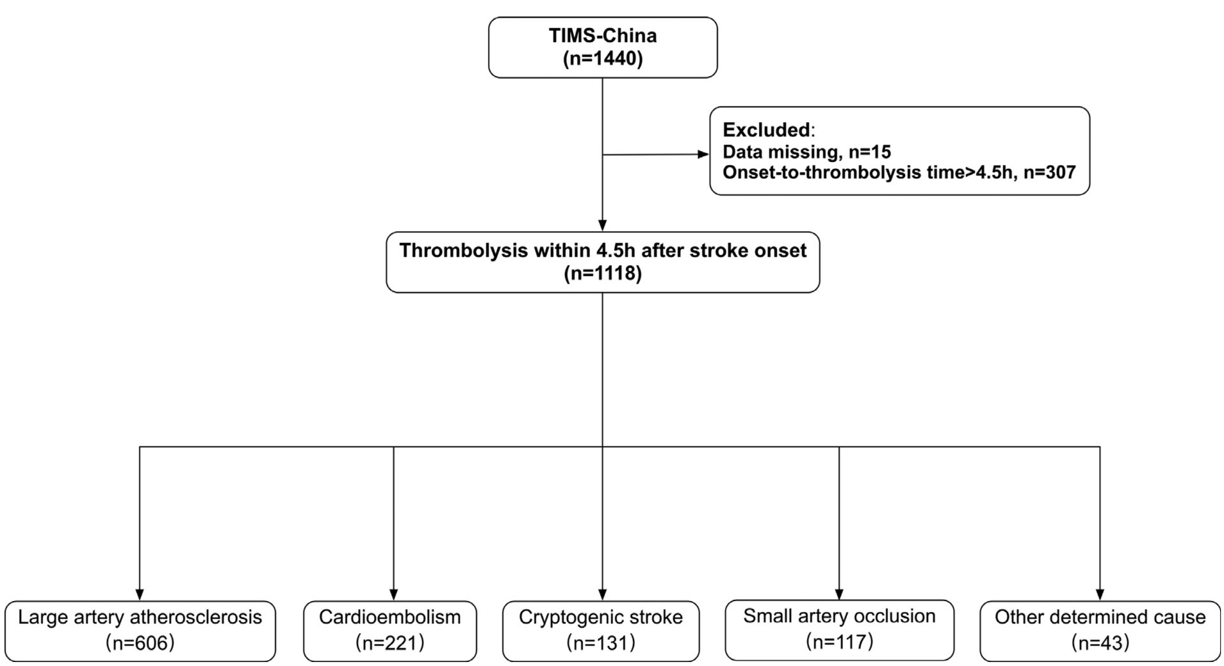

Figure 1. *Flow chart of eligible patients. Abbreviation: TIMS-China, Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China.*

Table 1. *Demographic and baseline clinical characteristics of all etiology subgroups*

Variables	LAA	SAO	CE	CS	Other cause	*P* Value
n	606	117	221	131	43	
age	63.58 ± 10.82	61.13 ± 11.75	67.24 ± 10.22	59.73 ± 12.70	60.12 ± 13.03	<.0001
male	398 (65.68)	73 (62.39)	101 (45.70)	82 (62.60)	26 (60.47)	<.0001
Independence (mRS, 0-1) before stroke	569 (94.21)	117 (100.00)	213 (96.82)	131 (100.00)	41 (95.35)	.003
Atrial fibrillation	40 (6.60)	7 (5.98)	145 (65.61)	6 (4.58)	3 (6.98)	<.0001
TIA	60 (9.90)	15 (12.82)	12 (5.43)	10 (7.63)	5 (11.63)	.1536
Hypertension	374 (61.82)	70 (59.83)	130 (58.82)	63 (48.09)	24 (55.81)	.0746
Diabetes mellitus	131 (21.62)	21 (17.95)	28 (12.67)	11 (8.40)	4 (9.30)	.0004
Hyperlipidemia	48 (7.92)	5 (4.27)	12 (5.45)	4 (3.05)	3 (6.98)	.1988
Previous stroke	126 (20.79)	16 (13.68)	46 (20.81)	12 (9.16)	6 (13.95)	.0117
Current smoking	234 (38.61)	48 (41.03)	38 (17.19)	51 (38.93)	15 (34.88)	<.0001
Previous smoking	272 (44.88)	52 (44.44)	50 (22.62)	57 (43.51)	18 (41.86)	<.0001
Median blood glucose, mmol/L	8.00 ± 3.42	7.62 ± 2.93	7.43 ± 2.34	7.15 ± 2.15	6.94 ± 1.48	.0878
Receiving antiplatelet drug in 24 h prior to thrombolysis (%)	87 (14.36)	13 (11.11)	44 (19.91)	6 (4.58)	5 (11.63)	.0017
Receiving anticoagulants in 24 h prior to thrombolysis (%)	6 (.99)	1 (.85)	8 (3.62)	3 (2.29)	1 (2.33)	.0819
Systolic blood pressure, mm Hg	150.00 ± 20.77	151.44 ± 20.14	145.00 ± 21.61	142.01 ± 20.30	144.51 ± 18.61	.0001
Diastolic blood pressure, mm Hg	86.08 ± 12.35	88.40 ± 11.47	85.68 ± 13.77	83.11 ± 12.74	87.09 ± 13.38	.0212
Median NIHSS score (IQR)	11 (8-16)	7 (5-10)	15 (10-19)	10 (6-13)	7 (3-12)	<.0001
Median stroke onset to treatment time (IQR), h	2.83 (2.33-3.20)	2.73 (2.33-3.00)	2.83 (2.33-3.43)	2.75 (2.17-3.17)	3.33 (2.55-4.00)	.0013
INR prior to thrombolysis	1.01 ± .12	1.04 ± .34	1.03 ± .12	1.01 ± .10	.98 ± .14	.0111
Patients with standard dosage of rt-PA (%)	413 (68.15)	76 (64.96)	154 (69.68)	98 (74.81)	37 (86.05)	.0619
Mean rt-PA dose (mg)	56.84 ± 10.68	57.08 ± 10.79	54.75 ± 12.40	58.15 ± 9.73	58.57 ± 11.68	.0138
Mean weight (kg)	66.98 ± 11.23	66.55 ± 11.43	64.15 ± 13.21	67.29 ± 11.41	66.37 ± 11.93	.0125

Abbreviations: IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; TIA, transient ischemic attack. Variables are mean ± standard deviation or number (%).

Table 2. *Safety and functional outcomes of all etiology subgroups*

Outcome			Unadjusted OR (95% CI)	*P* Value	Adjusted OR*	*P* Value
SICH (per SITS-MOST)	LAA n/N (%)	5/606 (.83)	1	-	1	-
	SAO n/N (%)	0/117 (0.00)	-	-	-	-
	CE n/N (%)	13/221 (5.88)	7.512 (2.646-21.327)	.0002	18.567 (4.407-78.222)	<.0001
	CS n/N (%)	2/131 (1.53)	1.864 (.358-9.711)	.4599	4.411 (.688-28.287)	.1176
	Other cause	1/43 (2.33)	2.862 (.327-25.058)	.3422	6.115 (.571-65.455)	.1344
SICH (per ECASS II)	LAA n/N (%)	15/606 (2.48)	1	-	1	-
	SAO n/N (%)	0/117 (0.00)	-	-	-	-
	CE n/N (%)	23/221 (10.41)	4.577 (2.342-8.945)	<.0001	6.082 (2.451-15.095)	<.0001
	CS n/N (%)	2/131 (1.53)	.611 (.138-2.704)	.5161	.861 (.182-4.075)	.8504
	Other cause	1/43 (2.33)	.938 (.121-7.275)	.9512	1.398 (.168-11.639)	.7569
SICH (per NINDS)	LAA n/N (%)	27/606 (4.46)	1	-	1	-
	SAO n/N (%)	0/117 (0.00)	-	-	-	-
	CE n/N (%)	27/221 (12.22)	2.985 (1.709-5.213)	.0001	2.771 (1.294-5.935)	.0087
	CS n/N (%)	3/131 (2.29)	.503 (.150-1.682)	.2644	.615 (.177-2.133)	.4435
	Other cause	1/43 (2.33)	.511 (.068-3.850)	.5143	.721 (.092-5.672)	.756
Mortality at 7 d	LAA n/N (%)	32/605 (5.29)	1	-	1	-
	SAO n/N (%)	0/117 (0.00)	-	-	-	-
	CE n/N (%)	23/221 (10.41)	2.080 (1.189-3.640)	.0103	2.235 (1.004-4.979)	.049
	CS n/N (%)	2/131 (1.53)	.278 (.066-1.173)	.0814	.391 (.085-1.806)	.2292
	Other cause	1/43 (2.33)	.426 (.057-3.197)	.4069	.596 (.070-5.070)	.6354
Mortality at 3 mo	LAA n/N (%)	61/592 (10.30)	1	-	1	-
	SAO n/N (%)	1/115 (.87)	.076 (.010-.557)	.0111	.143 (.017-1.188)	.0717
	CE n/N (%)	41/220 (18.64)	1.994 (1.296-3.067)	.0017	1.767 (.944-3.308)	.0751
	CS n/N (%)	6/127 (4.72)	.432 (.182-1.022)	.056	.728 (.280-1.898)	.5168
	Other cause	1/43 (2.33)	.207 (.028-1.533)	.1232	.397 (.050-3.158)	.3828
mRS 0-1 at 3 mo	LAA n/N (%)	262/590 (44.41)	1	-	1	-
	SAO n/N (%)	74/115 (64.35)	2.259 (1.492-3.421)	.0001	1.383 (.872-2.191)	.168
	CE n/N (%)	82/220 (37.27)	.744 (.541-1.022)	.0681	.862 (.548-1.356)	.5208
	CS n/N (%)	81/127 (63.78)	2.204 (1.483-3.277)	<.0001	1.664 (1.069-2.589)	.0241
	Other cause	27/43 (62.79)	2.113 (1.115-4.004)	.0219	1.277 (.632-2.582)	.4957
mRS 0-2 at 3 mo	LAA n/N (%)	330/590 (55.93)	1	-	1	-
	SAO n/N (%)	90/115 (78.26)	2.836 (1.769-4.547)	<.0001	1.797 (1.060-3.044)	.0294
	CE n/N (%)	96/220 (43.64)	.610 (.446-.833)	.0019	.682 (.435-1.070)	.0958
	CS n/N (%)	95/127 (74.80)	2.339 (1.518-3.604)	.0001	1.754 (1.084-2.838)	.0221
	Other cause	29/43 (67.44)	1.632 (.845-3.152)	.1447	.925 (.448-1.911)	.8334

Abbreviations: CE, cardioembolism; CI, indicates confidence interval; CS, cryptogenic stroke; ECASS, European Cooperative Acute Stroke Study; LAA, large artery atherosclerosis; mRS, modified Rankin scale; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SAO, small artery occlusion; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Adjusted for gender, age, Independence (mRS, 0-1) before stroke, atrial fibrillation, diabetes mellitus, previous stroke, current smoking, previous smoking, receiving antiplatelet drug in 24 hours prior to thrombolysis, systolic blood pressure, diastolic blood pressure, median NIHSS score, INR prior to thrombolysis, mean rtPA dose, and mean weight.

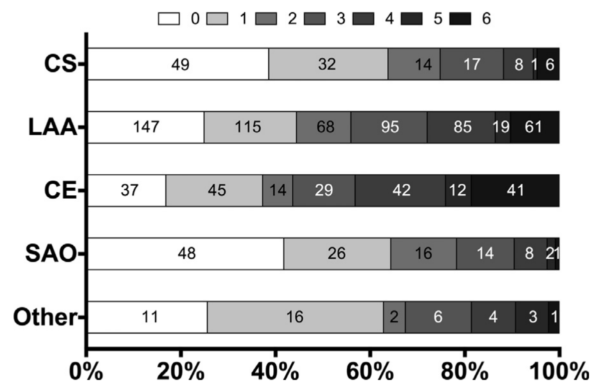

Figure 2. *The distribution of mRS at 90 days among all etiology subgroups. Abbreviations: CE, cardioembolism; CS, cryptogenic stroke; LAA, large artery atherosclerosis; Other, other determined cause; SAO, small artery occlusion.*

(74.8% versus 55.93%; OR 1.754, 95% CI: 1.084-2.838, *P* = .0221) between the CS and LAA groups after adjusting all confounders. However, patients with SAO had more functional independence outcome (78.26% versus 55.93%; OR 1.797, 95% CI: 1.060-3.044, *P* = .0294), but less excellent recovery outcome (64.35% versus 44.41%; OR 1.383, 95% CI: .872-2.191, *P* = .1680).

Discussion

The study demonstrated that after treatment with IVT, the patients suffering from CS presented a high rate of excellent clinical consequences (mRS, 0-1; 63.78%) and functional independence outcome (mRS, 0-2; 74.8%) after the adjustment of age, gender, independence before stroke, atrial fibrillation, diabetes mellitus, previous stroke, smoking, receiving antiplatelet drug in 24 hours prior to thrombolysis, blood pressure, NIHSS score, INR prior to thrombolysis, rt-PA dose, and weight. To the best of our knowledge, the results of this study first demonstrated the independent connection between CS and good consequences despite the confounders; for example, stroke severity. The evidence for the efficacy of IVT with rt-PA comes from the research by NINDS, which reports that ischemic stroke treatment with IVT within 3 hours enhances the clinical consequences during 3 months regardless of the stroke subtypes. However, these conclusions are based on the stroke subtypes determined before standard diagnostic evaluation and do not include the CS patients.[2] Hsia et al. compared different stroke subtypes after complete diagnostic evaluation was determined, and the results responding to thrombolytic therapy were reported in the NINDS trial. The study found that the efficacy of IVT within 3 hours was similar among different stroke subtypes. However, the stroke etiology was not deduced in 18% of the studies, and these subjects were not included in the comparison of the outcomes.[10] Mustanoja et al. reported the outcomes from the patients, including the CS patients, those receiving thrombolytic treatment in terms of stroke etiology. These findings differed from those in the current study such that patients with CS treated with IVT present a high rate of satisfactory outcomes in univariate and multivariate analyses. In this study, 130 (14%) patients with undetermined etiology might gain satisfactory outcomes in unadjusted analyses (OR 1.96, 95% CI: 1.30-2.96); however, after the adjustment of NIHSS, age, and sex at the baseline, the effect becomes nonsignificant (OR 1.23, 95% CI: .75-2.02).[11]

After standard examinations, the potential cause for 1 of 4 subjects suffering from ischemic stroke is absent. The standard workup was as follows: echocardiography, inpatient cardiac telemetry or 24-hour Holter monitoring, MRI or CT imaging of topographic characteristics of brain infarct, as well as, the evaluation of magnetic resonance angiography or computed tomographic angiography of neck artery and brain artery.[1] AIS patients with different etiologies may have different responses to rt-PA that depends on clot features, including size, composition, and origin.[12] Both in vitro and animal models demonstrated that clots formed under a variety of biochemical and physical conditions exhibit a differential susceptibility to lysis.[13] It has been proved that thrombus rich in original platelets with favorable histology formed under flow condition can resist thrombolysis than fresh blood clot that is abundant in fibrous proteins and red blood cells formed under hemolytic condition.[14,15] Most cryptogenic ischemic strokes show embolization in origins, such as proximal arterial source, heart resource, or venous source (with right-to-left shunts).[1] Recent studies about histopathological analysis of human thrombi retrieved from stroke patients during endovascular therapy state that it is cardioembolic for a majority of CSs.[16,17] Cardioembolic thrombi contain a high proportion of fibrin/platelet, low erythrocyte proportion, and large number of leucocytes, which might be insusceptible to thrombolytic agents. Our previous study[18] proved this phenomenon as the mechanism underlying cardioembolic stroke in Chinese patients; these patients exhibit thrombolysis as consequences. However, in current studies, CS patients had more efficacy outcomes than LAA patients, thereby indicating that although CS thrombi have the same histological compositions with cardioembolic thrombi, the size may be small. As reported by Marder et al., the thrombi retrieved from AIS subjects suffering from large-vessel occlusion postulate that the consequences are based on the size of the thrombi.[19]

Nevertheless, the present study has several limitations. First, this study was designed as a prospective observation cohort, and hence, to explore the stroke subtype, post hoc analysis was carried out. The confounders were not excluded completely by multivariate analysis. Furthermore, some hidden confounders were not collected, and the consequences necessitate a detailed interpretation. Second, classifying the ischemic stroke subtypes may be an arbitrary process and restricted by human error. Third, the relatively small sample size, especially in the other determined cause group might reduce the significant power of the test. Fourth, this study was conducted in Chinese population; thus, the analysis results may be affected by ethnic discrepancies. Thus, the study should cautiously interpret the findings that cannot be applied simply into the investigation of the populations in other countries.

In conclusion, after treatment by IVT, the subjects suffering from CS exhibit excellent clinical consequences and functional independence outcome than the LAA patients. Any obvious discrepancy was not observed in sICH rate between the LAA and CS groups. Briefly, IVT with rt-PA in 4.5 hours may be safe and effective for CS. In the case of subjects with the possibility of gaining IV alteplase, time dependence is an advantage of the therapy that needs to be implemented at an appropriate time.[20] With respect to etiology, AIS subjects in our clinical practice did not accept routine diagnoses before thrombolysis. The current results provided robust evidence that despite the subjects in the stroke subgroup, elevated neurological outcomes were observed within 4.5 hours.

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