Am J Transl Res 2023;15(5):3460-3467
www.ajtr.org /ISSN:1943-8141/AJTR0148151

Original Article

Recombinant tissue-type plasminogen activator (rt-PA) effectively restores neurological function and improves prognosis in acute ischemic stroke

Shouyun Zhang[1], Dezhen Wang[2], Lin Li[3]

[1]*The Encephalopathy Department, Zhecheng Hospital of Traditional Chinese Medicine, Shangqiu, Henan, China;* [2]*Emergency Department, Zhengzhou Central Hospital Affiliated to Zhengzhou University, No. 16, Tongbai North Road, Zhongyuan District, Zhengzhou, Henan, China;* [3]*Internal Medicine-Neurology, Zhengzhou Central Hospital Affiliated to Zhengzhou University, No. 16, Tongbai North Road, Zhongyuan District, Zhengzhou, Henan, China*

Received November 30, 2022; Accepted March 7, 2023; Epub May 15, 2023; Published May 30, 2023

Abstract: Objective: To evaluate the clinical efficacy of intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke. Methods: A total of 76 patients with acute ischemic stroke admitted to the Encephalopathy Dept. of Zhecheng Hospital of Traditional Chinese Medicine between February 2021 and June 2022 were recruited in this prospective trial (ClinicalTrials.gov, NCT03884410) and patients were randomized 1:1 to receive either aspirin plus clopidogrel (control group) or aspirin plus clopidogrel and rt-PA intravenous thrombolytic therapy (experimental group), with 38 cases in each group. The treatment efficiency, National Institute of Health stroke scale (NIHSS) scores, daily living ability, coagulation function, serum Lipoprotein-associated phospholipaseA2 (Lp-PLA2), homocysteine (HCY), hypersensitive C-reactive protein (hsCRP) levels, adverse events, and prognosis were evaluated and compared between the two groups. Results: Intravenous thrombolysis with rt-PA resulted in a better treatment outcome of patients versus aspirin plus clopidogrel ($P<0.05$). Patients with rt-PA exhibited better improvement in neurological function than those with aspirin plus clopidogrel, as shown by the lower NIHSS scores ($P<0.05$). Intravenous thrombolysis with rt-PA resulted in a better quality of life of patients than aspirin plus clopidogrel, indicated by the higher Barthel Index (BI) levels ($P<0.05$). The lower von Willebrand factor (vWF) and Factor VIII (F) levels indicated better coagulation function of patients with rt-PA versus those with aspirin plus clopidogrel ($P<0.05$). The lower serum concentrations of Lp-PLA2, HCY, and hsCRP suggested patients with rt-PA had milder inflammatory responses versus those without rt-PA ($P<0.05$). There was no significant difference in the incidence of adverse events in the two groups ($P>0.05$). Intravenous thrombolytic therapy with rt-PA better enhanced the prognosis of patients than with aspirin plus clopidogrel ($P<0.05$). Conclusion: Compared with conventional pharmacological regimens, additional rt-PA intravenous thrombolytic therapy improves the clinical outcome of patients with acute ischemic stroke, promotes neurological recovery, and enhances patient prognosis without increasing the risk of patient-related adverse events.

Keywords: Recombinant tissue-type fibrinogen activator, intravenous thrombolysis, acute ischemic stroke, clinical efficacy

Introduction

Acute ischemic stroke (AIS) accounts for 72.3% of all strokes in China and features a high incidence, recurrence, disability and mortality [1, 2]. Acute ischemic stroke is caused by cerebral artery vascular occlusion, which gives rise to a reduced blood supply to brain tissue, resulting in hypoxia and ischemic necrosis of brain tissue [3]. Early restoration of blood flow and timely reperfusion of infarcted arteries are essential to reduce the mortality of AIS [4]. Antiplatelet drugs including aspirin and Bolivar are recommended for the management of AIS patients [5]. However, their efficacy remains inconsistent among AIS patients [6]. Clinical practice has reported a poor thrombolytic effect of drug therapy for patients with AIS, whereas high-dose administration may increase the risk of adverse reactions [7, 8]. Research indicates that efficient revascularization therapy is the key to protect the life and health of AIS patients,

reduce brain tissue damage in ischemic areas, and improve patient prognosis [9].

Recombinant tissue-type plasminogen activator (rt-PA), also known as alteplase, is a glycoprotein that can directly activate plasminogen-converted plasmin, which can induce plasmin and result in fibrin degradation and thrombolysis [10-12]. For patients with AIS, intravenous injection of rt-PA is recommended for vascular recanalization, which provides more rapid and effective thrombolysis than conventional pharmacological thrombolytic regimens [13, 14]. Research has shown a strong correlation between the treatment benefits of AIS patients and the duration of rt-PA use, and the longer the interval between the onset of disease and intervention, the poorer the treatment benefits with rt-PA [15]. Moreover, rt-PA increases the risk of bleeding-related diseases. At present, there are few studies on the safety of rt-PA in AIS. Evidence suggests that the best timing for rt-PA intravenous thrombolysis for patients with AIS is 4.5 h, and that for every 1-minute reduction in the time-lapses from onset to intravenous thrombolysis, the patient's disability-free survival increases by an average of 1.5 d [16, 17]. Therefore, the onset-to-visit time of 76 patients with AIS included in the present study was all within 4.5 h. No clinical randomized controlled studies on direct comparison of rt-PA thrombolysis with conventional drugs in patients with AIS have been conducted in China, but there is evidence from numerous studies that patients with AIS can benefit from rt-PA thrombolytic therapy [18].

To this end, this study was undertaken to evaluate the clinical efficacy of intravenous thrombolysis with rt-PA for acute ischemic stroke.

Materials and methods

Participants

This study was a prospective trial, and we registered our trial on ClinicalTrials.gov, with a clinical trial number of NCT03884410. In total, 76 patients with acute ischemic stroke admitted to the encephalopathy Dept. of Zhecheng Hospital of Traditional Chinese Medicine between February 2021 and June 2022 were recruited and assigned via random number table method to either a control group or an experimental group, with 38 cases in each group. The control group received conventional antithrombotic therapy, and the experimental group received additional rt-PA intravenous thrombolytic therapy. This study has been reviewed and approved by the Ethics Committee of Zhecheng Hospital of Traditional Chinese Medicine (No. 2020123002T). All patients and their families were informed and signed the relevant informed consent forms for this study. All operations in this study comply with the ethical guidelines of the Declaration of Helsinki for clinical research [19].

Inclusion and exclusion criteria

Inclusion criteria: 1) patients were diagnosed with AIS by MRI or CT; 2) patients were first diagnosed with AIS, and the time lapse between onset and consultation was <4.5 h; 3) aged over 18 years; 4) with tolerance to rt-PA intravenous thrombolytic therapy; 5) patients with good kidney, lung, heart and liver functions.

Exclusion criteria: 1) Incomplete clinical data (age, sex, baseline National Institute of Health stroke scale (NIHSS), time of symptom onset, time to hospital arrival or admission, time to IV rt-PA treatment); 2) History of endovascular therapy; 3) Intracranial hemorrhage (ICH), transient ischaemic attack (TIA), subarachnoid haemorrhage (SAH), or nonspecific stroke; 4) Time-lapse of more than 7 days between onset and treatment; 5) Intracranial hemorrhage or previous history of intracranial hemorrhage; 6) Imaging findings revealed a large infarct with an infarct size greater than 1/3 of the cerebral hemisphere; 7) Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg; 8) Received low molecular weight heparin treatment within 24 hours or Factor Xa inhibitors or thrombin inhibitors within 48 hours; 9) INR>1.7 or prothrombin time >15 seconds.

Treatment

Patients in both groups were given basic interventions such as microcirculation improvement, maintenance of water and electrolyte balance and symptomatic treatment of combined underlying diseases after admission. Patients in both groups received 100 mg of oral aspirin (Bayer HealthCare Co., Ltd., State Pharmacopoeia J20171021) and 150-300 mg of oral clopidogrel (Sanofi Pharmaceutical Co., Ltd., State Pharmacopoeia J20180029) daily.

The experimental group additionally received 0.9 mg/kg of rt-PA (Guangzhou Mingkang Biological Engineering Co., Ltd., State Drug Quorum S20150001) intravenously. The drug solution was diluted with sterilized injection water brought by the drug, of which 10% rt-PA was injected intravenously within 1 min, and the remaining 90% was infused intravenously by an infusion pump. Twenty-four hrs after rt-PA therapy, patients in the experimental group received the same regimen of conventional dual antibiotic (aspirin + clopidogrel) therapy.

Outcome measures

The primary outcome of this study was clinical efficacy and National Institute of Health stroke scale (NIHSS) score. The secondary outcome indicator is daily living ability, coagulation index level, serum lipoprotein-associated phospholipaseA2 (Lp-PLA2), homocysteine (HCY), hypersensitive C-reactive protein (hsCRP) levels, and adverse events.

Clinical efficacy: The clinical efficacy of the patients was evaluated according to the degree of neurological deficits and the improvement of the patients' living ability after 2 weeks of treatment. Cured: the patient's post-treatment neurological deficit scores were reduced by 90%-100% after treatment, and the patient had basically recovered living ability. Markedly effective: the patients' post-treatment neurological deficit scores were reduced by 46%-89% after treatment and they could partially complete self-care. Effective: the patient's post-treatment neurological deficit score was reduced by 18%-45% after treatment, and the patient could not perform self-care abilities. Ineffective: the patients' post-treatment neurological deficit scores did not change significantly compared with those before treatment.

Changes in NIHSS at different time points [20]: patients' neurological function was assessed at admission (T0), 1 d of treatment (T1), 7 d of treatment (T2), and 14 d of treatment (T3) using the NIHSS scale, which has a total score of 42. The higher the score, the more severe the neurological deficit.

Daily living ability: Before and after treatment, the Barthel index (BI) was used to evaluate patients' daily living abilities. This scale includes bathing, eating, going to the toilet, wearing and taking off clothes, going up and down stairs, and urine and feces control. The full score of this scale is 100 points. The higher the patient score, the better their daily living ability.

Coagulation function: Before and after treatment, 5 ml of fasting venous blood was collected from the patients, and the levels of von Willebrand factor (vWF) and Factor VIII (F) were determined using automatic coagulation analyzer.

Serum Lp-PLA2, HCY, and hsCRP levels: 5 ml of fasting venous blood was collected. The serum concentration of Lp-PLA2 was determined using enzyme-linked immunoadsorption assay, the HCY concentrations were measured by fluorescence immunoassay, and the serum level of hsCRP was determined by immunometric turbidity assay.

Adverse events: Possible adverse events during treatment including intracranial hemorrhage, liver function injury, renal function injury, and death were recorded after 1 month after intervention.

Prognosis: The prognosis of patients was assessed by the modified Rankin Score (mRS) [21] score after 2 weeks intervention, and the assessment criteria were dichotomized into good prognosis with an mRS score of ≤2 and poor prognosis with an mRS score of >2.

Statistical analysis

The data of this study were organized and analyzed using SPSS 22.0, and GraphPad Prism 8 was used to plot the graphics. Measurement data were expressed as mean ± standard deviation ($\overline{x}$ ± s) and analyzed using a t-test. Paired t-test was used for comparisons before and after treatment in the same group. Count data were expressed as the number of cases (%) and tested using the chi-square test. Statistical significance in the differences were indicated by $P<0.05$.

Results

Comparison of general characteristics

In the control group, there were 21 male and 17 female patients, aged 63.47±7.22 years. In the

Table 1. Comparison of general characteristics

	Control group (*N*=38)	Experimental group (*N*=38)	t/χ^2	*P*
Gender (Male/Female)	21/17	23/15	0.216	0.642
Age (years)	63.47±7.22	63.53±7.27	-0.036	0.971
BMI (kg/m^2)	23.84±2.19	23.82±2.26	0.039	0.969
Onset to visit time (h)	3.32±0.57	3.19±0.59	0.977	0.332
SBP (mmHg)	144.67±18.56	143.96±18.49	0.167	0.868
DBP (mmHg)	83.18±9.27	82.76±9.16	0.199	0.843
Blood glucose (mmol/L)	5.13±1.94	5.21±1.87	-0.183	0.855
Underlying disease				
Hypertension	23	24	0.056	0.813
Diabetes mellitus	6	5	0.106	0.744
Coronary heart disease	8	9	0.076	0.783

Note: SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Table 2. Comparison of clinical efficacy

	Control group (*N*=38)	Experimental group (*N*=38)	X^2	*P*
Cured	2	6		
Markedly effective	11	14		
Effective	16	16		
Ineffective	9	2		
Total efficacy (%)	76.3% (29/38)	94.7% (36/38)	5.208	0.022

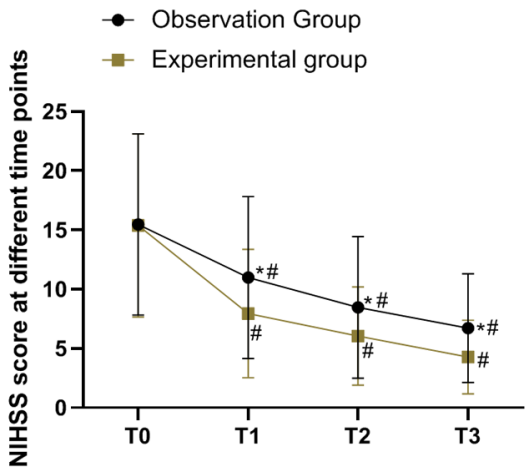

Figure 1. Comparison of National Institute of Health stroke scale (NIHSS) scores. Note: *Compared with the Experimental group, P<0.05. #Compared with T0, P<0.05.

experimental group, there were 23 male and 15 female patients, aged 63.53±7.27 years. The two groups were well-balanced in terms of general characteristics (P>0.05) (**Table 1**).

Comparison of clinical efficacy

Patients treated by intravenous thrombolysis with rt-PA showed better treatment response than those in the control group (P<0.05) (**Table 2**).

Comparison of NIHSS scores

Patients with rt-PA exhibited more improvement in neurological function than those with aspirin plus clopidogrel (P<0.05) (**Figure 1**).

Comparison of daily life ability

Intravenous thrombolysis with rt-PA resulted in better quality of life of patients than aspirin plus clopidogrel, evinced by the higher BI levels (P<0.05) (**Figure 2**).

Comparison of the levels of the coagulation index

There is no significance in vWF and F VIII levels between the two groups before treatment (P>0.05). The lower vWF and F levels indicated better coagulation function of patients with rt-PA versus those with aspirin plus clopidogrel (P<0.05) (**Figure 3**).

Serum levels of Lp-PLA2, HCY, and hsCRP were compared

Patients with rt-PA exhibited more significantly mitigated inflammatory responses versus those without rt-PA, indicated by the lower serum concentrations of Lp-PLA2, HCY, and hsCRP (P<0.05) (**Table 3**).

Comparison of adverse events

There was no significant difference in the incidence of adverse events in the two groups (P>0.05), suggesting that rt-PA did not add safety risks to patients (**Table 4**).

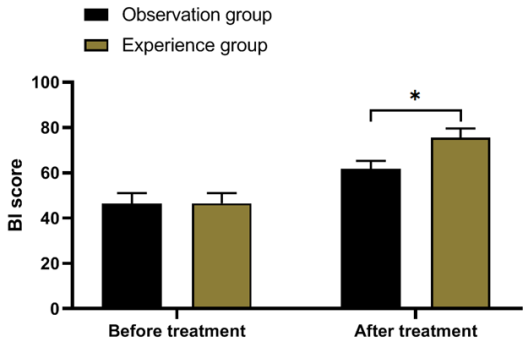

Figure 2. Comparison of daily living ability. BI, Barthel. Note: *indicates P<0.05.

Comparison of prognosis

Rt-PA intravenous thrombolytic therapy was associated with a significantly higher patient prognosis of 63.2% (24/38) versus 31.6% (12/38) of traditional treatment (P<0.05). Intravenous thrombolytic therapy with rt-PA offered more enrichment in enhancing the prognosis of patients than aspirin plus clopidogrel only (P<0.05) (**Table 5**).

Discussion

AIS is a major public health issue with high incidence, recurrence, disability, and death rates, and it is associated with irreversible damage to ischemic brain tissue [22, 23]. The results of the current study showed that intravenous thrombolysis with rt-PA provided better treatment response and quality of life for patients versus aspirin plus clopidogrel, confirming that rt-PA improves the therapeutic effect of AIS patients. Moreover, patients with rt-PA exhibited more improvement in neurological function than those with aspirin plus clopidogrel, indicating that early intervention with rt-PA in patients with AIS effectively promotes neurological recovery and improves the prognosis of patients. There is no clinical consensus regarding the effect of rt-PA thrombolytic therapy on the occurrence of adverse events in patients with AIS.

The results of a meta-analysis of 18 studies showed that in 2,676 patients with AIS who received IVT, intravenous rt-PA administration significantly improved neurological recovery after 14 days and quality of life after 90 days [15]. A study indicated that approximately 47% of patients with AIS missed the optimal timing of thrombolysis due to the absence of symptoms or rapid change in neurological symptoms, and nearly 40% of such patients had a poor outcome [24]. Liu et al. revealed an excellent outcome in 71% of patients with AIS who received thrombolytic therapy, while the result dropped to 29% of patients without thrombolytic therapy, which was consistent with the results of the current study [23]. A study on a global survey of clinical experts' opinions on current indications and contraindications for thrombolytic therapy also indicated that thrombolytic interventions should be considered for patients with AIS when their NIHSS score is >2 on admission [17]. In addition, a retrospective analysis of factors influencing the outcome of intravenous rt-PA 3 to 4.5 hours after the onset of AIS found that severe stroke, an age of 80 years, sHTN, or previous stroke/diabetes were influencing factors [25]. Atherosclerotic plaque rupture is the key to cerebral thrombosis. Various coagulation factors regulate the coagulation mechanism. Factor VIII is the regulator that initiates and activates the chain reaction of the coagulation function of the body and can form a complex with vWF, so the increase of its level will further promote the formation of thrombosis [26, 27]. The results of this study showed that the vWF and F levels in the experimental group were significantly lower than those of the control group, which suggested that rt-PA intravenous thrombolysis could effectively improve coagulation function in patients with acute ischemic stroke. Lp-PLA2 is a new inflammatory molecule related to cardiovascular diseases [28]. It promotes the formation of adhesion factors and macrokines and hydrolysis of lipid metabolism and inflammation and thrombosis process. HCY and hsCRP are closely related to inflammation and atherosclerosis process in cerebrovascular patients, and are considered important index to predict the occurrence and development of AIS [29]. The results of the present study showed that patients with rt-PA exhibited more significantly mitigated inflammtory responses versus those without rt-PA, suggesting that rt-PA intravenous thrombolytic therapy contributes to mitigating the inflammatory responses.

In conclusion, the results of the present study suggest that the rt-PA intravenous thrombolytic therapy regimen may further improve the clinical outcomes of patients with AIS, promote

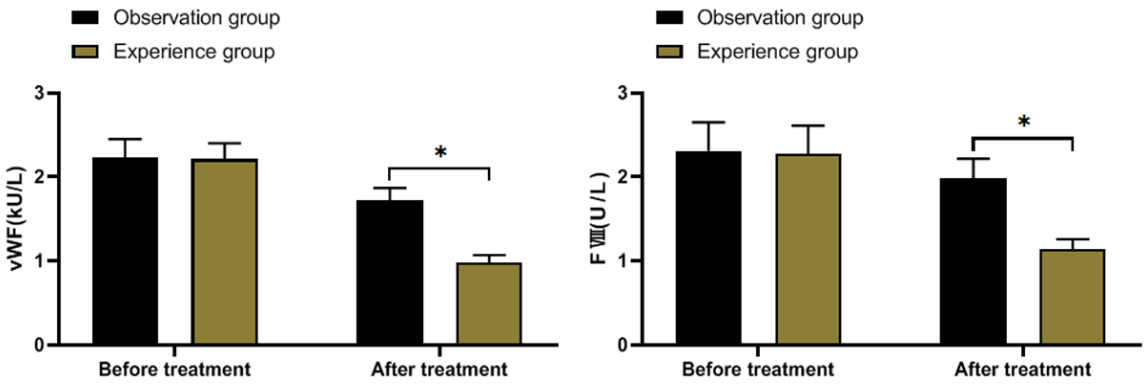

Figure 3. Comparison of the coagulation index levels. Note: *indicates P<0.05. vWF: von Willebrand factor. F: Factor VIII.

Table 3. Serum levels of Lp-PLA2, HCY, and hsCRP

	Control group (*N*=38)	Experimental group (*N*=38)	*t*	*P*
Lp-PLA2 (μg/L)				
Before treatment	58.39±6.78*	59.27±7.34*	0.543	0.589
After treatment	29.49±5.63	19.48±4.97	8.217	<0.001
HCY (μmol/L)				
Before treatment	21.56±3.28*	21.49±3.46*	0.091	0.928
After treatment	18.16±2.85	15.72±2.23	4.156	<0.001
hsCRP (mg/L)				
Before treatment	14.45±3.62	14.83±3.47	0.467	0.642
After treatment	10.39±3.12	7.13±2.38	5.121	<0.001

Note: Lp-PLA2: lipoprotein-associated phospholipaseA2, HCY: homocysteine, hsCRP: hypersensitive C-reactive protein; *indicates that the comparison between parameters before and after treatment within the same group was significant.

Table 4. Comparison of adverse events

	Control group (*N*=38)	Experimental group (*N*=38)	χ^2	*P*
Intracranial hemorrhage	0	1		
Hepatic impairment	2	1		
Renal impairment	1	2		
Death	0	0		
Total incidence (%)	7.9% (3/38)	10.5% (4/38)	0.157	0.692

Table 5. Comparison of prognosis

	Control group (*N*=38)	Experimental group (*N*=38)	χ^2	*P*
mRS≤2	12	26	7.600	0.006
mRS>2	24	14		

Note: mRS: modified Rankin Score.

neurological recovery, and contribute to the prognosis of patients compared with conventional pharmacological regimens, without increasing the risk of patient-related adverse events. However, the reliability of this study may be compromised by factors such as it being from a single center and having a small sample size. Therefore, randomized controlled trials with multiple centers and larger sample sizes are required to provide more reliable results.

Conclusion

Compared with conventional pharmacological regimens, rt-PA intravenous thrombolytic therapy improves the clinical outcome of patients with acute ischemic stroke, promotes neurological recovery, and enhances patient prognosis without increasing the risk of patient-related adverse events.

Disclosure of conflict of interest

None.

Address correspondence to: Shouyun Zhang, The Encephalopathy Department, Zhecheng Hospital of

Traditional Chinese Medicine, Shangqiu, Henan, China. E-mail: 13569358181@163.com

References

[1] Rabinstein AA. Update on treatment of acute ischemic stroke. Continuum (Minneap Minn) 2020; 26: 268-286.

[2] Mendelson SJ and Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. JAMA 2021; 325: 1088-1098.

[3] Herpich F and Rincon F. Management of acute ischemic stroke. Crit Care Med 2020; 48: 1654-1663.

[4] Jolugbo P and Ariëns RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. Stroke 2021; 52: 1131-1142.

[5] Conway J and Friedman BW. Aspirin after acute ischemic stroke. Am Fam Physician 2020; 102: Online.

[6] Feske SK. Ischemic Stroke. Am J Med 2021; 134: 1457-1464.

[7] Paul S and Candelario-Jalil E. Emerging neuroprotective strategies for the treatment of ischemic stroke: an overview of clinical and preclinical studies. Exp Neurol 2021; 335: 113518.

[8] Ho JP. Acute ischemic stroke: emergency department management after the 3-hour window. Emerg Med Pract 2021; 23: 1-33.

[9] Nagaraja N, Kubilis PS, Hoh BL, Wilson CA, Khanna AY and Kelly AG. Trends of acute ischemic stroke reperfusion therapies from 2012 to 2016 in the United States. World Neurosurg 2021; 150: e621-e630.

[10] Liu M, Pan Y, Zhou L and Wang Y. Low-dose rt-PA may not decrease the incidence of symptomatic intracranial haemorrhage in patients with high risk of symptomatic intracranial haemorrhage. Neurol Res 2019; 41: 473-479.

[11] Yang WY, Li YF, Wang ZR, Yu TX, Xu DJ, Yang N, Niu XY, Cai XL, Zhuo WY, Wu XM, Yan M, Zhou JS, Zhang HW, Liang ZG, Wu WJ, Cheng JH, Huang LA, Zhang YS, Guan Y, Tan ZF, Lu D, He N, Dong DW, Zhu HL, Yang B, Shen QY and Xu AD. Combined therapy of intensive statin plus intravenous rt-PA in acute ischemic stroke: the INSPIRE randomized clinical trial. J Neurol 2021; 268: 2560-2569.

[12] Liu X, Li T, Diao S, Cai X, Kong Y, Zhang L, Wang Z, Li R, Zhou Y and Fang Q. The global burden of cerebral small vessel disease related to neurological deficit severity and clinical outcomes of acute ischemic stroke after IV rt-PA treatment. Neurol Sci 2019; 40: 1157-1166.

[13] Sawaguchi Y and Wang Z. Ultrasound acceleration of rt-pa thrombolysis depends on acoustic intensity. Biol Pharm Bull 2017; 40: 97-103.

[14] Grotta JC. Fifty years of acute ischemic stroke treatment: a personal history. Cerebrovasc Dis 2021; 50: 666-680.

[15] Wu J, Wu J, Wang L and Liu J. Urinary kallidinogenase plus rt-Pa intravenous thrombolysis for acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. Comput Math Methods Med 2022; 2022: 1500669.

[16] Xiang W, Tian C, Lin J, Wu X, Pang G, Zhou L, Pan S and Deng Z. Plasma let-7i and miR-15a expression are associated with the effect of recombinant tissue plasminogen activator treatment in acute ischemic stroke patients. Thromb Res 2017; 158: 121-125.

[17] Chen Z, Xu C, Zhong W, Gong X, Hu H, Zhang X, Chen Y, Li Q, Luo Z, Chen Z and Lou M. Iodinated contrast agents reduce the efficacy of intravenous recombinant tissue-type plasminogen activator in acute ischemic stroke patients: a multicenter cohort study. Transl Stroke Res 2021; 12: 530-539.

[18] Khandelwal P, Yavagal DR and Sacco RL. Acute ischemic stroke intervention. J Am Coll Cardiol 2016; 67: 2631-2644.

[19] Ebinger M, Siegerink B, Kunz A, Wendt M, Weber JE, Schwabauer E, Geisler F, Freitag E, Lange J, Behrens J, Erdur H, Ganeshan R, Liman T, Scheitz JF, Schlemm L, Harmel P, Zieschang K, Lorenz-Meyer I, Napierkowski I, Waldschmidt C, Nolte CH, Grittner U, Wiener E, Bohner G, Nabavi DG, Schmehl I, Ekkernkamp A, Jungehulsing GJ, Mackert BM, Hartmann A, Rohmann JL, Endres M and Audebert HJ. Association between dispatch of mobile stroke units and functional outcomes among patients with acute ischemic stroke in Berlin. JAMA 2021; 325: 454-466.

[20] Renú A, Millán M, San Román L, Blasco J, Martí-Fàbregas J, Terceño M, Amaro S, Serena J, Urra X, Laredo C, Barranco R, Camps-Renom P, Zarco F, Oleaga L, Cardona P, Castaño C, Macho J, Cuadrado-Godía E, Vivas E, López-Rueda A, Guimaraens L, Ramos-Pachón A, Roquer J, Muchada M, Tomasello A, Dávalos A, Torres F and Chamorro Á; CHOICE Investigators. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: The CHOICE Randomized Clinical Trial. JAMA 2022; 327: 826-835.

[21] Bonaventura A, Montecucco F and Dallegri F. Update on the effects of treatment with recombinant tissue-type plasminogen activator (rt-PA) in acute ischemic stroke. Expert Opin Biol Ther 2016; 16: 1323-1340.

[22] Zhu J, Wang S, Chen Z and Cheng Q. Efficacy of rosuvastatin combined with rt-Pa intravenous thrombolytic therapy for elderly acute ischemic

stroke patients. Comput Math Methods Med 2022; 2022: 9403693.
[23] Liu J, Huang J, Xu H and Dai H. Nonatrial fibrillation was associated with early neurological improvement after intravenous thrombolysis With rt-PA in patients with acute ischemic stroke. Neurologist 2020; 25: 28-32.
[24] Che R, Zhao W, Ma Q, Jiang F, Wu L, Yu Z, Zhang Q, Dong K, Song H, Huang X and Ji X. rt-PA with remote ischemic postconditioning for acute ischemic stroke. Ann Clin Transl Neurol 2019; 6: 364-372.
[25] Alderazi YJ, Chang J, Yang JP, Teleb M, Chapple K, Awad A and Restrepo L. Impact of protocol deviations in acute ischemic stroke treated with intravenous rt-PA within 4.5 hours after symptom onset. Neurohospitalist 2012; 2: 82-86.
[26] Bentzon JF, Otsuka F, Virmani R and Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014; 114: 1852-1866.
[27] Vergallo R and Crea F. Atherosclerotic plaque healing. N Engl J Med 2020; 383: 846-857.
[28] Epps KC and Wilensky RL. Lp-PLA$_2$- a novel risk factor for high-risk coronary and carotid artery disease. J Intern Med 2011; 269: 94-106.
[29] Lauretta MP, Melotti RM, Sangermano C, George AM, Badenes R and Bilotta F. Homocysteine plasmatic concentration in brain-injured neurocritical care patients: systematic review of clinical evidence. J Clin Med 2022; 11: 394.