doi.org/10.36721/PJPS.2026.39.8.224.1

Intravenous tirofiban in non-LVO progressive stroke beyond the thrombolysis window

Ming Zhou[1,2#], Ying Zhang[2#], Xin Zhao[2], Pengfei Chang[2], Jiangbo Xie[2], Tao Liu[2], Haixia Wang[3]* and Jinbao Wang[2]*

[1]College of Traditional Chinese Medicine, Shandong Second Medical University, Weifang, Shandong 261053, China.
[2]Department of Encephalopathy, Weifang Hospital of Traditional Chinese Medicine, Shandong Second Medical University, Weifang, Shandong 261041, China.
[3]Department of Traditional Chinese Medicine, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong 261032, China.

Abstract: **Background**: Neurological worsening after hospital admission frequently correlates with poor clinical prognosis. However, treatment options are limited for acute ischemic stroke patients who are outside the thrombolytic time window and do not have large vessel occlusion (LVO). **Objectives**: This study evaluated the safety and efficacy of intravenous tirofiban in this population. **Methods**: A total of 44 patients diagnosed with progressive ischemic stroke were analyzed, defined as an increase of ≥2 points on the NIHSS or a ≥1-point worsening in limb motor score within 24 hours of symptom onset. of these, 26 received intravenous tirofiban in addition to dual antiplatelet therapy, while the remaining 18 received dual antiplatelet therapy alone. The primary efficacy endpoints were the NIHSS score at 7 days and the proportion of patients achieving a superior functional outcome [modified Rankin Scale (mRS) score 0–1] at 3 months. Symptomatic intracranial hemorrhage, systemic bleeding events and thrombocytopenia were monitored. **Results**: The tirofiban group showed greater neurological improvement at 7 days ($p < 0.001$) and an increased favorable outcome at 90 days (80.77% vs 27.78%, $p = 0.001$). Logistic regression confirmed tirofiban as an independent parameter of favorable outcome (adjusted OR 15.67, 95% CI: 2.97–82.61, $p = 0.001$). Neither group presented symptomatic intracranial hemorrhage, systemic bleeding, or thrombocytopenia. **Conclusion**: Intravenous tirofiban may represent a potential therapeutic option for patients with progressive ischemic stroke beyond the thrombolytic window and without LVO, showing an association with improved neurological recovery and functional outcomes. Its clinical efficacy and safety shall be further confirmed through large-scale, randomized, prospective studies.

Keywords: Acute ischemic stroke; Antiplatelet therapy; Functional outcome; Progressive stroke; Tirofiban

Submitted on 31-10-2025 – Revised on 13-01-2026 – Accepted on 21-01-2026

INTRODUCTION

Stroke persists as a leading cause of mortality and chronic disability around the world, represented by acute ischemic stroke (AIS) (Kongsui *et al*., 2025; Plotnikov *et al*., 2025), the pathophysiology of which involves oxidative stress, neuroinflammatory responses, compromise of the blood-brain barrier and other interconnected events (Zheng *et al*., 2025). While intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) represents the cornerstone of AIS management, its real-world application is significantly constrained (Luo *et al*., 2025). A narrow therapeutic window, rigorous eligibility criteria and concerns over hemorrhagic complications collectively result in fewer than 2% of patients receiving this treatment (Guzman *et al*., 2025; Goh *et al*., 2025; Edlow and Tarnutzer, 2025). Further limitations encompass post-thrombolytic arterial re-occlusion and experimental approaches such as co-administration with ERK1/2 inhibitors like U0126 introduce additional complexity without established clinical benefit (e.g., U0126)—increasing treatment complexity (Orset *et al*., 2021). For individuals presenting beyond the thrombolysis window with confirmed large vessel occlusion (LVO), endovascular thrombectomy offers a potent alternative, guided by advanced neuroimaging (Mortezaei *et al*., 2025; Rodriguez-Calienes *et al*., 2025). However, this significant gap in acute care protocols for progressive, non-LVO AIS patients beyond the thrombolysis window remains unaddressed.

Management of progressive AIS remains challenging. Endovascular therapy (EVT) (Wu *et al*., 2025), tirofiban administration (Wang *et al*., 2025a; Qiao *et al*., 2025) and various adjunctive therapies have been attempted in selected patients, but their roles are still not well defined. Progressive stroke is thought to result primarily from *in situ* thrombus propagation or recurrent microembolization within the same vascular territory rather than reperfusion injury (de la Riva *et al*., 2024; Marta-Enguita *et al*., 2024). Therefore, inhibiting platelet aggregation and reducing thrombus burden may help prevent further neurological deterioration (Kitano *et al*., 2022). As a potent and reversible glycoprotein IIb/IIIa antagonist, tirofiban provides immediate inhibition of platelet aggregation, an effect that is swiftly reversed after cessation due to its brief

**Corresponding author:* e-mail: wanghaixia@sdsmu.edu.cn ; drwangjinbao@sina.com
#These authors contributed equally and are the co-first authors.

half-life (Wang *et al*., 2025b). Originally developed for the management of acute coronary syndromes, tirofiban has recently attracted increasing attention for potential therapeutic use in cerebrovascular disorders (Guven *et al*., 2025; Hu *et al*., 2025).

Previous studies have mainly focused on patients with LVO undergoing mechanical thrombectomy, in whom tirofiban has been used as a perioperative adjunct to prevent re-occlusion or manage early neurological worsening (Luo *et al*., 2023; Liu *et al*., 2023). Nevertheless, robust clinical evidence is lacking to support tirofiban administration in progressive AIS patients ineligible for thrombolysis and without LVO, leaving their management undefined. Consequently, despite the clinical challenge, evidence regarding the use of intravenous tirofiban in non-LVO progressive strokes beyond the thrombolysis window remains limited. Against this backdrop, this study evaluated its safety and efficacy.

MATERIALS AND METHODS

Study design and patient selection

This retrospective, non-randomized controlled trial (RCT) was carried out at Weifang Traditional Chinese Medicine Hospital. The study protocol was reviewed and approved by the Ethics Committee of Weifang Traditional Chinese Medicine Hospital (Approval No. 202403-106) and was conducted in accordance with the principles of the Declaration of Helsinki. Patient screening and enrollment were carried out between May 2021 and May 2022. As this was a retrospective exploratory study, no formal sample size calculation was performed. All consecutive patients included in the study met the inclusion criteria.

Inclusion criteria: defined with reference to established definitions and methodologies used in prior ischemic stroke studies and current clinical guidelines (Powers *et al*., 2019; Zi *et al*., 2023). Eligibility criteria included age ≥18 years, presentation between 5–24 hours after symptom onset and a confirmed AIS diagnosis without evidence of arterial occlusion on CTA or MRA. Neurological progression referred to the situation with an increase of ≥2 points in the NIHSS total score or a decline of ≥1 point in limb motor function documented within the first 24 hours of hospitalization. Written informed consent was obtained. Representative neuroimaging findings are presented in Fig. 1.

Exclusion criteria: with intracranial hemorrhage or subarachnoid hemorrhage, a history of major surgery or bleeding tendency within the previous three months, coagulation abnormalities or a platelet count below 100×10^9/L, or severe hepatic or renal dysfunction. Additional exclusion criteria included prior long-term use of anticoagulant therapy (such as warfarin or direct oral anticoagulants), severe comorbid conditions with a life expectancy < 3 months (e.g., advanced heart failure or active malignancy), pregnancy or lactation, or incomplete clinical or neuroimaging data.

Treatment protocol

All enrolled patients received an initial loading dose of 300 mg aspirin and 75 mg clopidogrel upon hospital admission (Jiang *et al*., 2025). Patients in the tirofiban group subsequently underwent intravenous administration with a loading infusion of 0.4μg/kg/min over 30-180 minutes, immediately after which they received a continuous maintenance infusion of 0.1μg/kg/min for 24-72 hours (Liu *et al*., 2024). Dual antiplatelet therapy (DAPT) was initiated sequentially after tirofiban, guided by individual clinical assessment. Patients received oral aspirin (100 mg) and clopidogrel (75 mg) after initial tirofiban exposure, with a brief overlap during the transition phase. DAPT (aspirin 100 mg plus clopidogrel 75 mg daily) was then continued for 21 days, followed by 69 days of single antiplatelet therapy (aspirin 100 mg or clopidogrel 75 mg daily). For the reduction of the risk of hemorrhagic transformation, patients with hypertension received intravenous antihypertensive therapy during tirofiban administration to maintain systolic blood pressure (SBP) within a target range of 140–160 mmHg, in accordance with recent reviews on acute-phase stroke blood pressure management and peri-procedural care strategies (Guo *et al*., 2022; De Georgia *et al*., 2023).

The control cohort, selected from a prospective stroke registry, received standard medical management identical to the intervention group but without tirofiban. Their antithrombotic protocol consisted of a 300 mg clopidogrel loading dose, followed by daily maintenance with 100 mg aspirin and 75 mg clopidogrel (Kleindorfer *et al*., 2021).

Safety outcomes

Safety assessment encompassed 90-day occurrences of symptomatic intracranial hemorrhage (sICH), any intracranial hemorrhage, major systemic bleeding, thrombocytopenia and all-cause mortality. The diagnosis of sICH required a neurologically significant decline, defined as a worsening in the NIHSS score, together with neuroimaging confirmation of hemorrhage after exclusion of alternative explanations. Thrombocytopenia was defined as a platelet count $\leq100{,}000/mm^3$, with counts tracked daily during the hospital stay (Zi *et al*., 2023). A comprehensive documentation of all systemic bleeding events was maintained.

Efficacy outcomes

The NIHSS score on day 7, indicating early neurological recovery and the 3-month mRS for long-term functional outcomes were analyzed. An mRS score of 0–1 at 3 months was dichotomized as a favorable prognosis.

Propensity score matching (PSM) and statistical analysis

Baseline demographic and clinical variables were summarized descriptively. To reduce potential selection bias, a 1:1 PSM procedure was applied utilizing nearest-neighbor matching without replacement. The propensity score model included age, sex, baseline NIHSS score and lesion location. An SMD value below 0.10 was considered indicative of adequate group balance. To determine the independent association between tirofiban therapy and favorable 90-day outcomes (mRS 0-1), a logistic regression analysis was conducted, adjusting for age and baseline NIHSS. Adjusted ORs and their 95% CIs were generated, with a two-tailed p-value < 0.05 establishing statistical significance. Given the limited sample size and number of outcome events, the multivariable logistic regression model selected only a few clinically essential covariates to avoid overfitting. The entire analytical process was conducted using SPSS (version 23.0; IBM Corp.).

RESULTS

Baseline information

A total of 57 patients met the initial inclusion criteria and were included in the overall cohort. The PSM achieved an acceptable balance across key baseline covariates of age, sex, baseline NIHSS score, and lesion location. After 1:1 PSM, 44 patients were retained for the matched analysis, with 26 and 18 in the tirofiban and control groups, respectively (Table 1).

Trends in NIHSS and mRS scores

At admission, NIHSS scores did not differ a lot between the tirofiban and control groups, indicating comparable baseline neurological deficits. Both groups experienced neurological deterioration within the first 24 hours after admission, reaching peak NIHSS values during this period. Thereafter, NIHSS scores gradually decreased over time in both groups, indicating neurological recovery during follow-up. Regarding functional outcomes, the mRS score distribution at 90 days suggested a shift toward better functional recovery in the tirofiban group. The temporal trends in neurological and functional outcomes are illustrated in Fig. 2.

Between-group comparison of neurological and functional outcomes

Consistent with the observed temporal trends, NIHSS scores did not differ significantly between the two groups at baseline or at peak deterioration ($p > 0.05$). By day 7, tirofiban-treated patients demonstrated significantly lower NIHSS scores ($p<0.001$) and greater score reductions from baseline (ΔNIHSS, $p=0.002$), indicating enhanced neurological recovery. These short-term benefits were paralleled by superior 90-day functional outcomes, with the tirofiban group exhibiting lower mRS scores ($p<0.001$) and a rising rate of favorable outcomes (80.77% vs. 27.78%, $p<0.01$). In multivariate analysis, tirofiban independently predicted a favorable 90-day prognosis ($p<0.01$; Table 2, Fig. 3).

Multivariate logistic regression analysis

After accounting for age, baseline NIHSS and sex, tirofiban treatment remained strongly linked to favorable 90-day outcomes (mRS 0-1). The adjusted OR was 15.67 (95% CI: 2.97-82.61; $p=0.001$). In comparison, none of the other factors examined showed a clear association with clinical outcomes (all $p > 0.05$; Table 3).

Safety outcomes

In this cohort, no intracranial hemorrhage (symptomatic or asymptomatic), thrombocytopenia, or clinically significant systemic bleeding was observed in either group during hospitalization. However, given the limited sample size, this study was not powered to detect rare safety events. Therefore, these findings should be interpreted as descriptive observations rather than definitive evidence of safety.

DISCUSSION

In this study, early intravenous tirofiban administration, compared with conventional dual antiplatelet therapy, was associated with significantly accelerated neurological improvement on day 7 and a higher rate of functional independence at 90 days in patients with progressive stroke, without an increased risk of hemorrhagic events.

In this study, tirofiban may accelerate early neurological recovery in patients with progressive AIS and improve functional outcomes at 90 days (mRS 0–1), without increasing the risk of hemorrhagic complications. All of these are consistent with previous reports on the use of tirofiban in AIS (de Almeida Monteiro *et al*., 2025). In addition, based on the findings from a systematic review and meta-analysis (de Souza *et al.,* 2025), tirofiban, compared with standard treatment, improves 90-day functional outcomes (mRS 0–1), which aligns with our present results. However, in Yuri's analysis, tirofiban did not show a significant advantage in short-term neurological status as assessed by the 7-day NIHSS score.

According to multiple studies, tirofiban, when administered in combination with reperfusion therapies, does not substantially increase the risk of symptomatic intracranial hemorrhage or all-cause mortality (de Almeida Monteiro *et al*., 2025; Monteiro *et al*., 2024). Moreover, early evidence from the SaTIS trial indicates that tirofiban did not significantly increase the risk of intracranial hemorrhage in AIS patients. Moreover, combining tirofiban with low-dose rt-PA has been shown to be safe, without an increased bleeding risk (Liang *et al*., 2022).

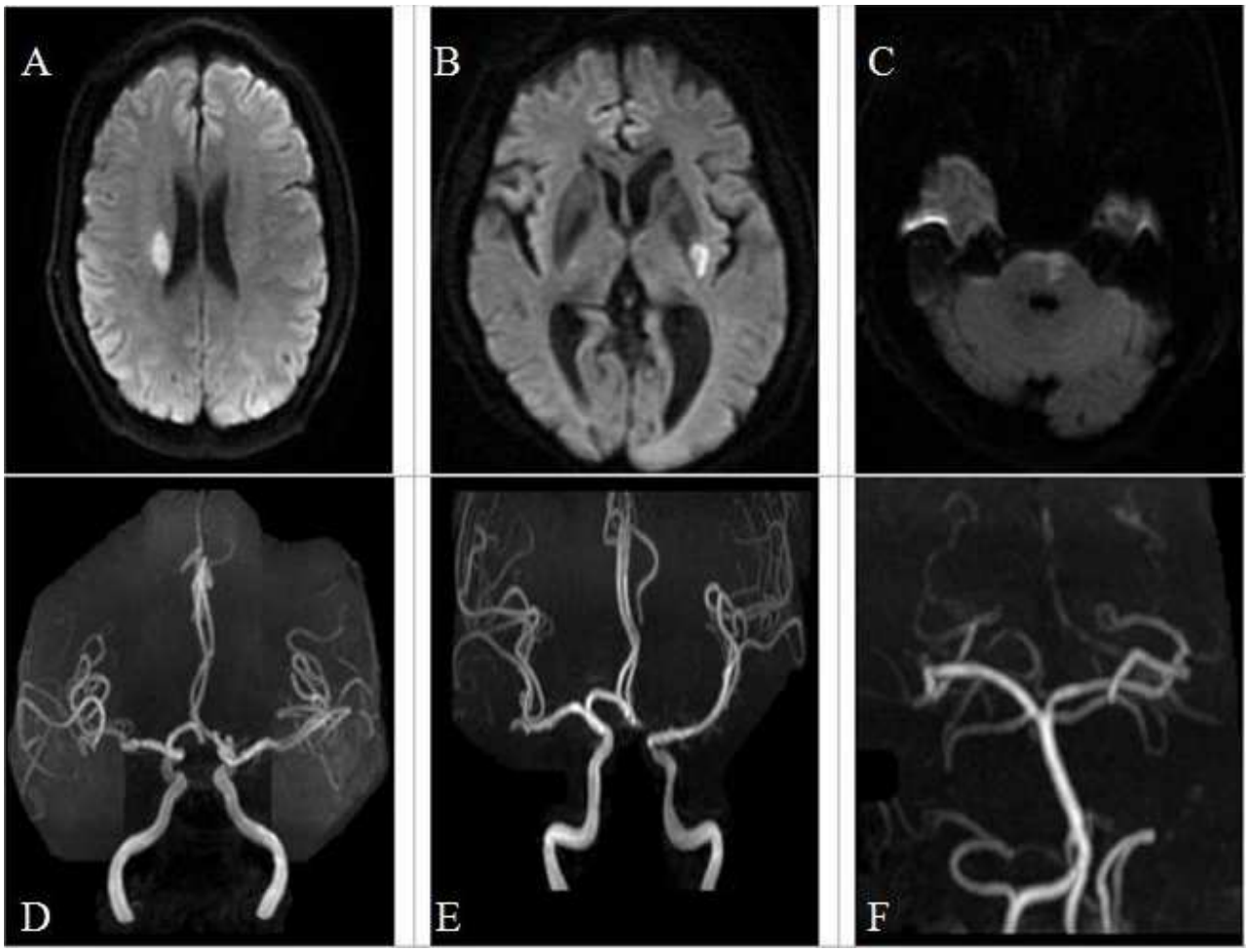

Fig. 1: Example of cases meeting inclusion criteria.
Case 1: (A) Diffusion-weighted imaging (DWI) revealed AIS in right corona radiate; (D) MRA revealed no occlusion but significant right middle cerebral artery stenosis. Case 2; (B) DWI revealed AIS in the left internal capsule; (E) MRA revealed no occlusion or significant stenosis in the left middle cerebral artery. Case 3; (C) DWI revealed AIS in left pons; (F) MRA revealed no occlusion but significant stenosis in the basilar artery.

Table 1: Baseline demographic and clinical characteristics of the two groups

Parameter	Tirofiban group (n=26)	Control group (n=18)	*P-value*	SMD
Gender			0.96	0.089
Female, n (%)	9 (34.62%)	6 (35.29%)		
Male, n (%)	17 (65.38)	11 (64.71)	0.92	
NIHSS_baseline	2.96±1.40	3.11±1.37		0.108
Age, median (IQR), y	63.50 (56.00 – 72.00)	60.00 (54.75 – 65.00)	0.82	0.352
Hypertension, n (%)	20 (76.92)	12 (66.67)	0.62	0.229
Diabetes mellitus, n (%)	4 (15.38)	3 (16.67)	0.99	0.035
Previous ischemic stroke, n (%)	2 (7.69)	1 (5.56)	0.54	0.086
Cardiovascular disease, n (%)	2 (7.69)	0 (0.00)	0.21	0.408
Alcohol use, n (%)	1 (3.85)	1 (5.56)	0.99	0.081
Smoking, n (%)	4 (15.38)	6 (33.33)	0.25	0.428
Lesion location				
– *Corona radiata*	4 (15.38)	3 (16.67)	0.99	0.035
– *Internal capsule*	13 (50.00)	9 (50.00)	0.99	0.000
– *Pons*	9 (34.62)	6 (33.33)	0.99	0.027

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; SMD, standardized mean difference.

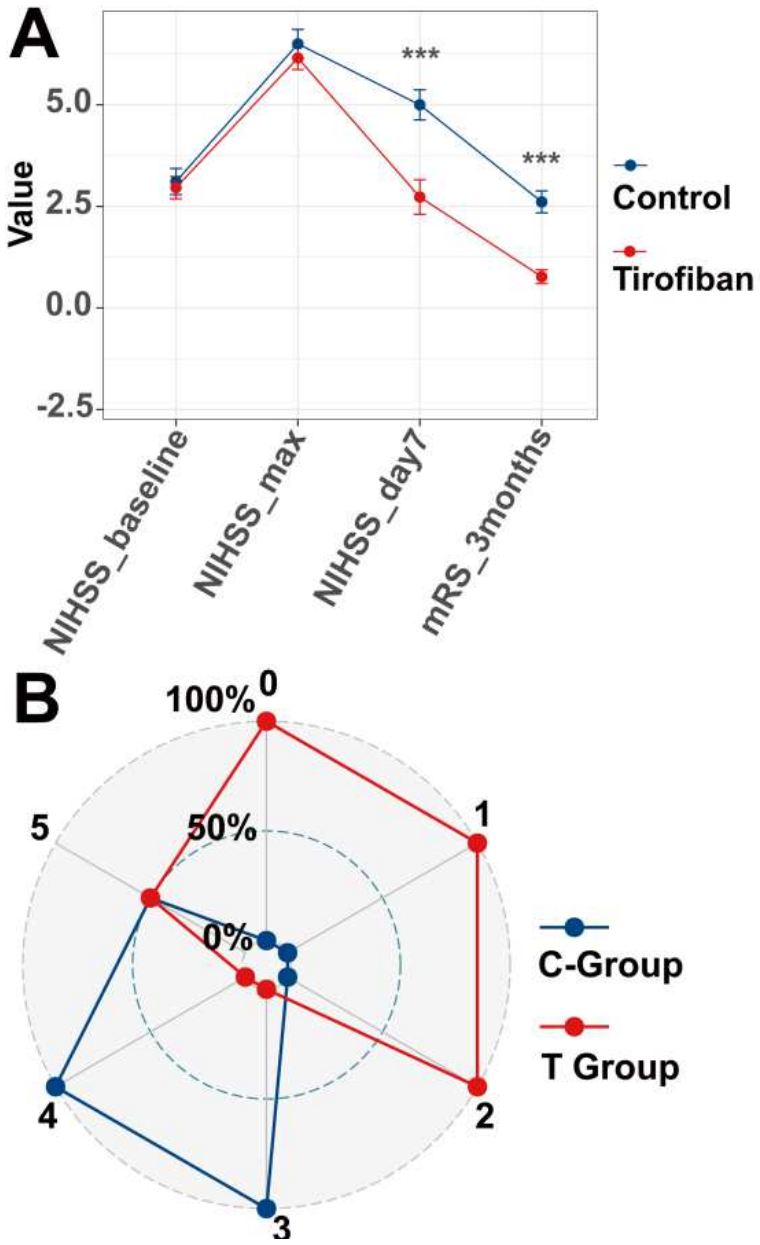

Fig. 2: Temporal changes in neurological function and distribution of functional outcomes between groups. (A) Time-dependent trends of NIHSS and mRS outcomes between two groups (**$P < 0.01$, ***$P < 0.001$); (B) Functional outcome distribution (mRS scores at 90 days) between groups. T group = tirofiban group; C group = control group; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale.

Table 2: Comparison of NIHSS and mRS outcomes between groups

Outcome	Tirofiban group (n=26)	Control group (n=18)	Test value	*P*-value
Baseline NIHSS score, median (IQR)	3.00 (2.00 – 4.00)	3.00 (2.00 – 4.00)	229.50	0.91
Maximum NIHSS score, median (IQR)	6.00 (5.00 – 7.00)	6.00 (5.00 – 8.00)	197.00	0.36
NIHSS at day 7, median (IQR)	2.00 (1.00 – 3.75)	5.00 (3.00 – 6.00)	85.50	<0.001
Change in NIHSS score (ΔNIHSS), median (IQR)	0.00 (– 1.00 – 2.00)	– 2.00 (– 3.00 – – 1.00)	361.50	<0.01
mRS at 90 days, median (IQR)	1.00 (0.00 – 1.00)	3.00 (1.00 – 3.33)	54.50	<0.001
mRS 0 – 1 at 90 days, n (%)	21 (80.77%)	5 (27.78%)	10.26	<0.01

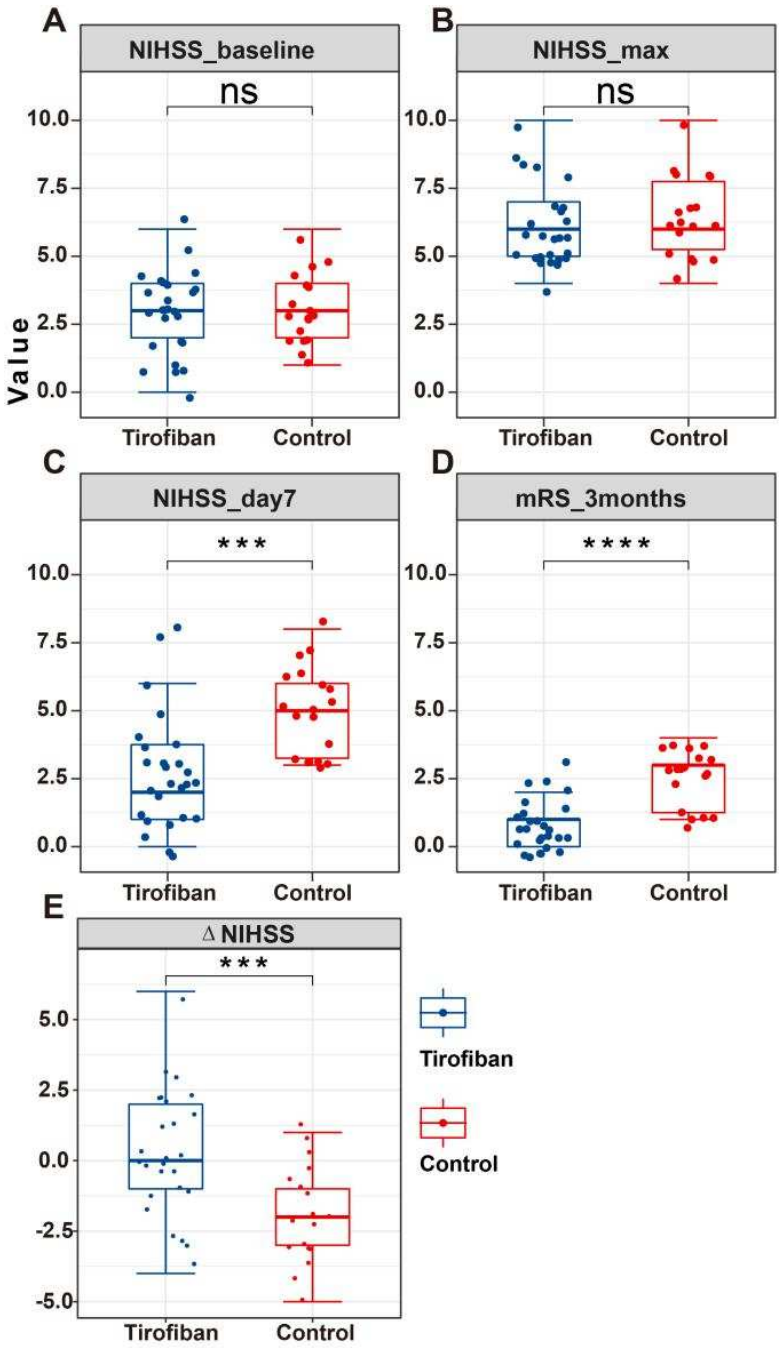

Fig. 3: Comparison of NIHSS and mRS outcomes between the tirofiban and control groups. (A) NIHSS scores at baseline; (B) maximum NIHSS within 24 h after admission; (C) NIHSS scores at day 7; (D) mRS scores at 90 days; (E) ΔNIHSS (baseline − day 7). Boxes denote the interquartile range, horizontal lines reflect medians, and whiskers represent the 5th–95th percentiles. ***p < 0.01; ****p < 0.001; ns = not significant.

Table 3. Multivariate logistic regression for favorable functional outcome (mRS 0–1 at 90 days).

Variable	Adjusted OR	95% CI	*P*-value
Tirofiban treatment	15.67	2.97 – 82.61	<0.01
Age (per year increase)	0.94	0.85 – 1.04	0.231
Baseline NIHSS score (per point increase)	0.83	0.44 – 1.56	0.562
Male sex	2.86	0.57 – 14.32	0.202

In patients with acute LVO undergoing endovascular therapy, several perioperative studies have indicated that tirofiban may reduce intraoperative thrombus formation and improve reperfusion quality (Jiao *et al*., 2024; Kim *et al*., 2020; Bu *et al*., 2024). Furthermore, a previous study (Mandava *et al*., 2008) reported that tirofiban might delay neurological deterioration in patients suffering small-vessel occlusion-induced progressive stroke, which is consistent with the trend toward neurological recovery observed in our study. In contrast, the SETIS trial including a proportion of patients with LVO and initiated treatment earlier (within 6 hours of symptom onset), did not demonstrate a clear functional benefit (Liu *et al*., 2016). Collectively, prior evidence on the efficacy of tirofiban remains inconclusive, owing to substantial heterogeneity across study populations.

Distinct from previous investigations, the present study specifically focused on patients suffering progressive stroke who missed the intravenous thrombolysis time window and had no evidence of LVO—an understudied population in earlier research. A continuous low-dose intravenous infusion strategy was adopted, which may provide stable antithrombotic effects while minimizing hemorrhagic risk. Additionally, maintaining SBP within a moderate range (140–160 mmHg) may help preserve collateral perfusion, thereby reducing the risk of hemorrhagic transformation. Notably, no cases of symptomatic intracranial hemorrhage were observed in our cohort, which may be attributable to the dosing strategy and blood pressure management.

The favorable outcomes observed with tirofiban in the present cohort are mechanistically grounded in the distinct pathophysiology of progressive cerebral ischemia. Neurological decline in non-LVO stroke is driven by dynamic processes such as progressive thrombosis, microembolization and microcirculatory failure (Chen *et al*., 2022; Alves *et al*., 2019; Dhoisne *et al*., 2023), which perpetuate ischemic injury despite the absence of a proximal occlusion (Rzeplinski *et al*., 2025; Su *et al*., 2022). Tirofiban, as a rapid-onset, reversible GP IIb/IIIa inhibitor, directly targets this pathology by immediately inhibiting platelet aggregation (Rivet *et al*., 2025; Cui *et al*., 2022). The absence of symptomatic intracranial hemorrhage in the present series further validates the integrated safety strategy of combining sustained low-dose infusion with rigorous hemodynamic control, demonstrating that antithrombotic efficacy can be achieved without compromising safety.

This study acknowledges limitations that suggest promising directions for future inquiry. First, the single-center retrospective study involves a relatively small sample size, which prevents the findings from being generalized to other studies and reduces statistical power. Second, treatment allocation was non-randomized; although PSM was applied to balance key baseline characteristics, selection bias and residual confounding cannot be completely eliminated. In addition, several potentially important clinical confounders—such as stroke etiology, detailed blood pressure parameters and the timing of antithrombotic therapy initiation—were not included in the multivariable regression model, which may have influenced the estimated treatment effect. Third, while a history of hypertension was recorded as a baseline variable, dynamic blood pressure measurements during hospitalization were not systematically quantified. From an imaging perspective, only lesion location was compared between groups; more detailed imaging characteristics, including infarct volume, perfusion deficits and the degree of arterial stenosis, were not consistently available for analysis. Consequently, the potential impact of these factors on clinical outcomes could not be fully assessed. Fourth, the tirofiban dosing regimen was individualized in real-world clinical practice, particularly regarding the duration of the loading infusion. Given the absence of prespecified subgroup analyses to evaluate the effects of different dosing strategies, the reported findings should be interpreted with caution. Finally, although no intracranial hemorrhage, thrombocytopenia, or clinically significant systemic bleeding was observed, the limited sample size precludes a robust assessment of rare safety events. Therefore, the safety findings should be considered descriptive rather than definitive. Future large-scale, multicenter, prospective RCTs incorporating standardized blood pressure monitoring, quantitative imaging assessments (including infarct volume and perfusion parameters) and relevant biomarkers are warranted to further validate the efficacy and safety of intravenous tirofiban in patients suffering progressive ischemic stroke without LVO.

CONCLUSION

In conclusion, early intravenous administration of tirofiban possibly accelerates neurological recovery and enhances functional outcomes in progressive stroke patients who miss the thrombolytic window and do not have LVO, without increasing the risk of hemorrhagic complications. These findings provide supplementary evidence supporting antiplatelet intervention in this underrepresented stroke subgroup. Nevertheless, given the retrospective design and limited sample size, these observations should be interpreted with caution and confirmed in future RCTs.

Acknowledgments
The authors would like to thank the medical staff of the Department of Neurology at Weifang Hospital of Traditional Chinese Medicine for their support during data collection and patient follow-up. The authors also thank all patients and their families for participating in this study.

Authors' contributions
Ming Zhou and Ying Zhang: Made equal contributions to this work and were responsible for data collection and

manuscript drafting; Xin Zhao and Pengfei Chang: Participated in data analysis and literature review; Jiangbo Xie and Tao Liu: Contributed to patient follow-up and data verification; Haixia Wang and Jinbao Wang: Took charge of study conception and design, research progress supervision and manuscript revision and are the corresponding authors. The final manuscript has been read and approved by all authors.

Funding
The Scientific Research Development Fund of Shandong Second Medical University (Grant No. 2024FYQ038).

Data availability statement
The datasets generated during and/or analysed during the current study can be obtained from the corresponding author on reasonable request.

Ethical approval
The study protocol was reviewed and approved by the Ethics Committee of Weifang Traditional Chinese Medicine Hospital (Approval No. 202403-106). All procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
https://www.pjps.pk/uploads/2026/05/SUP1780129052.pdf

REFERENCES

Alves HC, Treurniet KM, Jansen IGHJ, Yoo AJ, Dutra BG, Zhang G, Yo L, van Es A, Emmer BJ, van den Berg R, van den Wijngaard IR, Lycklama A Nijeholt GJ, Vos JA, Roos Y, Schonewille W, Marquering HA and Majoie C (2019). Thrombus migration paradox in patients with acute ischemic stroke. *Stroke.,* **50**(11): 3156-3163.

Bu Z, Sun D, Ma G, Jia B, Tong X, Huo X, Wang A, Ma N, Gao F, Mo D, Song L, Sun X, Deng Y, Li X, Wang B, Luo G, Su D and Miao Z (2024). The impact of intraarterial, intravenous and combined tirofiban on endovascular treatment for acute intracranial atherosclerotic occlusion. *Front. Neurol.,* **15**: 1336098.

Chen J, Zhang Z, Nie X, Xu Y, Liu C, Zhao X, Miao Z, Wang Y and Liu L (2022). Thrombus magnetic susceptibility is associated with recanalization and clinical outcome in patients with ischemic stroke. *Neuroimage. Clin.,* **36**: 103183.

Cui J, Li H, Chen Z, Dong T, He X, Wei Y, Li Z, Duan J, Cao T, Chen Q, Ma D, Zhou Y, Wang B, Shi M, Zhang Q, Xiong L and Qin D (2022). Thrombo-inflammation and immunological response in ischemic stroke: Focusing on platelet-tregs interaction. *Front. Cell. Neurosci,* **16**: 955385.

de Almeida Monteiro G, Leite M, Goncalves OR, Ferreira MY, Mutarelli A, Marinheiro G, Araujo B, Leal PRL, Ribeiro EML, Figueiredo EG and Telles JPM (2025). Efficacy and safety of intravenous tirofiban combined with reperfusion therapy versus reperfusion therapy alone in acute ischemic stroke: A meta-analysis of randomized controlled trials. *J. Thromb. Thrombolysis.,* **58**(4): 526–537.

De Georgia M, Bowen T, Duncan KR and Chebl AB (2023). Blood pressure management in ischemic stroke patients undergoing mechanical thrombectomy. *Neurol. Res. Pract.,* **5**(1): 12.

de la Riva P, Marta-Enguita J, Rodriguez-Antiguedad A, Bergareche A and de Munain AL (2024). Understanding endothelial dysfunction and its role in ischemic stroke after the outbreak of recanalization therapies. *Int. J. Mol. Sci.,* **25**(21): 11631.

de Souza Y, Berton G, Carolino G, Omuro H, Toscano S, Leite M, De Souza AL and de Pacheco E (2025). Effects of tirofiban on functional outcomes in patients with acute ischemic stroke ineligible for reperfusion therapy: A systematic review and meta-analysis of randomized studies (P12-13.008). *Neurology.,* **104**(7_Supplement_1): 2.

Dhoisne M, Puy L, Bretzner M, Bricout N, Behal H, Cordonnier C and Henon H (2023). Early reocclusion after successful mechanical thrombectomy for large artery occlusion-related stroke. *Int. J. Stroke.,* **18**(6): 712-719.

Edlow JA and Tarnutzer AA (2025). Intravenous thrombolysis in patients with acute dizziness or imbalance and suspected ischemic stroke-systematic review. *J. Neurol.,* **272**(1): 91.

Goh R, Ng F, Jannes J, Kleinig T, Sorby-Adams A, Suann B and Bacchi S (2025). Female Sex is associated with reduced thrombolytic administration in an Australian stroke cohort: A multicentre retrospective cohort study. *J. Stroke. Cerebrovasc. Dis.*, **34**(4): 108255.

Guo QH, Liu CH and Wang JG (2022). Blood pressure goals in acute stroke. *Am. J. Hypertens.,* **35**(6): 483-499.

Guven G, Cetin I, Kilic S, Acaroglu S, Aslanger KE and Sonsoz MR (2025). Do we need to perform control angiography in patients undergoing percutaneous coronary intervention after tirofiban infusion? *Catheter. Cardiovasc. Interv.,* **105**(6): 1279-1286.

Guzman M, Lavados PM, Cavada G, Brunser AM and Olavarria VV (2025). Emergency department workflow times of intravenous thrombolysis with tenecteplase versus alteplase in acute ischemic stroke: A prospective cohort study before and during the COVID-19 pandemic. *Cerebrovasc. Dis. Extra.*, **15**(1): 102-109.

Hu Y, Chen L, Zhu T, Xu Q, Chen Z, Qian Z and Wang L (2025). Impact of tirofiban and cilostazol on cardiac

recovery in elderly patients with acute coronary syndrome. *Med. Sci. Monit.,* **31**: e947831.

Jiang Y, Huang W, Zhang Y and Ji Q (2025). Tirofiban in acute ischemic stroke: mechanistic rationale, clinical advances and emerging therapeutic strategies. *Drugs.,* **85**(10): 1269-1287.

Jiao Y, Wang X, Guan Y, Wang X, Li Z, Xiang X and Zhang Z (2024). Therapeutic efficacy of tirofiban combined with thrombus aspiration and stent thrombectomy in the treatment of large vessel occlusion ischemic stroke. *Neurologist.,* **30**(3): 140-144.

Kim YW, Sohn SI, Yoo J, Hong JH, Kim CH, Kang DH, Kim YS, Lee SJ, Hong JM, Choi JW, Hwang YH and Lee JS (2020). Local tirofiban infusion for remnant stenosis in large vessel occlusion: Tirofiban ASSIST study. *BMC. Neurol.,* **20**(1), 284.

Kitano T, Hori Y, Okazaki S, Shimada Y, Iwamoto T, Kanki H, Sugiyama S, Sasaki T, Nakamura H, Oyama N, Hoshi T, Beck G, Takai H, Matsubara H, Mizuno H, Nishimura H, Tamaki R, Iida J, Iba J, Uno M, Kishima H, Fushimi S, Hattori S, Murayama S, Morii E, Sakaguchi Y, Yagita Y, Shimazu T, Mochizuki H and Todo K (2022). An older thrombus delays reperfusion after mechanical thrombectomy for ischemic stroke. *Thromb. Haemost.,* **122**(3): 415-426.

Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, Lennon O, Meschia JF, Nguyen TN, Pollak PM, Santangeli A, Sharrief AZ, Smith SC Jr., Turan TN and Williams LS (2021). 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American heart association/American stroke association. *Stroke.,* **52**(7): e364-e467.

Kongsui R, Thongrong S and Jittiwat J (2025). *In-vivo* neuroprotective effects of alpinetin against experimental ischemic stroke damage through antioxidant and anti-inflammatory mechanisms. *Int. J. Mol. Sci.,* **26**(11): 5093.

Liang Z, Zhang J, Huang S, Yang S, Xu L, Xiang W and Zhang M (2022). Safety and efficacy of low-dose rt-PA with tirofiban to treat acute non-cardiogenic stroke: A single-center randomized controlled study. *BMC. Neurol.,* **22**(1), 280.

Liu C, Yang X, Liu M, Wang J and Li G (2023). Meta-analysis of the efficacy and safety of tirofiban in patients with acute ischaemic stroke undergoing mechanical thrombectomy. *Clin. Neurol. Neurosurg.,* **228**: 107702.

Liu R, Liang Z, Li W, Zhan L, Xu L, Yang S, Zheng G, Jiang L, Xie L, Sun Z and Hu Y (2024). Adding Tirofiban on top of recombinant tissue plasminogen activator may improve clinical outcome in acute stroke patients. *J. Stroke.,* **26**(1): 121-124.

Liu X, Fang Q and Kim H (2016). Preclinical studies of mesenchymal stem cell (MSC) administration in chronic obstructive pulmonary disease (COPD): A systematic review and meta-analysis. *PLoS. One.,* **11**(6): e0157099.

Luo MY, Qu Y, Zhang P, Abuduxukuer R, Wang LJ, Yang LC, Li ZG, Liu XD, Han C, Li D, Wang WJ, Lv DP, Liu M, Gao J, Xu J, Jiang Y, Chen HN, Li FJ, Sun LM, Sun QD, Sun SY, Zhang Y, Guo ZN and Yang Y (2025). Prediction of outcomes following intravenous thrombolysis in patients with acute ischemic stroke using serum UCH-L1, S100β and NSE: A multicenter prospective cohort study employing machine learning methods. *Ther. Adv. Neurol. Disord.,* **18**: 17562864251342429.

Luo Y, Chu M, Wang D, Gu X, Wang D, Zheng J and Zhao J (2023). Early antithrombotic therapy in patients with postinterventional cerebral hyperdensity reduces early neurological deterioration after mechanical thrombectomy. *BMC. Neurol.,* **23**(1): 443.

Mandava P, Thiagarajan P and Kent TA (2008). Glycoprotein IIb/IIIa antagonists in acute ischaemic stroke: Current status and future directions. *Drugs.,* **68**(8): 1019-1028.

Marta-Enguita J, Machado FJD, Orbe J and Muñoz R (2024). Thrombus composition and its implication in ischemic stroke assessment and revascularization treatments. *Neurologia (Engl Ed).,* **40**(1): 77-88.

Monteiro GA, Mutarelli A, Leite M, Marinheiro G, Araujo B, Gonçalves OR, Cavalcante-Neto JF, Leal PRL, da Ponte KF, Figueiredo EG and Telles JPM (2024). Efficacy and safety of intravenous tirofiban versus standard medical treatment in acute ischemic stroke: A meta-analysis of randomized controlled trials. *Clin. Neurol. Neurosurg.,* **247**: 108602.

Mortezaei A, Essibayi MA, Hajikarimloo B, Taghlabi KM, Majidpoor J, Altschul D, Dmytriw AA, Rahmani M, Abdalkader T, Nguyen TN and Kasab SA (2025). Endovascular thrombectomy in late-window stroke: Do perfusion imaging and large infarcts really matter? A systematic review and meta-analysis of 10 randomized clinical trials. *Clin. Neurol. Neurosurg.,* **255**: 108955.

Orset C, Arkelius K, Anfray A, Warfvinge K, Vivien D and Ansar S. Combination treatment with U0126 and rt-PA prevents adverse effects of the delayed rt-PA treatment after acute ischemic stroke. *Sci. Rep.,* **11**(1): 11993.

Plotnikov MB, Anishchenko AM, Khlebnikov AI and Schepetkin IA (2025). Regulation of blood-brain barrier permeability via JNK signaling pathway: Mechanisms and potential therapeutic strategies for ischemic stroke, Alzheimer's disease and brain tumors. *Molecules.,* **30**(11): 2353.

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV and Tirschwell DL (2019). Guidelines for the early management of patients with acute ischemic stroke: 2019 Update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke

Association. *Stroke.,* **50**(12): e344-e418.

Qiao Y, Zhao M, Wang J, Li S, Yang T, Wang P, Ji X, Ma Q and Zhao W (2025). Stroke etiology was associated with tirofiban efficacy in acute ischemic stroke without endovascular treatment: A pre-specified subgroup analysis of the TREND trial. *Int. J. Stroke.*, **20**(8): 977-986.

Rivet S, Churilov L, Yassi N, Kleinig TJ, Thijs V, Wu T, Dewey H, Desmond PM, Parsons MW, Donnan GA, Davis SM, Mitchell PJ, Campbell BCV and Ng FC (2025). Persistent tissue-level hypoperfusion (No-Reflow) negates the clinical benefit of successful thrombectomy. *Stroke.,* **56**(6):1451-1459.

Rodriguez-Calienes A, Borjas N, Sanikommu S, Chavez-Ecos FA, Vilca-Salas MI, Rodrigues PB, Morán-Mariños C, Yavagal DR, Asdaghi N and Ortega-Gutierrez S (2025). Endovascular thrombectomy versus best medical therapy for large vessel occlusion stroke beyond 24 hours: A systematic review and meta-analysis. *Stroke.,* **56**(11): 3127-3137.

Rzeplin Ski R, Tarka S, Tomaszewski M, Kucewicz M, Acewicz A, Małachowski J and Ciszek B (2025). Narrowings of the deep cerebral perforating arteries ostia: Geometry, structure, and clinical implications. *J. Stroke.,* **27**(1): 52-64.

Su C, Yang X, Wei S and Zhao R (2022). Association of cerebral small vessel disease with gait and balance disorders. *Front. Aging. Neurosci.,* **14**: 834496.

Wang J, Qiao S, Li C, Li C, Wu C, Wang P, Yang T, Ji X, Ma Q and Zhao W (2025). Effects of tirofiban in preventing neurological deterioration in acute ischemic stroke with intracranial artery stenosis: A post hoc analysis of the TREND Trial. *Eur. Stroke. J.*, **10**(3): 919-928.

Wang M, Zhang F, Guo Q, Wang W, Wu K and Chen H (2025). Efficacy, safety, and effect on platelet activation of the timing of administration of tirofiban in patients with acute ischemic stroke. *Am J Transl Res,* **17**(2): 791-805.

Wu Y, Su R, Feng X, Mao A, Nguyen TN, Cai L, Li Q, Guo Q, Yang Q, Sang H, Yang G, Qiu Z, Xie F and Li C (2025). Long-term outcome of endovascular thrombectomy in patients with acute ischemic stroke: A systematic review and meta-analysis. *J. Neurol.,* **272**(1): 101.

Zheng Y, Tan X, Wang R, Mao R and Guo J (2025). Targeting ferroptosis with natural products in stroke: Therapeutic mechanisms and translational opportunities. *Front. Pharmacol.,* **16**: 1586345.

Zi W, Song J, Kong W, Huang J, Guo C, He W, Yu Y, Zhang B, Geng W, Tan X, Tian Y, Liu Z, Cao M, Cheng D, Li B, Huang W, Liu J, Wang P, Yu Z, Liang H, Yang S, Tang M, Liu W, Huang X, Liu S, Tang Y, Wu Y, Yao L, Shi Z, He P, Zhao H, Chen Z, Luo J, Wan Y, Shi Q, Wang M, Yang D, Chen X, Huang F, Mu H, Li H, Li Z, Zheng J, Xie S, Cai T, Peng Y, Xie W, Qiu Z, Liu C, Yue C, Li L, Tian Y, Yang D, Miao J, Yang J, Hu J, Nogueira RG, Wang D, Saver JL, Li F and Yang Q (2023). Tirofiban for stroke without large or medium-sized vessel occlusion. *N. Engl. J. Med.,* **388**(22): 2025-2036.