Efficacy of Tirofiban Administered at Different Time Points after Intravenous Thrombolytic Therapy with Alteplase in Patients with Acute Ischemic Stroke

Jin Liu, MD, Qiuyan Shi, MD, Yuan Sun, MD, Jingyuan He, MD, Bin Yang, MD, Chunyang Zhang, MD, and Rui Guo, MD

Objective: To evaluate the efficacy of tirofiban administered at different time points within 24 hours of intravenous thrombolysis with alteplase in acute ischemic stroke. *Methods:* Patients who underwent intravenous thrombolysis with alteplase and fulfilled other inclusion criteria were randomly divided into 4 groups according to the time points of tirofiban administration: Group A (2 h), Group B (2-12 h), Group C (12-24 h), and Group D (control). The changes in National Institutes of Health Stroke Scale score, modified Rankin Scale score, and adverse events were analyzed. *Results:* At 7 ± 1 day, the efficacy in Group A was better than that in Group C ($P = .006$) and Group D ($P = .001$), but there was no significant difference in the efficacy between Groups A and B ($P = .268$). Similarly, at 14 ± 2 d, the efficacy in Group A was better than that in Group C ($P = .026$) and Group D ($P = .001$), but there was no significant difference in the efficacy between Groups A and B ($P = .394$). As evaluated by the modified Rankin Scale, the prognosis in Groups A, B, and C was better than that in Group D ($P = .042$, .008, .027, respectively), which was unrelated to the time points of tirofiban administration. There was no significant difference in the incidence of adverse events among the four groups. *Conclusions:* Tirofiban combined with alteplase is effective and safe, and particularly beneficial when administered at 2 hour and 2-12 hours after intravenous thrombolysis with alteplase in acute ischemic stroke.
Key Words: Acute ischemic stroke—alteplase—tirofiban—thrombolytic therapy
© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Acute ischemic stroke (AIS) has a high morbidity and mortality rate. Presently, intravenous thrombolysis with alteplase within 4.5 hours of onset is preferred in the management of AIS.[1] Re-occlusion may still occur in some patients, especially those with combined great vessel occlusion. In these patients, the vascular recanalization rate after thrombolysis with alteplase is only 13%-18%,[2] which due to the activation of platelets. Because of the risk of cerebral hemorrhage from early use of platelet aggregation inhibitors after intravenous thrombolysis, clinical guidelines do not recommend the use of antiplatelet drugs within 24 hours of thrombolysis.[3-5]

The platelet glycoprotein (GP) IIb/IIIa receptor plays a key role in platelet aggregation and thrombosis and is the ultimate common pathway of platelet aggregation.[6] Tirofiban (TIR), a GPIIb/IIIa receptor antagonist, can competitively inhibit the GPIIb/IIIa receptor. The incidence of TIR-induced severe thrombocytopenia is only 0.5%-2%. The half-life of TIR is about 2 hours, and TIR-induced prolonged bleeding time can be restored to normal within 3 hours of its stoppage.[7] TIR has been widely used in patients with acute coronary syndrome.[8-11] Studies have shown that periodic administration of TIR after alteplase thrombolysis may be safe and more effective as compared to alteplase without increasing the risk of adverse events, such as symptomatic intracranial hemorrhage.[12,13]

Antithrombotic therapy within the first 24 hours of onset of stroke may be beneficial in some patients.[14] There are, however, no systematic studies evaluating the specific time points within the first 24 hours post-thrombolysis at which the GPIIb/IIIa receptor antagonists are most active. This study was performed to evaluate and compare the short-term and long-term efficacy and safety of TIR in combination with alteplase administered at different time points in patients with AIS. Furthermore, the efficacy of TIR administered at different time points within the first 24 hours after intravenous thrombolysis with alteplase in patients with AIS was observed and compared. The goal was to improve the quality of life in these patients by preventing the occurrence of certain ischemic injuries (e.g., re-occlusion) by early rapid initiation of platelet aggregation inhibitors, such as GPIIb/IIIa receptor antagonists.

Materials and Methods

Patients

A total of 240 patients with confirmed diagnosis of AIS, who underwent standard intravenous thrombolysis, and who were admitted in the Affiliated Hospital of North China University of Science and Technology from January 2016 to December 2017 were enrolled in this study. The study participants included 132 males and 108 females, with a mean age of 67.50 ± 7.01 years. The baseline demographic characteristics of the study patients are shown in Table 1.

The inclusion criteria were as follows: (i) patients who had fulfilled the guidelines for the diagnosis and treatment of AIS in China, 2014 and who underwent standard intravenous thrombolysis, (ii) administration of intravenous thrombolytic therapy with alteplase within 3 hours (age 18-85 years) or 3-4.5 hours (age 18-80 years) of the onset of stroke, (iii) presence of symptoms of AIS-induced neurological deficits, and (iv) ability of the patient or family members to sign the informed consent form.

The exclusion criteria were: (i) National Institutes of Health Stroke Scale (NIHSS) score less than or equal to 3 points before thrombolytic therapy, (II) NIHSS score greater than 15 points (right cerebral hemisphere infarction) or NIHSS score greater than 20 points (left cerebral hemisphere and brain stem) before thrombolytic therapy, (iii) blood pressure greater than 180/100 mm Hg during thrombolysis and not returning to normal despite the use of antihypertensive drugs, (iv) aggravation of symptom and confirmation of hemorrhage during thrombolysis by brain CT scan, (v) patients undergoing endovascular treatment (following the guidelines for endovascular treatment for AIS in China, 2015), (vi) patients with life expectancy less than 3 months, (vii) patients with allergy to drugs used in this study, and (viii) patients or family members unwilling to participate in the study.

Treatment Groups

The patients who fulfilled the inclusion criteria first underwent intravenous thrombolysis with 0.9 mg/kg alteplase (Actilyse, Boehringer Ingelheim Pharma GmbH & Co. KG, Shanghai, China) and then were randomly divided into 4 groups according to the time points of TIR (Lunan Pharmaceutical Group Corporation, Shandong, China) administration: Group A (within 2 h of thrombolysis), Group B (within 2-12 h of thrombolysis), Group C (within 12-24 h of thrombolysis), and Group D (control group receiving standard treatment). The dose of TIR was 5 μg/kg administered as an intravenous bolus dose followed by an intravenous infusion of 0.1 μgkg^{-1}min^{-1} for 24 hours.

The results of intracranial hemorrhage in routine brain CT scan were negative for all the patients. The patients then underwent multimodal MRI (DWI, MRA) through green channel, to assess the DWI-ASPECT. The patients underwent multi-modal MRI (T2W1, T1W1, and MRA) of the brain again after 24 hours of thrombolysis to assess the condition of recanalization of the blood vessels. The degree of recanalization was graded with the Thrombolysis in Myocardial Infarction

Table 1. *Baseline data*

Variable	A	B	C	D	*P* value
Age ($\bar{x} \pm s$)	66.26 ± 6.01	68.05 ± 8.25	67.90 ± 6.83	67.71 ± 6.72	.496
M, n (%)	32 (56)	33 (55)	32 (53)	35 (56)	.991
Stroke, N (%)	6 (11)	9 (15)	7 (12)	10 (16)	.794
Hypertension, N (%)	43 (75)	40 (67)	46 (77)	45 (71)	.609
Coronary heart disease, N (%)	5 (9)	3 (5)	4 (7)	5 (8)	.867
Diabetes, N (%)	12 (21)	20 (33)	17 (28)	21 (33)	.412
Atrial fibrillation, N (%)	10 (18)	14 (23)	13 (22)	11 (17)	.804
Hyperlipidemia, N (%)	14 (25)	23 (38)	18 (30)	15 (24)	.270
Smoking, N (%)	14 (25)	17 (28)	13 (22)	11 (17)	.532
Antiplatelet, N (%)	16 (28)	22 (36)	19 (31)	23 (36)	.712
Anticoagulation, N (%)	2 (3)	4 (7)	6 (10)	5 (8)	.579

(TIMI) score.[15] The TIMI score of 0 point is defined as occlusion and 1-2 points is defined as stenosis. Revascularization was defined as an improvement of greater than or equal to 1 in TIMI score in the occluded vessels at 24 hours after treatment.

Data Collection

The NIHSS score in the 4 groups at different time points (prethrombolysis [T1], 7 ± 1 d, 14 ± 2 d, and 90 ± 7 d, and post-thrombolysis [T2-4]), as well as the modified Rankin Scale (mRS) score at T4 were obtained. The proportion of patients with an NIHSS score of 0-1 point at any time point or 4 points less than the baseline score in the different groups were calculated[16,17] to evaluate the corresponding drug efficacy. The proportion of patients with mRS score of 0-2 points in the four groups at T4[18,19] were also calculated. The proportion of patients with symptomatic bleeding, nonsymptomatic bleeding, bleeding from other body parts, other complications, and death were evaluated. Different evaluation methods were used to investigate the drug efficacy in the 4 groups.

Statistical Analyses

All data underwent strict proofreading before entering in an Excel spreadsheet and a data library was built. ANOVA for continuous variables and Chi-square test for categorical variables were performed. All analyses were performed using SPSS version 22.0 and the significance level was set at 0.05.

Results

Stroke Characteristics

In this study, the mean transit time of the patients from the onset of stroke to a hospital was 2.72 ± 0.88. The prethrombolysis NIHSS score of the included patients was between 8 and 12 points. The ASPECT-DWI score of the patients[20,21] was 7.96 ± 1.34. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype, large artery atherosclerosis, cardioembolism, small artery occlusion, other/undetermined stroke, and undefined stroke was present in 159 (66.3%), 30 (12.5%), 40 (16.7%), 7 (2.9%), and 4 (1.6%) patients, respectively. Complications, such as pulmonary infection urinary infection were found in 34 (14.2%) and 30 (12.5%) patients. There were no significant differences among the four groups (P > .05, Table 2).

Vessel Occlusion and Recanalization Rate

We analyzed 135 patients with occlusion or stenosis. There were 6 patients with internal carotid artery (ICA) occlusion, of which 1 case achieved recanalization and the recanalization rate was 16.7%; 17 patients of middle cerebral artery (MCA) M1, of which 8 cases achieved recanalization and the recanalization rate was 47.1%; 87 patients of MCA M2 and branching, of which 63 cases achieved recanalization and the recanalization rate was 72.4%; 25 cases of vertebrobasilar artery (VBA), of which 11 cases achieved recanalization and the recanalization rate was 44.0%. The recanalization rate of M2 and branching was higher than ICA/M1/VBA (P=.011, .040, and .008), and no statistically significant difference was found among the other groups (P>.05). This demonstrated that the recanalization was associated with infarction location (Table 3).

Among patients with occlusion or stenosis, 83 patients achieved recanalization after 24 hours of thrombolysis, and the overall recanalization rate was 61.5%. The number of patients with ICA occlusion or stenosis in Groups A, B, C, and D were 2, 2, 1, and 1, respectively, and only one patient in Group A achieved recanalization. The highest recanalization rate after MCA M1 occlusion was found in Group B (66.7%). Both Groups A and B had a similar and good recanalization rate (75.0%) after occlusion of MCA M2 and its branches. After VBA occlusion, both Groups B and D

Table 2. *Stroke characteristics*

Variable	A	B	C	D	P value
Time from onset to hospital ($\overline{x}$± s)	2.62 ± 0.91	2.75 ± 0.84	2.65 ± 0.90	2.85 ± 0.87	.461
The NHISS scores before thrombolysis	10.11 ± 5.04	9.25 ± 4.52	9.10 ± 4.38	10.38 ± 4.68	.505
ASPECT-DWI ($\overline{x}$± s)	7.85 ± 1.41	7.91 ± 1.27	7.96 ± 1.20	8.09 ± 1.46	.798
TOAST subtypes, N (%)					.766
Large artery atherosclerosis	35 (61)	42 (70)	37 (61)	45 (71)	
Cardioembolism	8 (14)	6 (10)	10 (16)	6 (9)	
Small artery occlusion	10 (17)	8 (13)	12 (20)	10 (15)	
Other/undetermined	3 (5)	2 (3)	0	2 (3)	
Undefined	1 (2)	2 (3)	1 (2)	0	
Pulmonary infection, N (%)	6 (10)	13 (18)	5 (8)	10 (15)	.305
Urinary infection, N (%)	5 (8)	8 (13)	5 (8)	12 (19)	.242

Table 3. *Comparison of vessels and recanalization rate among four groups (n, %)*

Group	ICA stenosis or occlusion	recanalization	M1 stenosis or occlusion	recanalization	M2 and branching stenosis or occlusion	recanalization	VBA stenosis or occlusion	recanalization
A	2	1(50.0)	5	2(40.0)	24	18(75.0)	4	1(25.0)
B	2	0	3	2(66.7)	20	15(75.0)	6	3(50.0)
C	1	0	3	1(33.3)	19	13(68.4)	7	3(42.8)
D	1	0	6	3(50.0)	24	17(70.8)	8	4(50.0)
sum	6	1(16.7)	17	8(47.1)	87	63(72.4)	25	11(44.0)
X^2		2.400		0.811		0.329		0.794
P		0.494		0.847		0.954		0.851

Note: There were no statistical significance between the four groups (P>0.05).

had a similar and good recanalization rate (50.0%). No statistical significance was, however, obtained ($P > .05$, Table 3) because of the small sample size.

Evaluation of Efficacy at T2

The efficacy in Group A was better than that in Groups C and D ($P = .006$ and .001, respectively). There was, however, no statistical significance in the efficacy between Groups A and B ($P = .268$), and between Groups B and C ($P = .090$). The efficacy in Group B was better than that in Group D ($P = .019$), and the efficacy in Groups C and D showed no significant difference ($P = .520$, Table 4).

The combined treatment group and alteplase alone group constituted of 120 (67.8%) and 31 patients (49.2%), respectively. The efficacy in the combined therapy group was better than that in the alteplase alone group ($P = .009$).

Efficacy Evaluation at T3

The efficacy in Group A was better than that in Groups C and D ($P = .026$ and .001, respectively), There was, however, no statistical significance in the efficacy between Groups A and B ($P = .394$). The efficacy in Group B was better than that in Groups C and D ($P = .002$ and .019, respectively), and the efficacy in Groups C and D showed no significant difference ($P = .230$, Table 4)

Table 4. *Comparison of efficacies among different groups at different time points (n, %)*

Group	n	T2	T3
A	57	45 (78.9)*▲	45 (78.9)*▲
B	60	42 (70.0)*	51 (85.0)*▲
C	60	33 (55.0)	36 (60.0)
D	63	31 (49.2)	31 (49.2)
X^2		14.256	23.066
P		.003	.000

Note:* Compared with group D, $P < .05$, ▲ compared with group C, $P < .05$.

The combined treatment group and alteplase alone group constituted of 132 (74.6%) and 31 patients (49.2%), respectively. The efficacy in the combined therapy group was better than that in the alteplase alone group ($P < .001$).

Evaluation Using mRS Score at T4

The prognosis in Groups A, B, and C was significantly better than that in Groups D at T4 ($P = .042$, .008, and .027, respectively). The difference in the mRS score among Groups A, B, and C, however, showed no significant difference ($P > .05$, Table 5).

The combined treatment group and alteplase alone group constituted of 143 (80.8%) and 39 patients (61.9%), respectively. The efficacy in the combined therapy group was better than that in the alteplase alone group ($P = .003$).

Adverse Events

The frequency of symptomatic intracranial hemorrhage was 1 (1.8%) in Group A and 0 (0%) in Groups B and C, respectively; The frequency of nonsymptomatic cerebral hemorrhage was 2 (3.5%) in Group A, 2 (3.3%) in Group B, 3 (5.0%) in Group C, and 3 (4.8%) in Group D. The frequency of bleeding at other body parts was 3 (5.3%) in Group A, 4 (6.7%) in Group B, 3 (5.0%) in Group C, and 5 (8.0%) in Group D. There was no incidence of death in any of the groups. There was no significant difference in the frequency of adverse events ($P > .05$, Table 6).

Table 5. *Comparison of prognosis among 4 groups using mRS score at T4 (n, %)*

Group	n	Good	Poor
A	57	45 (78.9)*	12 (21.1)*
B	60	50 (83.3)*	10 (16.7)*
C	60	48 (80.0)*	12 (20.0)*
D	63	39 (61.9)	24 (38.1)
X^2		9.381	9.381
P		.025	.025

Note: * Compared with group D, $P < .05$. The mRS score as 0-2 points is defined as good functional outcome, and the mRS score as 3-6 points is defined as poor functional outcome.[18,19]

Table 6. *Adverse events in 4 groups (n, %)*

Group	n	Symptomatic intracranial hemorrhage	Nonsymptomatic cerebral hemorrhage	Bleeding at other parts	Death
A	57	1 (1.8)	2 (3.5)	3 (5.3)	0
B	60	0	2 (3.3)	4 (6.7)	0
C	60	0	3 (5.0)	3 (5.0)	0
D	63	1 (1.6)	3 (4.8)	5 (8.0)	0

Note: There were no statistical significance in adverse events among the 4 groups ($P > .05$).

Discussion

The administration of antiplatelet drugs after intravenous thrombolysis is extremely important in patients with AIS. There is still variation in the timing of drug administration to achieve the optimal treatment. Early revascularization is associated with good prognosis and lower mortality rate and is widely used in patients with acute coronary syndrome and high-risk percutaneous coronary intervention.[22] Because of the risk of bleeding after thrombolysis, the current guidelines recommend traditional antiplatelet drugs to be initiated after 24 hours of thrombolysis. Therefore, it is required to look for a drug which can be used within 24 hours of thrombolysis to prevent blood vessel re-occlusion by confronting platelet aggregation, but without increasing the risk of complications, such as bleeding. This study has evaluated the optimal time of initiation of such a drug.

TIR competitively inhibits GPIIb/IIIa receptors, prevents binding of fibrinogen to the platelet receptors, and blocks platelet adhesion and aggregation. Its use may, however, increase the risk of bleeding due to potent inhibition of platelet aggregation. Studies have shown that alteplase combined with TIR is superior to alteplase alone for the treatment of myocardial reperfusion.[23] In this study, the NIHSS score of the patients was in the range of 8-12 points, and the proportion of patients with ASPECT-DWI score between 8 and 10 was 70%. Different methods were used to evaluate the AIS patients and the following results were obtained.

The recanalization rate in ICA was the highest in Group A, whereas the recanalization rate in M1 was the highest in Group B. The recanalization rate in M2 and its branches were highest in Groups A and B, whereas the recanalization rate in VBA was highest in Groups B and D. This indicates that early administration of TIR may improve the efficacy of intravenous thrombolysis, promote recanalization of blood vessels, improve recanalization rate, facilitate reperfusion in ischemic tissue, and reduce the infarct size. The recanalization rates were not significantly different among the four groups, which may be because of the small sample size.

The efficacy in Group A at T2 was better than that in Groups C and D, the efficacy in Group B was better than that in Group D, and there was no significant difference in the efficacy between Groups A and B. At T3, the efficacy in Group A was better than that in Groups C and D, the efficacy in Group B was better than Groups C and D, and there was no significant difference in the efficacy between Groups A and B. This implied that administration of TIR in Groups A and B produced similar and good results in terms of management of early clinical symptoms of AIS patients. Efficacy evaluation using the mRS score revealed that sequential administration of TIR after thrombolysis with intravenous alteplase can improve the prognosis of the patients 3 months later, although the timing of initiating of TIR therapy did not differ in the prognosis at three months.

There was no significant difference in the incidence of adverse events, such as bleeding and death among the four groups. Due to the strict screening criteria and the small number of enrolled patients, no death occurred within 3 months. Therefore, it can be inferred that the administration of TIR within 24 hours after intravenous thrombolysis is relatively safe in AIS patients who had fulfilled the inclusion criteria and underwent intravenous thrombolysis with alteplase.

There are some limitations in this study. Due to the small number of patients with embolism enrolled in this study, the results of these patients in the different groups were not significantly different. Therefore, the efficacy of TIR in patients with embolism could not be confirmed by this study, and a larger number of patients are required to evaluate this. Due to the differences in the time of onset, the location of the occluded vessels, the severity of the disease, body constitution, and underlying diseases, it is not clear whether endovascular treatment is needed after thrombolysis. In some patients with occlusion of the major vessels, the decision of endovascular treatment has to be taken by the treating physician in consultation with the relevant guidelines. Alteplase in combination with endovascular treatment is recommended in AIS based on the data obtained from randomized clinical trials (MR CLEAN, EXTEND-IA, SWIFT PRIME, etc.).[24-26] Our study, however, does not include a comparison with endovascular treatment. Therefore, further studies are required to evaluate the best treatment regimen for these patients. The actual recanalization rate may be higher due to limitations in the imaging interpretation and possible omission of small branches of the cerebral arteries.

Due to the strong correlation of age, blood glucose, and pre-thrombolytic NIHSS score with the post-thrombolytic prognosis.[27] The patients enrolled in this study were strictly screened according to the inclusion criteria and grouped randomly to achieve consistency in the baseline data and to reduce the impact of any variability on the final results. Despite randomization, the group allocation could still be affected by some factors, such as individual variations and existing conditions. Patients with high systolic blood pressure and atrial fibrillation are more at risk of hemorrhagic transformation after thrombolysis.[28] The study used the NIHSS score and mRS score, instead of using an imaging method to confirm vascular occlusion or recanalization, which may cause some errors in the interpretation of the results. The AIS patients with different incidence types were not stratified for analysis. The patients who were discharged within 3 months were told to follow their physician's advice and schedule the review visits, nevertheless, some patients still stopped their medications by themselves, thereby affecting the study results.

In summary, the results of this study showed that treatment with alteplase in combination with TIR can significantly improve the early and short-term clinical symptoms, reduce the degree of disability, and improve the quality of life in AIS patients. The results also show that early administration of TIR is more beneficial. Further, the incidence of adverse events, such as bleeding and death did not increase with TIR. In the different TIR groups, some of the results failed to show a significant difference, which may be because of a small sample size. Therefore, multi-center randomized blinded trials in larger samples are needed for the validation of the results of this study as well as for the appropriate extension of the follow-up periods.

References

1. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.
2. Asadi H, Dowling R, Yan B, et al. Advances in endovascular treatment of acute ischaemic stroke. Intern Med J 2015;45:798-805.
3. Barreto AD, Ford GA, Shen L, et al. Randomized, multi-center trial of ARTSS−2 (argatroban with recombinant tissue plasminogen activator for acute stroke). Stroke 2017;48:1608-1616.
4. Faigle R, Sharrief A, Marsh EB, et al. Predictors of critical care needs after IV thrombolysis for acute ischemic stroke. PLoS One 2014;12(9):e88652.
5. Powers WJ, Derdeyn CP, Biller J, et al. American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:3020-3035.
6. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Engl J Med 1995;332:1553-1559.
7. Möckel M, Bocksch W, Strohm S, et al. Facilitated percutaneous coronary intervention (PCI) in patients with acute ST-elevation myocardial infarction: comparison of prehospital tirofiban versus fibrinoly-sis before direct PCI. Int J Cardiol 2005;103:193-200.
8. Zhao H, Zhang J, Gu D, et al. Tirofiban facilitates the reperfusion process during endovascular thrombectomy in ICAS. Exp Therap Med 2017;14:3314-3318.
9. Song Y. Evaluation on the safety and efficacy of tirofiban in the treatment of acute coronary syndrome. J Huazhong Univ Sci Technolog Med Sci 2007;27:142-144.
10. Rasoul S, Ottervanger JP, de Boer MJ, et al. Routine upstream versus selective downstream use of tirofiban in non-ST elevation myocardial infarction patients scheduled for early invasive therapy; a randomized comparison. J Thromb Thrombol 2007;24:241-246.
11. Kaymaz C, Keleş N, Özdemir N, et al. The effects of tirofiban infusion on clinical and angiographic outcomes of patients with STEMI undergoing primary PCI. Esen Anatol J Cardiol 2016;5:899-906.
12. Li W, Lin L, Zhang M, et al. Safety and preliminary efficacy of early tirofiban treatment after alteplase in acute ischemic stroke patients. Stroke 2016;47:2649-2651.
13. Yeo LL, Paliwal P, Teoh HL, et al. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. JAMA Neurol 2013;70:353-358.
14. Jeong HG, Kim BJ, Yang MH, et al. Stroke outcomes with use of antithrombotics within 24 hours after recanalization treatment. Neurology 2016;87:996-1002.
15. Hohenhaus M, Schmidt WU, Brunecker P, et al. FLAIR vascular hyperintensities in acute ICA and MCA infarction: a marker for mismatch and stroke severity? Cerebrovasc Dis 2012;34:63-69.
16. Ghafoor F, Khan F, Shehna A. Real-world effectiveness of intravenous stroke thrombolysis is more than the expectation of practicing neurologists. J Neurosci Rural Pract 2018;9:331-335.
17. Dharmasaroja PA, Muengtaweepongsa S, Dharmasaroja P. Early outcome after intravenous thrombolysis in patients with acute ischemic stroke. Neurol India 2011;59:351-354.
18. Carvalho A, Cunha A, Gregório T, et al. Is the efficacy of endovascular treatment for acute ischemic stroke sex-related. Interv Neurol 2018;7:42-47.
19. Külkens S, Hacke W. Thrombolysis with alteplase for acute ischemic stroke: review of SITS-MOST and other Phase IV studies. Expert Rev Neurother 2007;7:783-788.
20. Nogawa S, Abe T, Shigematsu H, et al. DWI-aspects and NIHSS at baseline predict good responsiveness to endovascular thrombectomy following thrombolysis in large cerebral vessel occlusion. J Neurol Sci 2017;381:634.
21. Yuuka C, Taira N, Kazuyuki I, et al. P4-2 - DWI-ASPECTS and NIHSS at baseline predict responsiveness to the mechanical endovascular thrombectomy after

thrombolysis for acute ischemic stroke. J Stroke Cerebro-vasc Dis 2017;26:908.

22. Nazif TM, Mehran R, Lee EA, et al. Comparative effective-ness of upstream glycoprotein IIb/IIIa inhibitors in patients with moderate-and high-risk acute coronary syndromes: an Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) substudy. Am Heart J 2014;167:43-50.

23. Tas MH, Simsek Z, Ayan A, et al. Effects of tirofiban maintenance duration on myocardial perfusion defect severity in anterior myocardial infarction. Adv Ther 2013;30:834-844.

24. Mulder MJHL, Jansen IGH, Goldhoorn RB, et al. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN registry results. Circulation 2018;138:232-240.

25. Campbell BC, Mitchell PJ, Yan B, et al. A multicenter, ran-domized, controlled study to investigate Extending the time for thrombolysis in Emergency Neurological Deficits with Intra-arterial therapy (EXTEND-IA). Int J Stroke 2014;9:126-132.

26. Mokin M, Levy EI, Saver JL, et al. Predictive value of RAPID assessed perfusion thresholds on final infarct vol-ume in SWIFTPRIME (Solitaire with the intention for thrombectomy as primary endovascular treatment). Stroke 2017;48:932-938.

27. Tong X, Liao X, Pan Y, et al. Intravenous thrombolysis is more safe and effective for posterior circulation stroke: Data from the Thrombolysis Implementation and Moni-tor of Acute Ischemic Stroke in China (TIMS-China). Medicine 2016;95:e3848.

28. Wahlgren N, Ahmed N, Eriksson N, et al. Multivariable analysis of out-come predictors and adjustment of main outcome results to baseline data role in randomized con-trolled trials: Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). Stroke 2008;39: 3316-3322.