

Outcomes of Thrombolytic Therapy for Acute Ischemic Stroke in Chinese Patients

The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) Study

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Background and Purpose—The safety and efficacy of alteplase for ischemic stroke has not been examined in Chinese patients. We assessed the safety and efficacy of alteplase for acute ischemic stroke in daily clinical practice in Taiwan.

Methods—A prospective, multicenter, observational study was conducted in Taiwan from December 2004 to July 2008. Eligible patients (241) receiving alteplase were recruited and divided into 2 groups: standard dose (0.90 ± 0.02 mg/kg, $n=125$) and lower dose (0.72 ± 0.07 mg/kg, $n=116$). Primary outcome measures were safety: symptomatic intracerebral hemorrhage and death within 3 months. The secondary outcome measure was efficacy a modified Rankin scale of 0 to 2 after 3 months.

Results—The standard-dose group had higher rates of symptomatic intracerebral hemorrhage using National Institute of Neurological Diseases and Stroke, European Cooperative Acute Stroke Study, and Safe Implementation of Thrombolysis in Stroke-Monitoring Study definitions (10.4% versus 5.2%, 8.0% versus 2.6%, and 5.6% versus 1.7%, respectively) and mortality within 3 months (12.8% versus 6.9%), twice that of the lower-dose group. This pattern was more prominent in older patients. Significantly higher rates of symptomatic intracerebral hemorrhage per European Cooperative Acute Stroke Study (15.4% versus 3.3%, $P=0.0257$) and mortality (21.1% versus 5.0%, $P=0.0099$) and significantly lower independence rate (32.6% versus 53.6%, $P=0.0311$) were observed among patients ≥ 70 years old receiving the standard dose than those receiving the lower dose.

Conclusions—This study suggests that the standard dose of 0.9 mg/kg alteplase may not be optimal for treating aged Chinese patients. However, the dose of recombinant tissue plasminogen activator for ischemic stroke in Chinese patients should be based on more broad and convincing evidences and randomized trials of lower versus higher doses are needed. (*Stroke*. 2010;41:885-890.)

Key Words: Chinese ■ stroke ■ thrombolytic therapy

Several randomized controlled trials have demonstrated that in cases of acute ischemic stroke, the administration of recombinant tissue plasminogen activator (rtPA) treatment within 3 hours of symptom onset can improve functional outcomes without increases in severe disability and mortality.¹⁻³ Two observational studies, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) in Europe⁴ and the Canadian Alteplase for Stroke Effective-

ness Study (CASES),⁵ both confirmed that rtPA is safe and effective when the treatment protocol is closely followed. However, intracerebral hemorrhage remains the most feared side effect of rtPA.⁶

In America and Europe, the current rtPA dose for acute ischemic stroke is 0.9 mg/kg. However, because the optimal dose required for attaining a coronary potency rate of 65% to 80% is 0.5 to 0.75 mg/kg in Japan and China, far lower than

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in Europe and the United States (approximately 1.25 mg/kg),⁷⁻⁹ a lower dose (0.6 mg/kg) was used in the Japan Alteplase Clinical Trial (J-ACT).¹⁰ Because the safety and efficacy of rtPA in the J-ACT were comparable to that in the National Institute of Neurological Disorders (NINDS) study,¹ low-dose alteplase (0.6 mg/kg) for acute ischemic stroke was approved in Japan in 2005. Later studies in Japan also confirmed that low-dose therapy has similar outcomes compared with regular-dose therapy in Western patients.^{11,12}

At the end of 2003, Taiwan approved the indication of alteplase for acute ischemic stroke. However, information on the benefit–risk profile in the thrombolytic treatment of acute ischemic stroke in Chinese people was unavailable at that time. In view of this, the Taiwan Stroke Society initiated a multicenter, observational study, the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study, to determine if the thrombolytic therapy in routine clinical use was as safe and effective in Taiwan as in other countries.

Patients and Methods

Study Design

The TTT-AIS study was a prospective, multicenter, observational study for Taiwan hospitals that used rtPA to treat acute ischemic stroke. It was similar to the SITS-MOST, an Internet-based, academic, interactive thrombolysis therapy registration.⁴ Before launching the register, we conducted 4 rounds of rtPA workshops nationwide and organized National Institutes of Health Stroke Scale certification tests. All participating physicians had to be board-certified neurologists. The registered centers entered data online through a secure Internet connection. During business hours, research staff regularly monitored the quality of the entered data. They checked baseline data, unit dose, total dose, exact body weight, and initial and 24-hour cranial CT scan images for subsequent outcome follow-ups. The exact unit dose was calculated from total dose divided by exact body weight. Incomplete data were followed and completed by phone or e-mail. The study committee verified all the source data. The CT-reading committee members, who were blinded to patients' information, read all the CT images for presence of bleeding and reached consensus. The investigators from each participating hospital were responsible for registering all patients treated with rtPA in their hospitals, agreeing to a source data audit. Kaohsiung Medical University Hospital's Institutional Review Board approved the study proposal, and we obtained written informed consent from all patients. The register started in December 2004 and ended July 31, 2008. The rtPA indications and exclusion criteria were similar to the SITS-MOST⁴ study (Supplemental Table I; available online at <http://stroke.ahajournals.org>) We also excluded patients with a National Institutes of Health Stroke Scale (NIHSS) score of <6 at baseline and CT evidence of significant early ischemic change (affecting more than one third of the middle cerebral artery territory).

Outcome Measures

The primary outcome of the TTT-AIS study was safety, which was assessed by the occurrence of symptomatic intracerebral hemorrhage (SICH) and death within 3 months. We defined SICH as the NINDS study did: intracerebral hemorrhage with deterioration of any neurological symptoms (NIHSS score ≥ 1) or death. The radiological definition of hemorrhagic events followed the European Cooperative Acute Stroke Study (ECASS) classification.^{2,13} To facilitate comparison with other studies reported in the literature, we also added the outcome of the incidence rates of SICH defined in SITS-MOST⁴ (to be local or remote parenchymal hemorrhage Type 2 on the 22- to 36-hour posttreatment CT scan combined with a neurological deterioration of ≥ 4 points on the NIHSS from baseline or from the lowest NIHSS value between baseline and 24 hours or leading to

Table 1. Demographics and Baseline Characteristics of Patients With Standard Doses and Lower Doses of Alteplase

Variables	Lower Dose (0.72 \pm 0.07 mg/kg, n=116)	Standard Dose (0.90 \pm 0.02 mg/kg; n=125)	P Value
Age, years	66.7 \pm 13.3	64.9 \pm 11.7	0.2505
Gender, female/male	46/70	50/75	0.9504
Hospital, C/M	32/84	35/90	0.9429
Body weight, kg	66.7 \pm 12.3	66.0 \pm 13.1	0.6498
Hypertension	86 (74.1%)	86 (68.8%)	0.3597
Diabetes	28 (24.1%)	32 (25.6%)	0.7931
Hyperlipidemia	19 (16.4%)	19 (15.2%)	0.8018
Coronary artery disease	19 (16.4%)	16 (12.8%)	0.4307
Atrial fibrillation	51 (44.0%)	41 (32.8%)	0.0746
Smoking			
Current	31 (26.7%)	35 (28.0%)	0.8244
Previous	12 (10.3%)	12 (9.6%)	0.8470
Aspirin	17 (14.7%)	24 (19.2%)	0.3481
Clopidogrel/ ticlopidine	4 (3.4%)	5 (4.0%)	0.8214
Anticoagulant	6 (4.3%)	9 (7.2%)	0.5151
NIHSS	14.9 \pm 6.0 (15, 4–37)	15.9 \pm 5.6 (16, 4–33)	0.1886
Time to treatment	141.6 \pm 34.9	137.5 \pm 39.4	0.3347

C/M indicates treated in a community hospital/treated in a medical center.

death) and defined in ECASS^{2,13} as any hemorrhage plus a neurological deterioration of ≥ 4 points on the NIHSS baseline or from the lowest NIHSS value after baseline to 7 days or leading to death. The secondary outcome was efficacy, which measured functional outcomes, including the Barthel Index and the modified Rankin Scale (mRS) 3 months after treatment. A Barthel Index score of 95 to 100 and an mRS score of 0 to 1 at 3 months were considered good clinical outcomes; an mRS score of 0 to 2 was considered functional independence; and an mRS score of 5 to 6 was a bad clinical outcome.

Statistical Analysis

Data were analyzed using SPSS 17 software. Means \pm SD (for continuous variables) or percentages (for discrete variables) were calculated for all baseline data. Groups were compared using the Student *t* test for continuous variables and the χ^2 test for discrete variables. Mantel-Haenszel extension χ^2 tests were conducted for trend analyses of dose responses to SICH. ORs were calculated for all discrete variables to identify risk factors in univariate and multivariate analysis for SICH. All statistically significant levels were defined as $P < 0.05$.

Results

Characteristics of Patients in the Standard-Dose and Lower-Dose Groups

From December 2004 to July 2008, 244 eligible patients with acute ischemic strokes who had received thrombolytic therapy from 23 hospitals in Taiwan were enrolled. Three patients were excluded because rtPA administration was stopped prematurely during infusion due to the rapid deterioration of patients' vital signs. Thus, 241 patients' data were included for safety, efficacy, and dose–response analysis. Of these,

Table 2. Results of SITS-MOST, NINDS, J-ACT, and TTT-AIS

	SITS-MOST	NINDS	J-ACT	TTT-AIS
SICH per NINDS	7.3%	6.4%	5.8%	7.9%
SICH per ECASS	4.6%	N/A	N/A	5.4%
SICH per SITS-MOST	1.7%	N/A	N/A	3.7%
Death within 3 months	11.3%	17.0%	9.7%	10.0%
mRS 0–1 at 3 months	38.9%	39.0%	36.9%	39.3%
mRS 0–2 at 3 months	54.8%	N/A	N/A	53.4%
Barthel Index 95–100 at 3 months	N/A	50.0%	48.5%	43.6%
NIHSS improvement by ≥4 points or decreased to 0 at 24 hours	N/A	47.0%	49.5%	39.0%

N/A indicates not available.

236 (98%) completed the 1-month follow-up, and 219 (91%) completed the 3-month mRS; all completed the baseline image reports, and 234 (97%) completed the follow-up image reports. The dosage used varied even among the same medical facilities. We referred a unit dose of 0.90 ± 0.05 mg/kg (0.85 to 0.95) to the standard-dose group and <0.85 mg/kg to the lower-dose group, then 51.8% of patients were treated with the standard dose (125 patients; mean, 0.90 ± 0.02 mg/kg; median, 0.9 mg/kg; range, 0.86 to 0.95 mg/kg) and 48.2% with a lower dose (116 patients; mean 0.72 ± 0.07 mg/kg; median, 0.7 mg/kg; range, 0.55 to 0.84 mg/kg). The distribution of patients per dose interval of rtPA dosage used in the medical centers and community hospitals was similar (Supplemental Figure I, available online at <http://stroke.ahajournals.org>). Table 1 shows the baseline data and demographics of both groups.

Safety and Efficacy

Safety and efficacy outcomes are summarized in Table 2. The good functional outcomes at 3 months were comparable with the results of the SITS-MOST, NINDS, and J-ACT studies. The death within 3 months in this study was less than that in SITS-MOST and NINDS, but the rates of SICH were slightly higher than those of SITS-MOST, NINDS, and J-ACT studies. Because the ECASS II studies¹³ have nicely showed the relationship between age and SICH rates, the occurrence

of SICH per ECASS definition in this study was further analyzed for the safety outcome.

Univariate analyses showed that age ≥ 70 years (OR=4.12, 95% CI: 1.10 to 15.36; $P=0.0236$), standard dose of rtPA (OR=3.28, 95% CI: 0.88 to 12.21; $P=0.0630$), clopidogrel/ticlopidine use (OR=12.56, 95% CI: 3.13 to 50.38; $P<0.0001$), and anticoagulant use (OR=5.4, 95% CI: 1.31 to 22.23; $P=0.00097$) were associated with SICH (per ECASS definition). Multiple regression analysis showed that age ≥ 70 years ($P=0.0093$), standard dose of rtPA ($P=0.0321$), clopidogrel/ticlopidine use ($P=0.0008$), and anticoagulant use ($P=0.0293$) were the independent predictors for SICH after adjustment for hypertension, diabetes, coronary heart disease, atrial fibrillation, smoking, previous use of clopidogrel or anticoagulant, baseline NIHSS, treatment in a community hospital, and time to rtPA treatment. The relationship of age and dose of alteplase with SICH per ECASS definition is further illustrated in Figure 1. Figure 1A demonstrates a borderline positive trend for SICH increases with age ($P=0.0592$), and Figure 1B shows a nonsignificant trend for SICH increases with dose of alteplase ($P=0.1317$), but the SICH apparently increases at the standard dose.

Comparison of Outcomes Between Standard- and Lower-Dose Groups

Because the baseline data from both patient groups were similar (Table 1), we compared the safety and efficacy directly (Table 3). The lower-dose group had fewer SICHs and deaths within 3 months and more functional independence. The outcome differences were strengthened after considering the age and dose interaction. Patients aged ≥ 70 years who received both doses had similar baseline variables and clinical demographics (data not shown); yet, the patients who received the standard versus the lower dose had significantly increased mortality within 3 months (21.1% versus 5.0%; absolute difference: 16.1%, $P=0.0099$) and SICH per ECASS (15.4% versus 3.3%; absolute difference: 12.1%, $P=0.0257$) and significantly lower rates of independence (mRS 0 to 2) at 3 months (32.6% versus 53.6%; absolute difference: 21.0%, $P=0.0311$; Table 4). Figure 2 shows that the lower-dose group for both age categories (ie, <70 and

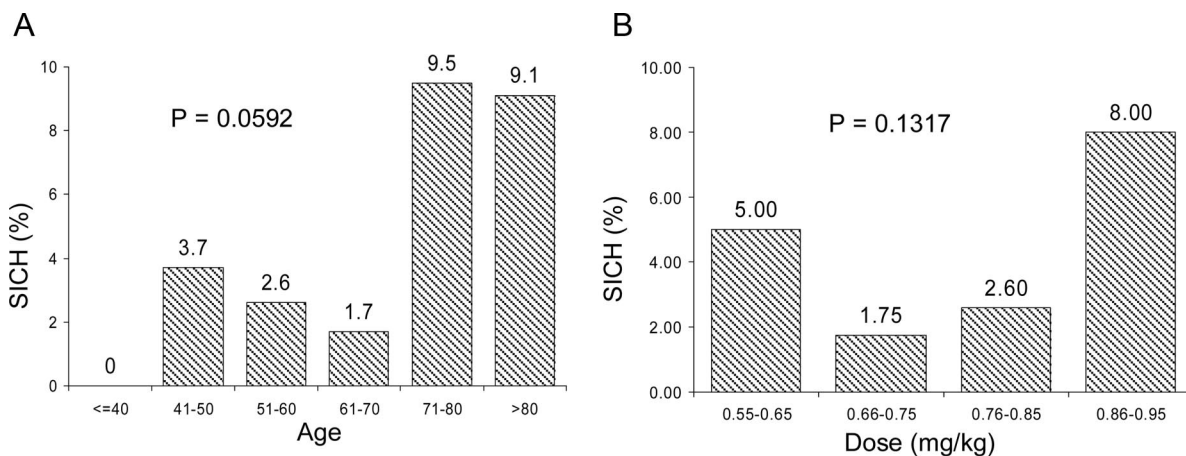


Figure 1. SICH on ECASS definition at different doses and ages. A, Rates of SICH in different age groups. B, Rates of SICH with different doses.

Table 3. Comparisons of Treatment Results Between Patients Receiving Standard Doses and Lower Doses of Alteplase

	Lower Dose (0.72±0.07 mg/kg, n=116)	Standard Dose (0.90±0.02 mg/kg, n=125)	P Value
SICH per NINDS	6 (5.2%)	13 (10.4%)	0.1324
SICH per ECASS	3 (2.6%)	10 (8.0%)	0.0630
SICH per SITS-MOST	2 (1.7%)	7 (5.6%)	0.1128
Mortality within 3 months	8 (6.9%)	16 (12.8%)	0.1262
mRS 0–2 at 3 months*	60 (58.8%)†	57 (48.7%)‡	0.1348
mRS 5 and 6 at 3 months*	19 (18.6%)†	25 (21.4%)‡	0.6137

*Patients completed 3-month assessment.

†n=102.

‡n=117.

≥70 years) demonstrated a higher percentage of functional independence (mRS 0 to 2).

Discussion

The overall safety and efficacy of the TTT-AIS study were similar to those of the J-ACT, NINDS, and SITS-MOST. The lower mortality rate of this study may reflect the fact that the 30-day mortality rate for ischemic stroke in Taiwan is approximately 5% to 8%.^{14,15} The slightly higher SICH obtained in our study, compared with J-ACT, NINDS, and SITS-MOST studies, could be attributed to variations in the dosages that we used. Because several studies implied that it is more appropriate to use a lower dose of anticoagulants or rtPA in Chinese patients than in whites,^{9,16–18} some neurologists in Taiwan inferred that the dose of rtPA for acute ischemic stroke should also be reduced for safety concerns. Therefore, approximately half of the patients received lower doses of rtPA in clinical practice (some by doctor's decision, some by calculation of the exact unit dose). Although this was also a kind of protocol violation, we were able to observe and

analyze the differences in the safety/efficacy outcomes between the standard- and lower-dose groups.

In this study, we found patients who were given the standard dose had twice the chance of SICH on NINDS, ECASS, and SITS-MOST definitions (10.4% versus 5.2%, 8.0% versus 2.6%, 5.6% versus 1.7%, respectively) and mortality within 3 months (12.8% versus 6.9%) compared with those on the lower dose (Table 3). Considering age, the SICH (ECASS definition) and mortality rates were statistically significantly higher in patients ≥70 years old who received the standard dose (Table 4). A significantly lower independence rate was also observed in these patients (Table 4). Thus, this study suggested that the standard dose of alteplase, 0.9 mg/kg, might not be optimal for treating aged Chinese patients. However, for patients aged <70 years, there were no statistical differences in any of the safety and efficacy parameters between the standard-dose and lower-dose groups.

Although this study did not demonstrate a significant trend for SICH increases with dose of alteplase increase, the SICH rate apparently increased at the standard dose (Figure 1B). The impact of different alteplase dosages on outcomes in the treatment of acute ischemic stroke is rarely discussed in the international neurological society except for the Japanese study.^{10–12} However, from dose-finding studies for rtPA¹⁹ and other thrombolytic drugs such as human tissue urokinase type plasminogen activator^{20,21} and desmoplasin,²² it is suggested that the higher the dose, the greater the chance of hemorrhage. The recent Japanese study¹² and our study also confirmed this notion. Besides the safety, clinicians are also concerned about the efficacy. It is a common argument that a “higher dosage may have greater efficacy.” However, this argument was not supported by the findings of the desmoplasin study (Desmoplasin In patients with Acute ischaemic Stroke [DIAS-2])²² and our study. Both studies showed that the functional independence rates in the higher-dose group were not better than those in the lower-dose group. Further large-sample studies will be needed to clarify this issue.

Our study also found that SICH increased as age increased. The occurrence of SICH surged as high as 9.5% in patients

Table 4. Comparisons of Treatment Results Between Patients Aged <70 Years and ≥70 Years Receiving Standard Doses or Lower Doses of Alteplase

	Age <70 Years			Age ≥70 Years		
	Lower Dose (0.72±0.07 mg/kg, n=56)	Standard Dose (0.90±0.02 mg/kg, n=73)	P Value	Lower Dose (0.72±0.07 mg/kg, n=60)	Standard Dose (0.90±0.02 mg/kg, n=52)	P Value
SICH per NINDS	1 (1.8%)	3 (4.11%)	0.4504	5 (8.3%)	10 (19.2%)	0.0913
SICH per ECASS	1 (1.8%)	2 (2.7%)	0.7216	2 (3.3%)	8 (15.4%)	0.0257
SICH per SITS-MOST	1 (1.8%)	2 (2.7%)	0.7216	1 (1.7%)	5 (9.6%)	0.0624
Death within 3 months	5 (8.9%)	5 (6.9%)	0.6612	3 (5.0%)	11 (21.1%)	0.0099
mRS 0–2 at 3 months*	30 (65.2%)†	41 (60.3%)‡	0.5947	30 (53.6%)§	16 (32.6%)	0.0311
mRS 5 and 6 at 3 months*	7 (15.2%)†	9 (13.2%)‡	0.7650	12 (21.4%)§	16 (32.6%)	0.1944

*Patients completed 3-month assessment.

†n=46.

‡n=68.

§n=56.

||n=49.

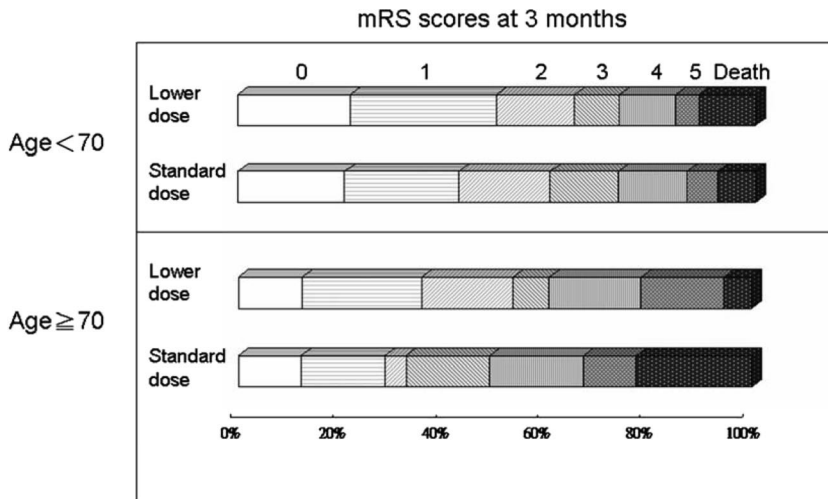


Figure 2. Distribution of mRS scores at 3 months in patients of different age and dose groups.

aged 71 to 80 years and 9.1% in patients aged >80 years who received standard doses (Figure 1A). The safety of rtPA use in patients >80 years old is still debated.²³ The ECASS and ECASS II studies¹³ first reported the relationship between age and rtPA outcome and concluded that older patients had a higher risk of severe hemorrhagic transformation after receiving rtPA. Therefore, in Europe, rtPA is not recommended for patients with stroke >80 years of age for fear of excessive risk of SICH. Yet, studies from North America, such as the tPA Stroke Survey²⁴ and CASES²⁵ revealed no association between age >80 years old and risks of SICH. Taiwan also followed the European license. However, only 42 patients >80 years of age were included in the randomized controlled trial of rtPA.³ Future trials including more patients who are elderly may resolve this problem. We demonstrated the age and the dosage interaction in Chinese patients, but the SICH rates is similar in patients aged 71 to 80 and aged >80 years. Future studies for thrombolytic drugs in different races are needed to clarify this issue.

This study has several limitations. First, many patients were not weighed in emergency rooms. However, we asked investigators to enter the total dose of rtPA administered in the emergency room and then to enter the exact body weight when patients were later weighed during their hospitalization so we could get the exact unit dose for analysis. Second, we did not know exactly why some doctors chose the lower dose for patients. Besides the safety concern, other factors might have influenced the doctor’s decision and that might bias the results. However, we just described the results of Taiwan doctors using rtPA in the real world. Third, some doctors used thrombolytic therapy in patients >80 years of age, and that was a protocol violation. However, there were more patients >80 years of age in the lower-dose group (n=8 versus n=3), which is considered disadvantageous for this group. Therefore, the results should not be biased. In addition, the anticoagulant was an independent risk for SICH in this study and it was used with an international normalized ratio <1.3 in 15 patients, 9 in the standard-dose group and 6 in the lower-dose group. SICH was found in 3 patients, 2 in the lower-dose group with 1 aged <70 years and 1 aged ≥70 years and 1 in the standard-dose group with age <70 years,

that is, anticoagulant use did not favor the results of the lower-dose group. Fourth, this study showed lower mortality in the elderly with lower doses than in the younger patients (Figure 2). This is against general experience. We consider the lower mortality in the elderly to have been merely chance. However, if we combined mRS 5 and 6 together as a bad clinical outcome, then the finding in Figure 2 is consistent with general clinical experience, that the bad outcome occurred more often in the elderly than in the younger patients. Fifth, this study is not randomized for the dosage so that the lower-dose group was actually exposed to a wide range of doses from 0.55 to 0.84 mg/kg, and we did not have a large enough sample size to determine the optimal dose for Chinese patients in this study. Sixth, the number of patients was relatively small; interpretation of the subgroup analyses (such as age) should be taken with caution because that the data may represent bias. Currently, we are organizing another observational study and expecting an additional ≥500 patients who have received thrombolytic therapy and can be added for analysis to determine the appropriate dose.

In conclusion, our study did not support use of standard-dose alteplase (0.9 mg/kg) for treatment of acute ischemic stroke in Chinese patients, particularly for the aged groups. However, the dose of rtPA for Chinese patients should be based on more broad and convincing evidence. A larger, prospective cohort of patients treated at lower doses will be needed to determine the optimal dose of alteplase for Chinese patients, and a randomized trial of lower versus higher doses would be required to assess whether people of Chinese origin should be given a lower dose of alteplase.

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Disclosures

None.

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