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Real-world comparison of tirofiban versus aspirin in acute non-large-vessel occlusion ischemic stroke: A retrospective cohort study

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Abstract: **Background**: Acute non-large-vessel occlusive ischemic stroke (ANLVOIS) is a common subtype of stroke. The core of treatment is to rapidly improve cerebral perfusion and reduce neurological injury. Aspirin is used in the acute phase, but its efficacy is limited in some patients. Tirofiban (a highly selective glycoprotein IIb/IIIa receptor antagonist) is widely used and there are few direct comparative studies of its efficacy and safety with those of the other drugs. **Objectives**: To compare the clinical efficacy and safety of the antiplatelet drugs tirofiban and aspirin in the treatment of ANLVOIS. **Methods**: This retrospective controlled study collected clinical data of ANLVOIS patients from Wuqiao County People's Hospital (Jan 2023–Dec 2024), grouped by treatment: Group A (n=55, aspirin alone) and Group B (n=58, tirofiban bridging to aspirin). NIHSS scores (pre-treatment, 1 week, and 3 months post-treatment) were analyzed for neurological function, and 3-month mRS scores were analyzed for prognosis. 90-day all-cause mortality, symptomatic intracranial hemorrhage (sICH) incidence and adverse event rate were compared. Statistical analyses were performed using SPSS 26.0. **Results**: Baseline characteristics were balanced between the two groups (P>0.05). At 7 days and 3 months post-treatment, NIHSS and mRS scores decreased significantly in both groups (P<0.05), with Group B having notably lower scores than Group A (P<0.05). The 90-day all-cause mortality, sICH incidence and adverse event rates were 1.7%, 3.4%, and 6.9% in Group B, respectively, compared with 3.6%, 5.5%, and 16.4% in Group A, with no significant intergroup differences (P>0.05). **Conclusion**: In this retrospective analysis, early treatment with tirofiban followed by aspirin was associated with better neurological and functional outcomes in ANLVOIS than aspirin alone, while maintaining a comparable safety profile. These real-world findings support the use of tirofiban-based induction as an effective acute-phase antiplatelet strategy.

Keywords: Aspirin; Acute non-large-vessel occlusive ischemic stroke; Ischemic stroke; Tirofiban

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INTRODUCTION

Acute non-large-vessel occlusive ischemic stroke (ANLVOIS) is an important subtype of ischemic stroke (IS), accounting for more than 60% of all cases of IS. Its pathophysiology is primarily characterized by small-artery occlusion, microthrombosis, or hypoperfusion (Greco *et al*., 2023). Unlike large vessel occlusion (LVO), ANLVOIS is generally not amenable to mechanical thrombectomy, so drug intervention has become the primary treatment (Martinez-Gutierrez *et al*., 2023). Current guidelines recommend initiating antiplatelet therapy within 48 hours of onset to reduce the risk of early neurological deterioration (END) and recurrence, of which aspirin is widely used as a first-line medication (Aoki *et al*., 2019). However, despite the establishment of standard treatment, about 15–30% of patients still have symptom progression or poor prognosis, suggesting significant limitations of existing therapies (Aoki *et al*., 2021). Currently, the main treatments for ANLVOIS include intravenous thrombolysis (such as alteplase) and antiplatelet therapy. For patients who meet the time window (usually ≤ 4.5 hours) and have no contraindications, intravenous thrombolysis can effectively promote reperfusion (Gong *et al*., 2019). However, because it is difficult to identify small vessel occlusion by imaging clearly and some patients exceed the treatment time window, most patients with ANLVOIS only receive antiplatelet therapy. Aspirin inhibits platelet aggregation by reducing thromboxane A_2 production through irreversible inhibition of cyclooxygenase-1 (COX-1), which is supported by clear evidence in secondary prevention (Sandercock *et al*., 2003). However, its antiplatelet effect is limited, and the phenomenon of "aspirin resistance" leads to poor efficacy in some patients (Sandercock *et al*., 2003). In addition, dual antiplatelet therapy (DAPT, such as aspirin combined with clopidogrel) has shown the advantage of reducing the recurrence risk in mild to moderate stroke, but the bleeding risk is increased, especially in the elderly or people with more comorbidities and should be used cautiously (Borghol *et al*., 2020).

Tirofiban is a highly selective and reversible glycoprotein IIb/IIIa receptor antagonist that prevents fibrinogen from binding to GP IIb/IIIa receptors on blood platelets, thereby effectively inhibiting platelet aggregation. Its action is much stronger than that of aspirin (Maeda *et al*., 2005). With a short half-life (approximately 2 hours), tirofiban offers a rapid onset and easy dose adjustment, making it

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suitable for short-term use in the acute phase (Olive-Gadea *et al*., 2025). Many clinical studies have explored its application value in IS. As an illustration, the TREND trial is a prospective, randomized, open-label study with endpoint-blinded evaluation (PROBE), designed to compare the efficacy of intravenous tirofiban and aspirin in preventing neurological deterioration in patients with acute noncardiac stroke (Zhang *et al*., 2022b) Subgroup analysis of the follow-up data from this study revealed that tirofiban markedly lowered the incidence of END in patients with large artery atherosclerosis as the etiology (Sun *et al*., 2024). A further multicenter randomized controlled trial, RESCUE BT-2, was to confirm tirofiban's safety profile and therapeutic efficacy relative to aspirin administered within 24 hours (Zi *et al*., 2022).

In contrast, aspirin prevents platelet aggregation by inhibiting platelet cyclooxygenase-1 and reducing thromboxane A_2 production. Many guidelines have recommended its therapeutic status in the acute phase of IS. A Cochrane systematic review showed that initiating aspirin therapy within 48 hours of onset significantly reduced the risk of death or dependency (Sandercock *et al*., 2003). In recent years, scholarly investigations have focused on optimizing antiplatelet strategies, such as short-term DAPT for mild stroke, but in the context of ANLVOIS, there remains a lack of individualized regimens for specific etiologies (Huang *et al*., 2021). Recent research indicates that tirofiban has potential for treating ANLVOIS. A randomized controlled trial involving 267 patients with ANLVOIS who did not receive intravenous thrombolysis confirmed that early use of tirofiban (≥ 72 hours) significantly improved the 90-day mRS score (modified Rankin scale) and failed to elevate the risk of symptomatic intracranial hemorrhage compared with conventional antiplatelet regimens (Olive-Gadea *et al*., 2025). Another meta-analysis also found that tirofiban combined with recombinant tissue plasminogen activator (rtPA) could improve recanalization rate and functional prognosis compared with rtPA alone, with good safety (Xia *et al*., 2022). Given its potent antiplatelet effect, tirofiban may theoretically benefit patients with active thrombus formation or those at risk of END, particularly in stroke subtypes involving artery-to-artery embolism or unstable plaques (Lin *et al*., 2017). However, whether its efficacy is modulated by individual platelet reactivity or specific thrombus dynamics remains a hypothesis-generating question requiring further investigation.

In conclusion, ANLVOIS urgently needs better antiplatelet strategies. Tirofiban is becoming a promising alternative or complementary treatment option due to its potent, rapid, and reversible pharmacological properties (Zi *et al*., 2022). In view of this, this study used a retrospective cohort study method to select patients with ANLVOIS treated in our hospital and compared the therapeutic effect and safety of tirofiban and aspirin, aiming to verify the clinical application value of the two drugs retrospectively, provide scientific reference for the optimization of clinical treatment options, so as to improve the treatment outcome of patients further, reduce the disability rate and promote the quality of life.

MATERIALS AND METHODS

Study subjects

This was a retrospective clinical study. A total of 124 patients with ANLVOIS who presented to Wuqiao County People's Hospital between January 2023 and December 2024 were initially identified as potential participants. According to the inclusion and exclusion criteria, 113 cases were finally included. Patients were divided into two groups based on treatment: those who received aspirin (Group A, n=55) and those who received tirofiban (Group B, n=58). Data were collected before treatment and at 1 week and 3 months after treatment to compare the clinical efficacy and safety of the antiplatelet drugs tirofiban and aspirin in the treatment of ANLVOIS. The flow chart is shown in Fig. 1.

Operational definition of ANLVOIS

In this study, ANLVOIS was operationally defined as an acute ischemic stroke (AIS) confirmed by diffusion-weighted imaging, with no evidence of intracranial large- or medium-vessel occlusion on intracranial or extracranial vascular imaging [including computed tomography angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA)]. Clinically, patients presented with acute neurological deficits in the suspected small-vessel territory, and those with a baseline NIHSS score ≥5 were included. Patients with potential cardioembolic sources (e.g., high-risk atrial fibrillation) were not excluded if they met the imaging criteria, as the diagnosis was based on vessel patency rather than etiology alone.

Basis for selecting treatment plan

The treatment plan in this study was determined by the treating physician based on clinical judgment and the individual patient's condition. Generally speaking, for patients at high risk of active thrombosis or early deterioration of neurological function upon admission (such as progressive stroke manifestations, fluctuating symptoms, or unstable plaques indicated by imaging), physicians are more inclined to choose intravenous administration of tirofiban; For patients with higher risk of bleeding (such as advanced age, history of gastrointestinal bleeding, poorly controlled hypertension) or contraindications to tirofiban (such as severe renal dysfunction), aspirin is preferred. In addition, the selection of some treatment plans is influenced by the patient's financial situation and their family members' wishes.

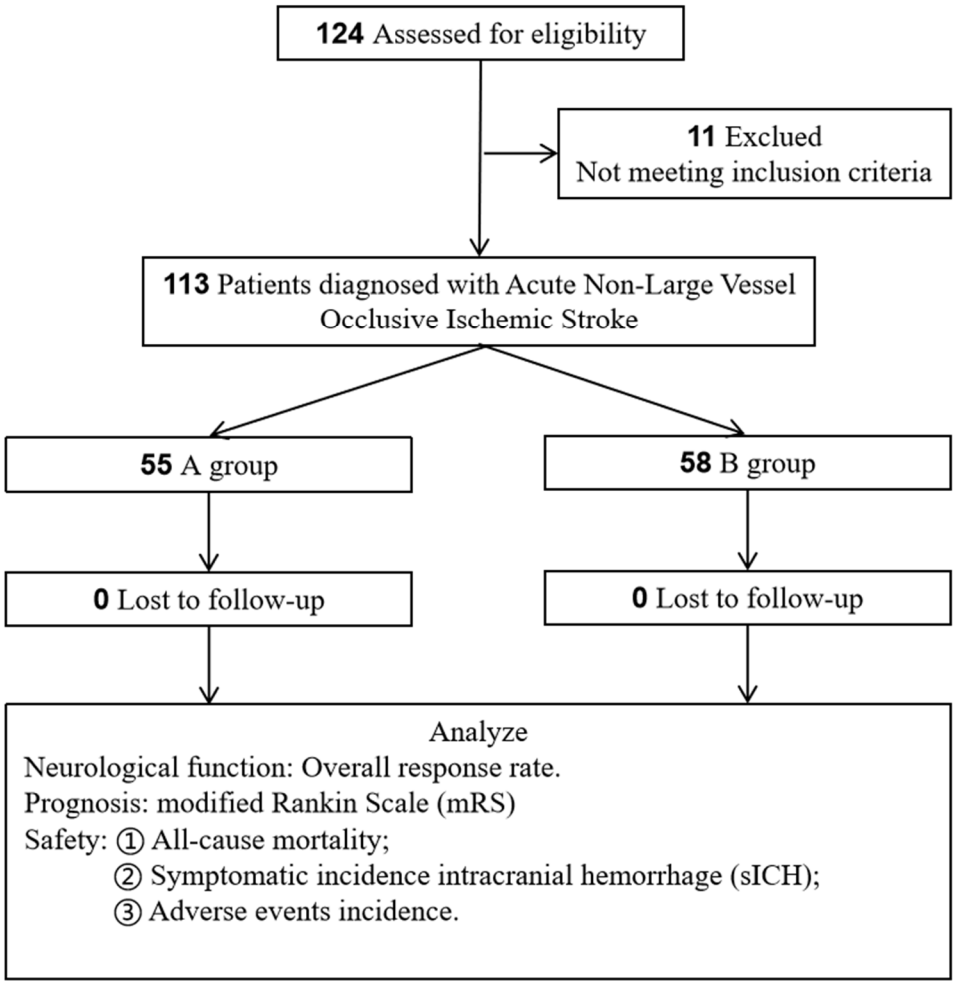

Fig. 1: Research flowchart

Inclusion criteria

(1) Have complete clinical data.
(2) Age > 18 years.
(3) AIS is diagnosed and meets any of the following conditions: (i) Last known normal time is within 24 h, but IVT cannot be performed due to exceeding the 4.5-hour time window or other contraindications, or EVT cannot be performed due to absence of large- or medium-vessel occlusion; (ii) The onset was within 24-96 h, but stroke progression occurred within 24 h [the National Institutes of Health Stroke Scale (NIHSS) score increased by 2 points] and IVT or EVT could not be performed; (iii) Neurological deterioration occurred within 24 h after IVT treatment (an increase of no fewer than 4 points in the NIHSS score); (iv) There was no neurological improvement within 4-24 h after IVT treatment, neurological improvement was defined as a decrease of 2 points in NIHSS score (Cho *et al*., 2020).
(4) Imaging findings from CTA, MRA and DSA confirmed that there was no occlusion of intracranial large or medium vessels (Cho *et al*., 2020).
(5) Baseline NIHSS score ≥ 5 on admission (Dirks *et al*., 2007).

Exclusion criteria

(1) History of neurological or psychiatric disease that could confound neurological assessments.
(2) Presence of any end-stage disease with life expectancy <6 months.
(3) Intracranial tumors (malignant or benign) that could mimic stroke or increase bleeding risk.
(4) Severe renal insufficiency (glomerular filtration rate <30 mL/min or serum creatinine >220 μmol/L [2.5 mg/dL]), as tirofiban is renally cleared.
(5) Major surgical procedure within 1 day before stroke onset, due to elevated bleeding risk (Dirks *et al*., 2007).
(6) Active bleeding tendency, evidenced by abnormal coagulation parameters (platelet count $<100\times10^9$/L, activated partial thromboplastin time >50 s, international normalized ratio >1.7), or use of oral anticoagulants within 48 hours before onset (Dirks *et al*., 2007).
(7) History of intracranial hemorrhage (Dirks *et al*., 2007).
(8) Evidence of intracranial hemorrhage on admission CT or MRI.

Ethical statement

The Wuqiao County People's Hospital's ethics committee

approved this study protocol. All data acquisition and retrospective analysis processes were in line with the requirements of the national measures for ethical review of biomedical research involving human beings and the Declaration of Helsinki (Wen *et al*., 2025). The study used anonymous retrospective medical record analysis without direct contact with subjects. All identifiable personal information has been de-identified to ensure data confidentiality.

Sample size estimation

This study is a retrospective, controlled clinical trial, with participants assigned to the observation or control group according to the treatment method. The study used independent sample t-test for data analysis and G*Power software for sample size calculation (Kim *et al*., 2017) According to the effect size level in previous studies (Sang *et al*., 2024, Qiao *et al*., 2025), the effect size selected for this study is 0.7, the significance level (α) is 0.05 (two-sided) and the statistical power (1- β) is 0.95. These parameters required 45 participants per group, for a total of 90. Finally, 113 participants were included in this study, exceeding the target sample size and meeting the statistical requirements.

Patient treatment measures

Group A (n=55): aspirin (manufacturer: Bayer Healthcare Co., Ltd., approval number: NMPA Approval No. J20171021, specification: 100 mg×30 tablets) was given orally, 100 mg/time, once a day, for 3 months (Sang *et al*., 2024).

Group B (n=58): tirofiban [manufacturer: Yuanda Pharmaceutical (China) Co., Ltd., approval number: Guoyao Zhunzi h20041165, specification: 100 mL] was given intravenously at 0.4 μg/(kg·min), which was adjusted to 0.1 μg/(kg·min) after 30 min and stopped after 24 h. After tirofiban treatment, it was switched to aspirin 100 mg/d for oral maintenance and continued for 3 months (Yuan *et al*., 2024). Thus, in Group B, tirofiban was administered only during the acute phase (first 24 hours), followed by standard aspirin maintenance.

The patients in both groups were given conventional basic treatments, such as controlling blood pressure, blood glucose, and blood lipids; improving cerebral circulation; and nourishing nerves, according to their condition, without using other antiplatelet or anticoagulant drugs.

Observation indicators

(1) *Baseline*: the gender, age, smoking history, alcohol abuse history, systolic blood pressure, history, NIHSS score and mRS score of patients at admission were collected;
(2) *Neurological function*: NIHSS score (Sang *et al*., 2024) before treatment, 1 week and 3 months after treatment was integrated and analyzed. This scale can evaluate the severity of neurological deficit of patients;
(3) *Prognosis*: the improved Rankin Scale (mRS) score (Sang *et al*., 2024) was used to evaluate the functional recovery status and independent living ability of stroke patients after 3 months of treatment;
(4) *Safety evaluation*: the all-cause mortality, the incidence of symptomatic intracranial hemorrhage (sICH) and the incidence of adverse events within 90 days were counted and compared between the two groups (Sang *et al*., 2024). Adverse reaction records: medical electronic sphygmomanometer (HEM-907, Omron) was used for blood pressure monitoring; Blood routine examination was performed using a fully automatic blood cell analyzer (dxh 800, Beckman Coulter); Urine routine examination was performed with a fully automatic urine analyzer (Cobas 6800, Roche); Stool routine examination stool samples were examined microscopically using a microscope (cx23, Olympus); Liver and kidney functions were examined using a fully automatic biochemical analyzer (7600-020, Hitachi); Electrocardiography was performed using an electrocardiograph (IMEC 12, Mindray). The medical staff closely observed the patient's physical condition and reaction during treatment and collected adverse reaction information from detailed medical records and patient self-reports. MedDRA (Wang *et al*., 2024a) was used as a standardized tool to ensure more accurate and consistent descriptions and grading of adverse reactions.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. For continuous variables such as age, the Kolmogorov–Smirnov test was used to assess normality. Variables with a normal distribution were expressed as mean ± standard deviation. Independent sample t-test is selected for comparison between groups. Paired t-test is used for the same group before and after treatment and repeated measures variance test is used for comparison between groups at different time points and Bonferroni method was used to correct for significance level. For counting data such as gender, it is expressed by frequency (percentage) [n (%)] and chi square (χ^2) test is used for comparison between groups. The difference was considered statistically significant when $P<0.05$.

RESULTS

Comparison of baseline characteristics between the two groups

Baseline characteristics of group A (n=55) and group B (n=58) are compared in table 1. No statistically significant differences were observed between the two groups in terms of gender, age, smoking history, alcohol abuse history, systolic blood pressure, medical history, NIHSS score and mRS score between the two groups ($P>0.05$), suggesting that the two groups had balanced baseline and good comparability.

Table 1: Baseline characteristics [mean±SD, n (%), M(min, max)]

Variables	A group	B group	*95% CI*	χ^2/t	P
n	55	58	-	-	-
Gender					
Male	28 (50.9)	30 (51.7)	-	0.008	0.931
Female	27 (49.0)	28 (48.2)			
Age (years)	64.3±4.6	65.1±3.4	-2.267 to 0.748	0.999	0.320
Smoking	11 (20.0)	13 (22.4)	-	0.098	0.754
Alcohol	12 (21.8)	11 (18.9)	-	0.142	0.707
Systolic blood pressure	146.1±6.0	147.2±6.9	-3.476 to 1.384	0.853	0.396
Medical history					
Hypertension	33 (60.0)	36 (62.1)	-	0.051	0.822
Atrial fibrillation	28 (50.9)	30 (51.7)	-	0.008	0.931
Diabetes	15 (27.3)	15 (25.9)	-	0.029	0.865
Hyperlipidemia	12 (21.8)	14 (24.1)	-	0.086	0.770
Ischemic stroke	14 (25.5)	15 (25.9)	-	0.003	0.960
Coronary heart disease	12 (21.8)	13 (22.4)	-	0.006	0.939
NIHSS	15.5±1.4	15.9±1.6	-0.940 to 0.167	1.384	0.169
mRS	4.2±1.1	4.1±1.0	-0.403 to 0.454	0.119	0.906

Note: CI: Confidence Interval. The same below.

Table 2: Comparison of NIHSS scores between two groups of patients [mean±SD]

	n	Pre-treatment	1 week after treatment	3 month after treatment
A group	55	15.5±1.4	10.2±0.9	4.4±0.6
B group	58	15.9±1.6	8.5±0.9	3.5±1.7
t	-	1.384	9.214	9.173
P	-	0.169	<0.001	<0.001
F	F-Time=2987.955		F-Group=51.180	F-Time*Group=19.081
P	<0.001		<0.001	<0.001

Note: According to the Mann Whitney U test, the differences in NIHSS scores between the two groups at 1 week and 3 months after treatment were still statistically significant (1 week: U=383.5, P<0.001; 3 months: U=388.5, P<0.001), consistent with the results of parameter testing.

Comparison of neurological function between the two groups

Table 2 presents a comparison of NIHSS scores in the two groups before and after treatment. Prior to treatment, no significant difference in NIHSS scores was observed between the two groups (P=0.169). At 1 week and 3 months post-treatment, the NIHSS level in group B was notably lower than that in group A (P<0.001). Repeated-measures analysis of variance (ANOVA) revealed statistical significance in NIHSS scores across groups (F=51.180, P<0.001), across time points (F=2987.955, P<0.001), and for the interaction between group and time (F=19.081, P<0.001). The results showed that tirofiban combined with bridging therapy could effectively recanalize the occluded vessels in patients with ANLVOIS and reduce neurological injury.

Comparison of prognosis between the two groups

When comparing the functional recovery status and independent living ability of the two groups before and after treatment, the mRS score results in table 3 showed that prior to treatment initiation, no significant difference was detected between the two study groups. (P=0.906). Following treatment (at 1 week and 3 months), the mRS score in group B was significantly lower than that in group A (P<0.001). The results of a repeated-measures ANOVA showed that mRS scores differed significantly between groups (F=16.289, P<0.001) and across time points (F=318.369, P<0.001), with the group-by-time interaction also reaching statistical significance (F=4.651, P<0.001). Inter-group comparison showed that the good-prognosis rate in group B was significantly higher than that in group A at 3 months (P<0.05). The results showed that, compared with aspirin alone, early use of tirofiban combined with aspirin for antiplatelet therapy in ANLVOIS is associated with better outcomes. To control for type I error due to multiple comparisons, we applied Bonferroni correction for the three primary outcomes, setting the significance

level at 0.05/3 = 0.0167. After Bonferroni correction, the difference in 3-month mRS remained significant (adjusted P = 0.003 < 0.0167).

Comparison of safety assessment between the two groups during treatment

The incidence of all-cause mortality, sICH and adverse events within 90 days was compared between the two groups. Table 4 presents the all-cause mortality and sICH rates during the treatment period. The results show that the mortality and incidence of sICH in group A were 3.6% and 5.5%, respectively, which were higher than 1.7% and 3.4% in group B, but the differences were not statistically significant (P=0.963, P=0.952). However, given the small number of events, these numerical differences should be interpreted with caution and do not constitute evidence of superior safety for tirofiban. Table 5 compares the incidence of adverse events within 3 months between the two groups. There were reocclusions of blood vessels, thrombocytopenia, gingival bleeding and occult blood in urine and feces in the two groups. The total incidence of group B (6.9%) was lower than that of group A (16.4%) and the difference was not statistically significant (P=0.115). Given the small absolute numbers, this trend should not be overinterpreted as evidence of a difference in safety profiles.

DISCUSSION

Efficacy outcomes: Neurological function and prognosis

As the primary efficacy outcome, NIHSS scores showed that the reduction in NIHSS was significantly greater in group B than in the aspirin group at 1 week and 3 months after treatment (P<0.001), achieved a greater reduction in neurological deficits by 1 week, and this improvement was more sustained at 3 months. This result is consistent with the conclusion of the open-label part of the TREND trial: initiating a tirofiban infusion for 24 h within 24 h of onset can significantly reduce the hazard of early END (Zhang *et al*., 2022c) The prespecified subgroup analysis of the RESCUE BT-2 multicenter RCT also confirmed that, among atherosclerotic patients without LVO, the median 90-day NIHSS in the tirofiban group was 1 point lower than in the aspirin group (Zi *et al*., 2022). The baseline NIHSS of this cohort was ≈ 15.7, which was higher than that of RESCUE BT-2 (≈ 9.3), suggesting that a similar benefit was still observed in the population with severe ANLVOIS. The antiplatelet strategies in the two groups differed only during the acute phase (the first 24 hours). Group B received intravenous tirofiban during this critical period before switching to oral aspirin, whereas Group A received aspirin alone throughout. Since both groups were maintained on the same long-term antiplatelet regimen (aspirin 100 mg/day) after the first 24 hours, the observed improvements in neurological function and long-term prognosis in Group B reflect the overall benefit of a treatment strategy that combines early, potent antiplatelet therapy with tirofiban followed by standard aspirin maintenance. The initial 24-hour tirofiban infusion likely plays a critical role in rapidly stabilizing the acute thrombotic process, which, when coupled with continued secondary prevention with aspirin, translates into sustained better outcomes at 3 months. Adjustment methods (regression, PSM) were considered but precluded by modest sample size and few outcome events. Thus, findings are exploratory and require confirmation in large prospective studies.

The mRS scale is a core indicator to examine the long-term functional recovery and independent living ability of stroke patients and is widely used in clinical practice and scientific research worldwide (Kasner, 2006). The reason mRS has become a core indicator is its strong correlation with patients' actual quality of life (Erler *et al*., 2022). The trend of mRS scores in this study was consistent with that of NIHSS scores: No significant intergroup difference was detected prior to treatment (P=0.906). After 1 week of intervention, group A was significantly higher than group B (P < 0.001) and it remained significantly higher than group B at 3 months of treatment (P < 0.001). The 3-month mRS binary analysis also showed the advantage of the tirofiban group (P=0.003) and Bonferroni correction still had statistical significance (P=0.003<0.016 after correction), further confirming the reliability of the results. The above results indicate that tirofiban can not only rapidly improve neurological function in the acute phase but also significantly improve long-term functional prognosis and enhance patients' ability to live independently. Beyond statistical significance, it is crucial to consider the clinical meaningfulness of the observed differences. For the NIHSS, a reduction of 2 to 4 points is generally accepted as the minimal clinically important difference in patients with AIS (Saver and Yafeh, 2007). In our study, the between-group difference in NIHSS at 1 week was 1.7 points (P<0.001), approaching the lower threshold of clinical relevance during the early recovery phase. At 3 months, the difference widened to 0.9 points (P<0.001), reflecting a sustained advantage. Regarding the mRS, a shift of 1 point is widely regarded as a clinically meaningful improvement in functional outcome (Broderick *et al*., 2017). The 0.7-point difference in 3-month mRS between Group B and Group A (P<0.001) therefore represents a meaningful improvement in patients' ability to live independently. These findings suggest that the benefits of tirofiban observed in our study are not merely statistical artifacts but translate into tangible improvements in patient-centered outcomes. A key consideration in interpreting our findings is the biological rationale for using a potent GP IIb/IIIa inhibitor in ANLVOIS. While pure small-vessel occlusion (e.g., lipohyalinosis) may not intuitively justify routine GP IIb/IIIa inhibition, the clinical entity of ANLVOIS in practice often encompasses heterogeneous mechanisms, including branch atheromatous disease and artery-to-artery embolization from non-stenotic plaques (Zi *et al*., 2023).

Table 3: Binary comparison of mRS scores of patients at 3 months [n (%)]

	Favorable outcome (mRS 0-2)	Unfavorable outcome (mRS 3-6)	χ^2	P
A group (n=55)	45 (81.8)	10 (18.2)	8.702	0.003
B group (n=58)	57 (98.3)	1 (1.7)		

Table 4: Comparison of mortality, sICH during treatment [n (%)]

	Mortality	χ^2	P	sICH	χ^2	P
A group (*n*=55)	2 (3.6)	0.002	0.963	3 (5.5)	0.004	0.952
B group (*n*=58)	1 (1.7)			2 (3.4)		

Table 5: Comparison of adverse events during treatment [n (%)]

	Vessel reocclusion	Thrombocytopenia	Gingival bleeding	Occult blood in urine and feces	Overall incidence rate	χ^2	P
A group (*n*=55)	4 (7.3)	2 (3.6)	1 (1.8)	2 (3.6)	16.4%	2.485	0.115
B group (*n*=58)	2 (3.4)	1 (1.7)	0 (0)	1 (1.7)	6.9%		

In these settings, dynamic thrombus progression or microthrombi formation—concepts we hypothesize but did not directly measure—may play a pivotal role. Our study was not designed to confirm these pathways mechanistically, but rather to provide an exploratory clinical comparison of two antiplatelet strategies. The observed benefit of tirofiban suggests that in a real-world ANLVOIS cohort, early potent antiplatelet therapy may be beneficial, though the precise biological substrate (e.g., plaque activity vs. microthrombosis) warrants dedicated imaging or biomarker studies.

Potential mechanisms underlying the benefits of tirofiban

At the mechanistic level, tirofiban reversibly blocks GP IIb/IIIa receptors, reducing platelet aggregation by >80% within 5 minutes and potently inhibiting fibrinogen-dependent platelet aggregation. This results in a rapid and potent antiplatelet effect, with an onset of action substantially faster than that of traditional antiplatelet agents (Zi *et al*., 2022). In contrast, aspirin mainly inhibits the production of thromboxane A_2 (TXA_2) by irreversibly acetylating cyclooxygenase-1 (COX-1). Its maximum platelet inhibition rate with monotherapy is usually only 60%–70%, and it takes 2–4 hours to achieve stable efficacy (Contursi *et al*., 2024;. This effect is consistent with tirofiban's ability to target the final pathway of platelet aggregation directly, and it also has the potential to dissolve or prevent the expansion of small-artery microthrombi with a diameter less than 200 μm (Yang *et al*., 2019). On the contrary, aspirin has a very limited effect on the dissolution of formed microthrombi, which mainly prevents new platelet activation and aggregation, so it has less effect on the existing microcirculatory obstruction (Fan *et al*., 2024). Therefore, under the framework of the hypothesis of "dynamic progression of thrombus", early potent antiplatelet can break the vicious cycle of microemboli hypoperfusion infarct expansion and explain the rapid decline of NIHSS.

The clinical benefit of tirofiban for treating AIS, especially the improvement of mRS score, cannot be entirely attributed to the rapid remission of early neurological deficits or "reduction of stroke severity". Increasing evidence suggests that this long-term improvement in functional prognosis may be closely related to its unique regulatory effect on cerebral collateral circulation. Traditional antiplatelet drugs such as aspirin primarily reduce thromboxane A_2 production by inhibiting cyclooxygenase-1 (COX-1), thereby inhibiting platelet activation, but their direct effects on formed microthrombi and the microcirculatory perfusion state are limited (Yang *et al*., 2019). Conversely, tirofiban is a highly selective nonpeptide antagonist of the glycoprotein (GP) IIb/IIIa receptor that can reversibly inhibit fibrinogen binding to this receptor. This leads to effective inhibition of the final common pathway of platelet aggregation, with greater directness and robustness (Garayzade *et al*., 2023). Recent perfusion computed tomography (CTP) studies have provided key imaging evidence for this. Studies have shown that in patients with acute LVO receiving endovascular therapy (EVT), the adjuvant use of tirofiban can significantly improve the leptomeningeal collateral flow index (LMA-CFI) by 15%–20% (Zhu *et al*., 2024). This effect is believed to stem from the strong inhibition of platelet interaction in the microcirculation by tirofiban, which reduces microthrombotic load, thereby reducing collateral resistance and promoting effective reperfusion in the ischemic penumbra (Zhu *et al*., 2024). It is worth noting that conventional aspirin doses did not show similar effects on improving collateral circulation hemodynamics, highlighting the unique advantages of tirofiban in microcirculation protection (Yang *et al*., 2019).

Safety profile

Safety evaluation outcomes demonstrated no statistically significant differences in 90-day all-cause mortality, incidence of sICH, or adverse event rate between the two groups(P>0.05): the all-cause mortality rate, sICH incidence rate and adverse event rate in group A were 3.6%,

5.5% and 16.4%, respectively, while those in group B were 1.7%, 3.4% and 6.9%, respectively and all safety indicators showed numerically lower values in the tirofiban group compared with the aspirin group, which confirmed that tirofiban was safe in the treatment of ANLVOIS and failed to elevate the risk of bleeding or other adverse events due to its stronger antiplatelet effect. The safety advantage of tirofiban primarily stems from its unique pharmacological properties and a reasonable dosing regimen. First of all, tirofiban is a reversible antiplatelet drug and the platelet function can recover rapidly after withdrawal. Compared with drugs that irreversibly inhibit platelets, its bleeding risk is easier to control (Zi *et al*., 2022); Secondly, the short-term administration scheme of 30 minute loading dose [0.4 μg/(kg-min)] + 24-hour maintenance dose [0.1 μg/(kg-min)] was adopted in this study, which avoided long-term high-intensity antiplatelet therapy and reduced the cumulative risk of bleeding events; In addition, strict exclusion criteria before treatment (such as excluding patients with active bleeding, severe renal insufficiency, coagulation abnormalities, etc.) further reduced the safety risk. sICH is the most serious adverse event in antiplatelet therapy for stroke. In this study, the incidence of sICH in the tirofiban group was 3.4%, lower than 5.5% in the aspirin group, with no statistically significant difference ($P>0.05$). This aligns with existing research findings. The study design of the RESCUE BT-2 trial (Zi *et al*., 2022) clearly proposed that the safety of tirofiban in AIS was equivalent to that of aspirin, and the TREND trial failed to detect that tirofiban elevated the risk of sICH (Wang *et al*., 2024b).

From the perspective of overall adverse event composition, although patients in both groups may have vascular reocclusion, decreased platelet count, gingival bleeding, urine / fecal occult blood and other events, the total incidence of tirofiban group (6.9%) is lower than that of group A (16.4%), but research data show that the total incidence of adverse events in tirofiban group may be lower. Nevertheless, it is important to emphasize that the absolute number of safety events in both groups was small, limiting the statistical power to detect true differences. The numerically lower incidence in the tirofiban group should not be interpreted as definitive evidence of superior safety and these findings warrant confirmation in larger prospective studies. This may be attributed to its more potent antiplatelet effect, which can more effectively inhibit thrombosis, thereby reducing the occurrence of vascular reocclusion (Zhang *et al*., 2022, Lu *et al*., 2023) (the incidence of vascular reocclusion in group A was 7.3% vs 3.4% in group B). At the same time, its reversible mechanism of action reduces the risk of excessive platelet reduction or continuous mucosal bleeding associated with long-term inhibition (Pereira da Silva *et al*., 2025;. Existing studies further supported its safety and found that the incidence of adverse events of tirofiban in the treatment of ischemic stroke without LVO was comparable to that of conventional antiplatelet drugs (Yu *et al*., 2022). The RCT study (Olive-Gadea *et al*., 2025) included 267 patients with ANLVOIS, and the incidence of sICH in the tirofiban group was only 2.7%, which was not different from that in the control group. In conclusion, for patients with ANLVOIS, the intensive treatment of short-term intravenous infusion of tirofiban in the acute phase not only ensures efficacy but also has controllable safety and even shows potential advantages in the incidence of some adverse events, providing strong data support for the clinical application of the drug (Monteiro *et al*., 2024).

Comparison with existing evidence and real-world implications

While recent randomized controlled trials (RCTs) such as TREND and RESCUE BT-2 have established the efficacy of tirofiban in well-controlled settings, their findings may not be fully generalizable to real-world clinical practice, particularly in secondary care centers where patient heterogeneity is greater and resources are limited. Furthermore, these RCTs often enrolled patients with moderate stroke severity (median NIHSS 9), leaving a gap in evidence regarding the drug's performance in more severe ANLVOIS populations or in patients managed outside of strict trial protocols. This retrospective study aims to bridge this gap by providing real-world evidence from a county-level hospital in China. By comparing tirofiban versus aspirin in a cohort with higher baseline NIHSS scores and more comorbid conditions, we seek to validate the external applicability of existing RCT data and offer practical insights for clinicians facing treatment decisions in everyday practice.

This study systematically compares the efficacy and safety of tirofiban and aspirin in patients diagnosed with ANLVOIS. The results showed that tirofiban was not only superior to aspirin in neurological function and long-term prognosis, but also had comparable safety and even had advantages in some aspects. This finding has important implications for clinical practice: for ANLVOIS patients ineligible for thrombolysis or thrombectomy, especially those individuals with high platelet activity or suspected thrombus progression, early use of tirofiban, followed by conversion to oral aspirin for long-term maintenance, may be an effective treatment strategy. This approach leverages tirofiban's rapid and powerful antiplatelet action in the critical acute phase while transitioning to the convenience, established safety profile and long-term secondary prevention benefits of aspirin. The single-center design and homogeneous Chinese population limit the generalizability of our findings to other ethnic groups or healthcare systems with different practice patterns. However, our real-world data from a secondary hospital complement RCTs by including patients with higher baseline severity (NIHSS ≈15.7), suggesting tirofiban may benefit even severe ANLVOIS in routine practice. Confirmation requires multicenter studies across diverse populations and guideline environments.

Limitations of the research

First, this study uses a retrospective design and has a relatively small sample size, which may introduce selection bias. Although baseline characteristics were balanced, not all potential confounders could be adjusted for. Therefore, our findings should be considered exploratory and future large-scale prospective studies are needed to confirm these results and account for a broader range of confounders. Second, whether the long-term effect in the tirofiban treatment group is entirely attributable to tirofiban requires further verification. Third, the small number of safety events limits statistical power; thus, findings should be interpreted cautiously. Fourth, owing to the retrospective design, precise symptom-onset-to-treatment times were not available, precluding analysis of time-dependent effects. Although all patients received tirofiban early in hospitalization, future prospective studies should investigate whether earlier administration is associated with greater improvement. Fifth, due to the retrospective design and the lack of advanced imaging or biomarker data, we are unable to determine the precise biological mechanisms underlying the observed benefits, such as microthrombus clearance or collateral blood flow enhancement. Prospective studies combining perfusion imaging or platelet function assays are needed in the future to elucidate these pathways. Sixth, because of the non-randomized design, treatment allocation was influenced by clinical judgment, potentially introducing confounding by indication. Although baseline characteristics were well balanced, residual confounding from unmeasured factors cannot be ruled out. Therefore, our findings should be considered exploratory and require validation in larger prospective studies.

CONCLUSION

This study demonstrated that in patients with ANLVOIS, an early treatment strategy combining tirofiban followed by aspirin was associated with superior neurological recovery and long-term functional outcomes compared with aspirin alone, without increased bleeding risk. These findings support consideration of a tirofiban induction followed by aspirin maintenance regimen as an effective antiplatelet strategy in selected patients during the acute phase.

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None.

Authors' contributions

Chengzong Cui: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions; Qingxia Meng: Participated in collecting, assessing and interpreting the data. Made significant contributions to data interpretation and manuscript preparation; Chengwen Cui and Yue Zhu: Provided substantial intellectual input during the drafting and revision of the manuscript.

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Data availability statement

The data supporting the findings of this study can be obtained from the corresponding author upon request.

Ethical approval

This study was approved by the Wuqiao County People's Hospital Ethics Committee Ethical approval number: No.WYLLSC-2026-001. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare no conflicts of interest.

Supplementary data

https://www.pjps.pk/uploads/2026/05/SUP1780141641.pdf

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