

EFFICACY AND SAFETY OF TIROFIBAN IN THE TREATMENT OF ACUTE ISCHEMIC STROKE BASED ON WEB OF SCIENCE DATABASE: A META-ANALYSIS

RUI ZHANG ^{1*}, ZHIYUN WANG ¹

¹Department of Neurology, Tianjin First Central Hospital, Tianjin, 300192, China

*corresponding author: zhangruihot@163.com

Manuscript received: May 2026

Abstract

The study aimed to explore the clinical efficacy and safety of tirofiban in the treatment of acute ischemic stroke (AIS) through a systematic review. The Web of Science database was searched using keywords including “tirofiban”, “acute ischemic stroke”, and related medical subject terms. Eight relevant articles were identified, published between 2013 and 2020 and meta-analysis of the extracted data was subsequently conducted using RevMan 5.3 statistical software. The results showed that the odds ratio (OR) of efficacy of tirofiban in AIS was found to be 1.36, and the effect was better than that without tirofiban; the OR of good prognosis of tirofiban in AIS was 1.36, which was better than that without tirofiban in good prognosis; the OR of bleeding in AIS treated with tirofiban was 1.09, which was not significantly different from that without tirofiban; the OR of recanalization in AIS treated with tirofiban was 1.51, which was better than that without tirofiban in recanalization; the OR of mortality in AIS treated with tirofiban was 0.88, which was lower than that without tirofiban in mortality. In conclusion, Tirofiban treatment of AIS can improve the prognosis of patients, improve the response rate after treatment, improve the ability of patients to live autonomously, and can reduce the risk of reocclusion and mortality.

Rezumat

Studiul a urmărit evaluarea eficacității și siguranței tirofibanului în tratamentul accidentului vascular cerebral ischemic acut (AVC), printr-o revizuire sistematică și meta-analiză a literaturii de specialitate. A fost efectuată o căutare în baza de date *Web of Science*, utilizând termenii „tirofiban”, „accident vascular cerebral ischemic acut” și termeni medicali asociați. Au fost incluse opt articole publicate între 2013 și 2020, iar datele extrase au fost analizate utilizând programul RevMan 5.3. Rezultatele au evidențiat o eficacitate terapeutică superioară în grupul tratat cu tirofiban (OR = 1,36), precum și o probabilitate mai mare de prognostic favorabil (OR = 1,36), comparativ cu pacienții care nu au primit acest tratament. Administrarea tirofibanului a fost asociată cu o rată mai mare de recanalizare vasculară (OR = 1,51) și o mortalitate mai redusă (OR = 0,88), fără o creștere semnificativă a riscului hemoragic (OR = 1,09). În concluzie, tirofibanul poate reprezenta o opțiune terapeutică utilă în AVC ischemic acut, contribuind la îmbunătățirea prognosticului și a recuperării funcționale.

Keywords: tirofiban, acute ischemic stroke, treatment, efficacy and safety, meta-analysis

Introduction

Acute ischemic stroke (AIS) is the leading cause of death worldwide. The high incidence rate, disability, and mortality of stroke have become a concern worldwide, while ischemic stroke is the main type of stroke patients (1, 2). The incidence of ischemic stroke is increasing year by year, and the standardized mortality rate of ischemic stroke in China has increased by 20.8% in the past few years. Early screening, prevention, and active treatment of ischemic stroke will help to improve the status of stroke in China (3-5). Ischemic penumbra is present in AIS and this part of brain tissue damage is reversible. By opening blood vessels in a short period of time, restoring blood supply to the ischemic penumbra, allowing nerve cells to survive and restore function, and reducing the cerebral infarction area, it can improve the early prognosis of AIS patients, restore neurological function,

and enhance life quality (6, 7). Activation of alteplase within 4.5 hours and urokinase within 6 hours of symptom onset for thrombolytic therapy has been shown to be beneficial in patients. However, due to the narrow thrombolysis time window, most patients with cerebral infarction fail to perform effective thrombolytic therapy, resulting in hemiplegic symptoms and even death, which seriously affects the quality of life and survival of patients (8-10). Therefore, there is an urgent need for an effective and safe method to treat AIS beyond the thrombolytic time window.

Tirofiban is one of the most widely used glycoprotein IIb/IIIa inhibitors, which has a short plasma/biological half-life and high affinity, and has good efficacy and tolerability in long-term functional prognosis and improvement of recanalization. The efficacy of tirofiban in acute coronary syndrome and its use after endovascular treatment and thrombolytic therapy in patients with acute stroke has been well-established,

and the tirofiban in AIS has been deemed safe in the Safety of Tirofiban in AIS (SaTIS trial) (11, 12). Available studies have shown that tirofiban is very promising in the treatment of AIS, and the use of tirofiban before dual antibody therapy in AIS patients achieves a rapid onset and highly effective antiplatelet effect (13, 14). In recent years, the application of tirofiban in AIS has received much attention, but there is still a lack of large clinical trials and studies to confirm its safety and effect in the application of tirofiban in AIS. Systematic evaluation of randomized controlled trials of tirofiban in AIS provides more basis for clinical research and application.

The high disability and mortality rates associated with AIS make it a global public health challenge. Although early reperfusion therapies, such as thrombolysis, can salvage the ischemic penumbra, the narrow time window means that most patients miss the opportunity for treatment, creating an urgent need for new strategies. Tirofiban, a highly selective glycoprotein IIb/IIIa receptor antagonist, has demonstrated potential in enhancing reperfusion rates and improving the functional outcomes due to its rapid onset and reversible inhibition of platelet aggregation. However, current evidence regarding its safety, efficacy, and optimal dosing regimen for AIS beyond the therapeutic time window is primarily derived from small-scale studies, lacking high-quality evidence. A systematic review of randomized controlled trials on tirofiban for the treatment of AIS could integrate existing data and provide valuable evidence for clinical decision-making and future research.

Materials and Methods

Literature recruitment

The Web of Science (WOS) database was searched so that literatures on tirofiban in the treatment of AIS can be collected worldwide. The relevant literatures published up to August 2022 were searched with search terms including “Cerebral Infarction”, “Brain Infarction”, “Stroke”, “Acute Ischemic Stroke”, “Tirofiban”, “Tirofiban Hyd” as the test terms. All database searches adopted a combination of subject and free words, and appropriate adjustment was performed regarding the specific database. Various research determined the search strategy. To avoid omissions, professional journals were searched manually, with people as the subjects. Multiple searches were needed to collect qualified papers, each of which was traced later. RevMan 5.3 from Cochrane Collaboration was employed for quality rating.

Criteria

Inclusion criteria: (1) patients with AIS; (2) patients were treated with tirofiban; (3) patients signed the relevant informed consent documents, and the clinical data were complete; (4) efficacy or safety endpoints were demonstrated (overall response (OR), complete

response (CR), partial response (PR), and adverse events).

Exclusion criteria: (1) case number of 10 or less; (2) multi-arm studies (> 2); prospective studies were preferentially selected to maximize the level of evidence, and retrospective studies were not included; existing randomized controlled trials were not included owing to various outcome measures; (3) conference abstracts, case reports, reviews, communication works, clinical experience reports with insufficient data, and non-human trials; (4) papers having insufficient, vague, or unextractable data.

Data extraction

Using a unified Excel (Microsoft, USA), two professionals screened papers and harvested data independently, with results cross-checked and discrepancies addressed by discussion. The harvested data included: (1) general data such as title, first author, publication years; (2) basic characteristics such as case number, age, gender; (3) treatment process: after tirofiban therapy, bleeding, recanalization rate; (4) bias risk determination: randomizations, blinding, and allocation concealment; (5) outcome indicators of interest and outcome measurements: OR, CR, PR, safety outcome adverse event.

Appraisal criteria

The quality assessment of diagnostic accuracy studies (QUADAS) criteria was adopted for paper quality rating, which was from Cochrane (USA) for treatment trials. Each evaluation indicator of the papers was rated as “conformity”, “non-conformity”, or “uncertainty”.

Statistical methods

RevMan 5.3 (Cochrane, USA) and Stata (Stata Corp, USA) were employed, with odds ratio (OR) as effect index for dichotomous variables, and mean difference for continuous variables. Later, point estimates and their 95% CI were assigned correspondingly. X² test ($\alpha = 0.1$) was performed for determination of heterogeneity, which was assessed in combination with I² quantitatively. Should there be no notable difference, further analysis was conducted with a fixed-effect model (FEM), otherwise a random-effect model should be adopted. Possible sources of heterogeneity were traced through subgroup analysis. Meta-analysis test level was $\alpha = 0.05$. Forest plots and summary receiver operating characteristic curves were fabricated, so did asymmetric linear regression of funnel plots. Funnel plots of various treatments examined potential publication bias.

Results and Discussion

Screening process and outcome

Three hundred fifty-one papers were harvested from Web of Science database, of which 24, 56, and 87 papers were excluded first due to repeated publication, ineligibility, and other excuses, respectively, leaving

184 preliminarily screened articles. Later, 74 articles were excluded regarding abstracts and titles, leaving 110 articles. Then, 65 articles remained after 45 research reports and reviews were excluded. Finally, 29 articles with incorrect study type were excluded

through full text reading, 24 were discarded due to incomplete or unavailable required treatment results, and 4 non-human ones were also discarded, leaving 8 articles included in this meta-analysis (15-22). Figure 1 shows a flow diagram of the retrieved works.

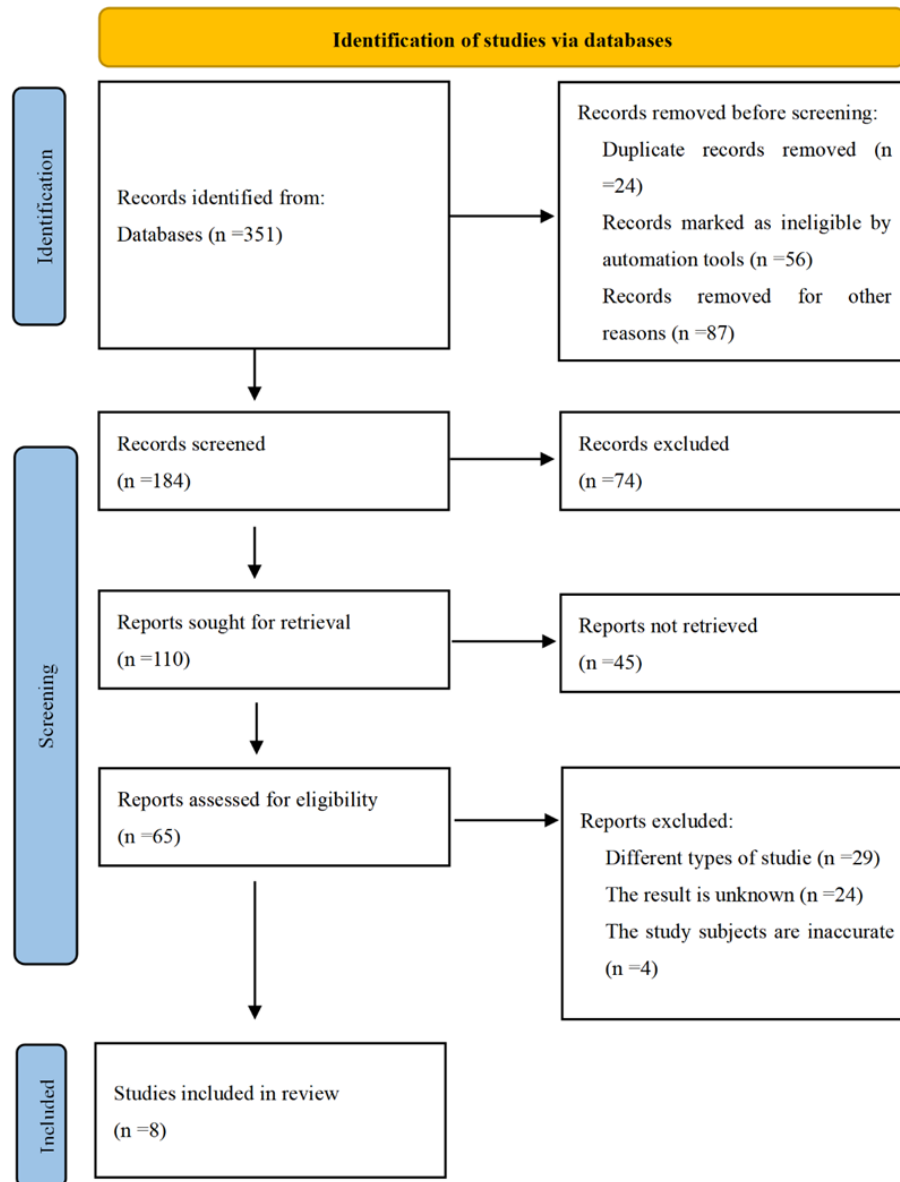


Figure 1.

Flow chart of search process

Of the eight studies, 1,368 AIS patients were treated with endovascular treatment, and 497 patients were treated with Stent retriever. Additionally, among the 8 literatures, the sample size varied from 50 to 432. 8 papers expounded in detail the process of the AIS

treatment by tirofiban, recorded the age of patients, medication methods, etc., analyzed various indicator changes preoperatively and postoperatively. The prognosis and recanalization effect of AIS after tirofiban treatment were also expounded (Table I).

Table I
Baseline data

First author	Year	Tirofiban protocol	Endovascular therapy	Mean age	Case
Kellert (15)	2013	0.4 µg/kg/min	Endovascular treatment	64.5/67.3	50/112
Luo (16)	2019	50 µg/min	Stent retriever	64/67.95	56/43
Pan (17)	2019	0.15 µg/kg/min	Endovascular treatment	69.5/74	82/129
Quan (18)	2019	0.2 - 0.25 mg/h	Endovascular treatment	NA	85/74

First author	Year	Tirofiban protocol	Endovascular therapy	Mean age	Case
Wu (19)	2018	1 mL/min	Stent retriever	70/71.5	94/124
Yang (20)	2020	0.1 µg/kg/min	Endovascular treatment	62.9	230/432
Zhao (21)	2017	0.2 - 0.25 mg/h	Stent retriever	64.7	90/90
Zhao (22)	2020	0.1 µg/kg/min	Endovascular treatment	68/68	89/85

Through quality rating, 5 studies (15, 18, 19, 20, 22) (62.5%) were rated as Level A, 2 studies (16, 21) (25.0%) were rated as Level B, and 1 study (17) (12.5%)

was rated as Level C. Figure 2 illustrates the risk bias evaluation chart and Figure 3 the risk bias summary chart produced by RevMan 5.3.

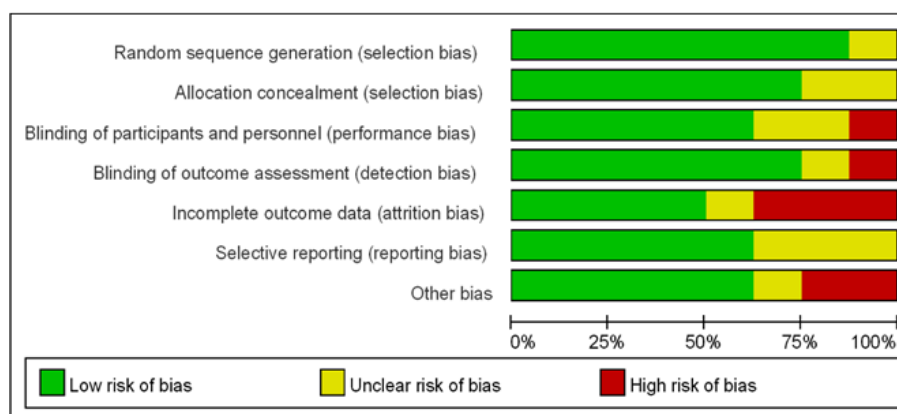


Figure 2.
Risk bias evaluation display *via* RevMan 5.3

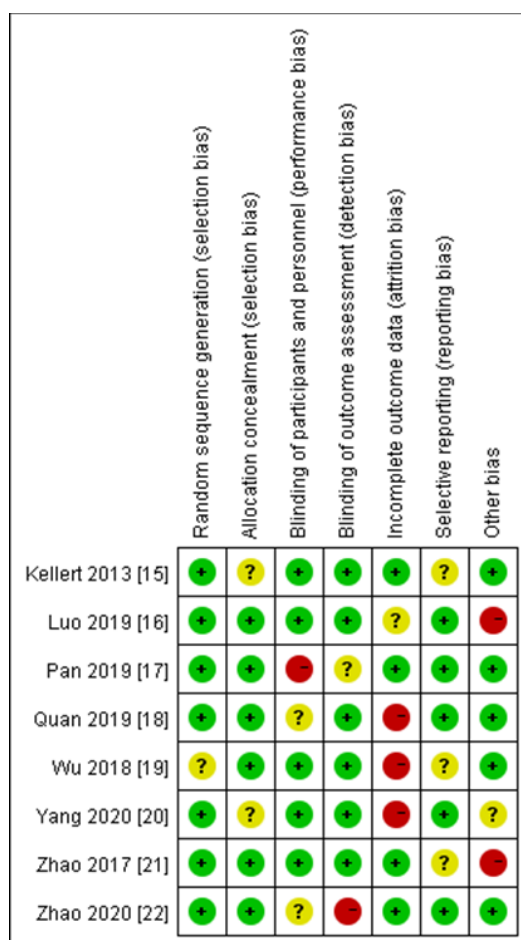


Figure 3.
Summary of risk bias plotted by RevMan 5.3. "+" low risk, "-" high risk, "?" unclear risk

Heterogeneity evaluation results

The heterogeneity among studies after treatment of AIS with tirofiban in the included literatures was evaluated. Effectiveness: no heterogeneity ($I^2 = 0.00\%$); good prognosis: no heterogeneity ($I^2 = 0.00\%$); bleeding events: low heterogeneity ($I^2 = 24\%$); recanalization rate: low heterogeneity ($I^2 = 32\%$); mortality: no heterogeneity ($I^2 = 0.00\%$). A random-effect model was utilized for summary analysis and funnel plot was fitted to further determine heterogeneity of data between two examination approaches and contrast the

differences in the indicators of different treatment modalities.

Meta-analysis of treatment effectiveness

The OR for effectiveness of tirofiban in AIS was 1.36, 95% CI (1.05, 1.76), $I^2 = 0.00\%$, and $P = 0.44$ in 8 articles (15-22). The OR showed no heterogeneity in the effectiveness of tirofiban treatment among groups. The lowest OR was 0.44 with a 95% CI of (0.06, 3.19) while the highest was 1.75 with a 95% CI of (1.24, 2.47) (Figure 4).

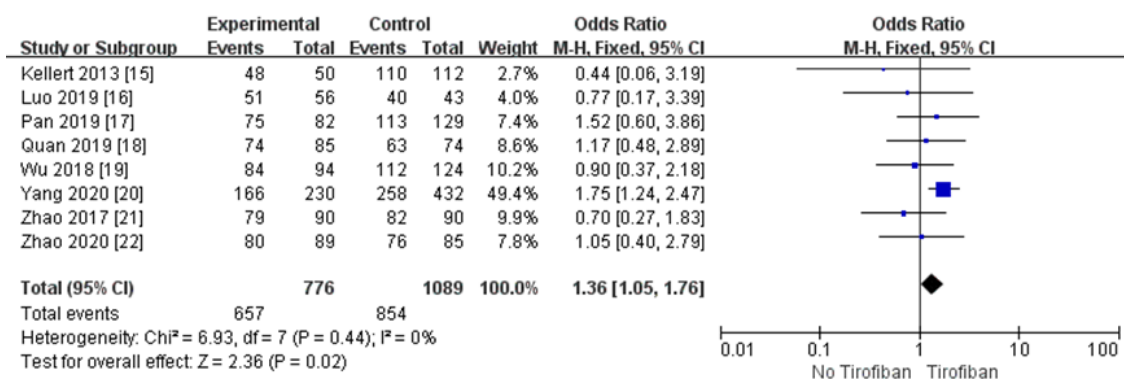


Figure 4.

Forest plot of AIS effectiveness after tirofiban treatment. CI: confidence interval; df: degree of freedom

A comprehensive analysis of treatment efficacy was performed, and Figure 5A reveals the heterogeneity test plot of the efficacy of tirofiban in AIS, showing that there was little heterogeneity gap across studies

and high accuracy. The efficacy funnel plot in Figure 5B suggests that the risk of bias across studies was slight. Thus, tirofiban was more effective than no tirofiban in the treatment of AIS.

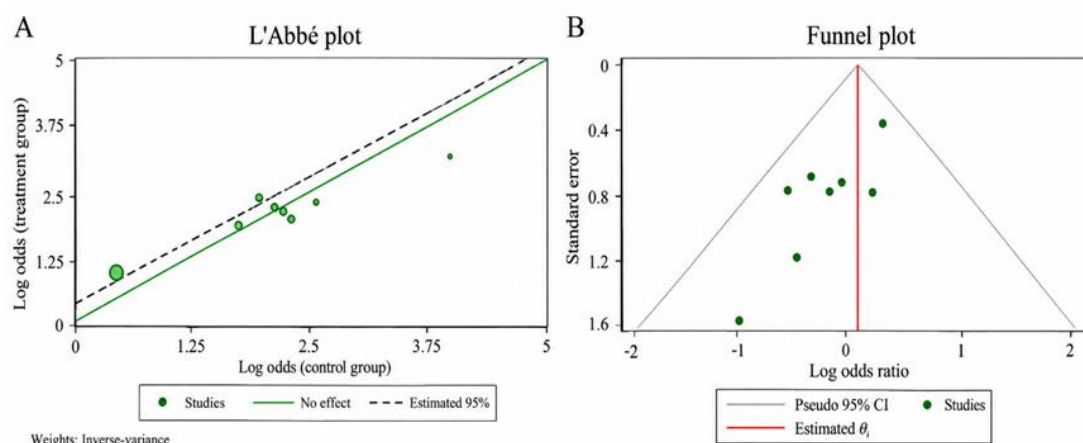


Figure 5.

A: Labbe heterogeneity test plot of efficacy. B: Funnel plot of effectiveness

Meta-analysis of good prognosis

Eight articles (15-22) had an OR of 1.36, 95% CI of (1.11, 1.67), $I^2 = 0.00\%$, $P = 0.50$ for good prognosis. OR suggested no heterogeneity among groups regarding good prognosis after tirofiban treatment. The lowest OR was 0.71 with 95% CI of (0.32, 1.60) while the highest was 1.75 with 95% CI of (0.99, 3.09) (Figure 6).

A comprehensive analysis of good prognosis illustrated in Figure 7A indicates a heterogeneity test plot of good prognosis of AIS after tirofiban treatment, suggesting that there was little heterogeneity gap among the studies and there was high accuracy. Figure 7B shows a small risk of bias across studies. According to the above results, tirofiban was better than no tirofiban in terms of good prognosis.

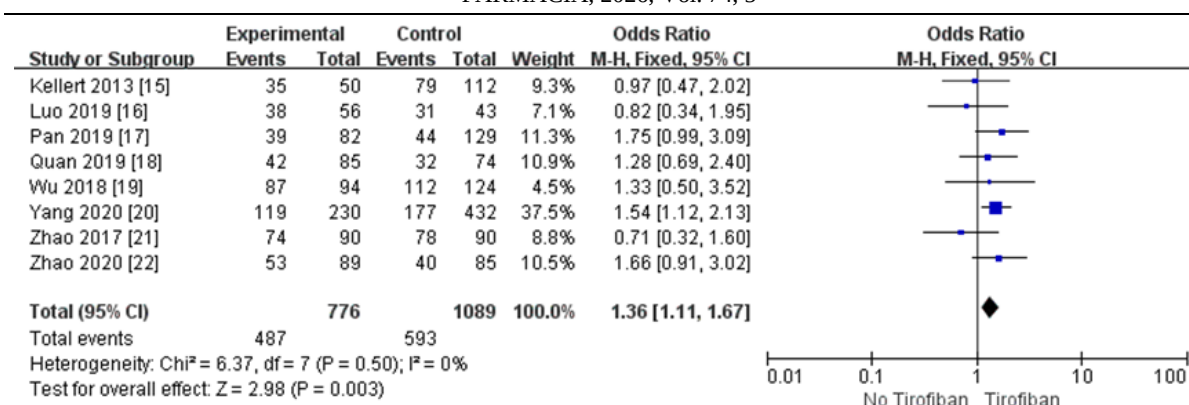


Figure 6.
Forest plot of good prognosis

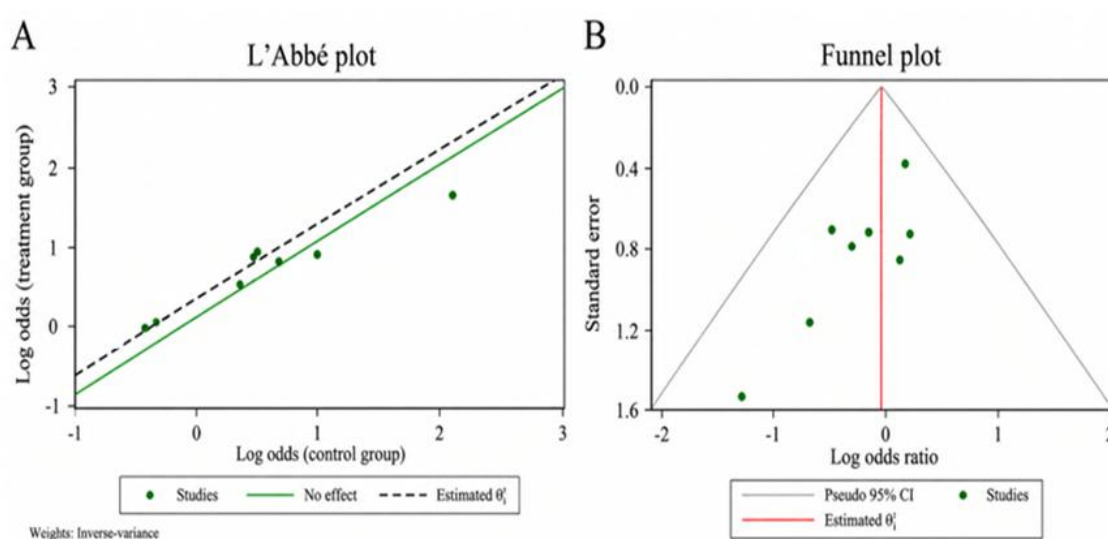


Figure 7.
A: L'Abbé heterogeneity test plot of good prognosis. B: Funnel plot of good prognosis

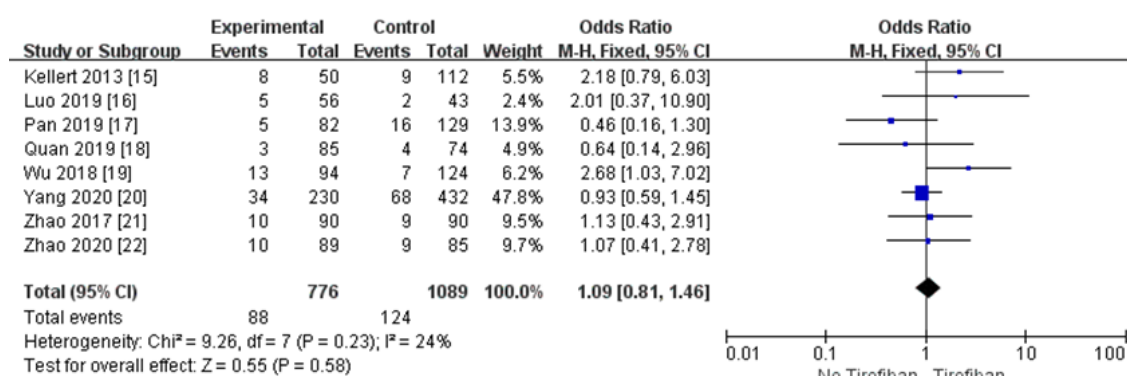
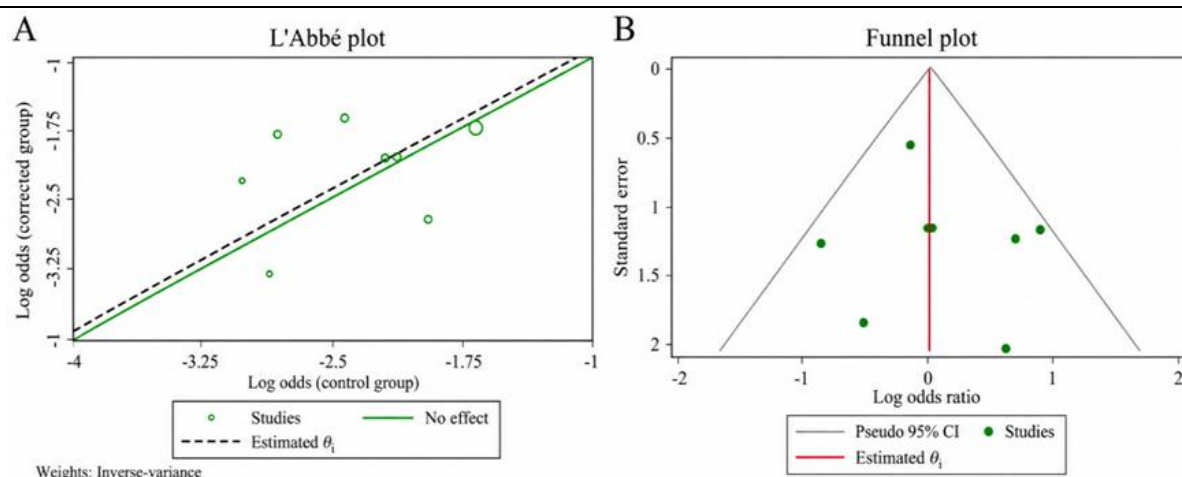


Figure 8.
Forest plot of bleeding

Meta-analysis of bleeding

The OR of bleeding in AIS treated with tirofiban in 8 articles (15-22) was 1.09, and 95% CI was (0.81, 1.46), $I^2 = 24\%$, $P = 0.23$. OR suggested low heterogeneity in bleeding across groups. The lowest OR was 0.46 with 95% CI of (0.16, 1.30) while the highest was 2.18 with 95% CI of (0.79, 6.03) (Figure 8).

Figure 9A shows the heterogeneity test plot of bleeding after tirofiban treatment through a comprehensive analysis of treated bleeding, indicating that there was little heterogeneity gap among the studies. Figure 9B indicates a small risk of bias across studies. Therefore, there was no obvious difference in bleeding between tirofiban and no tirofiban in AIS.

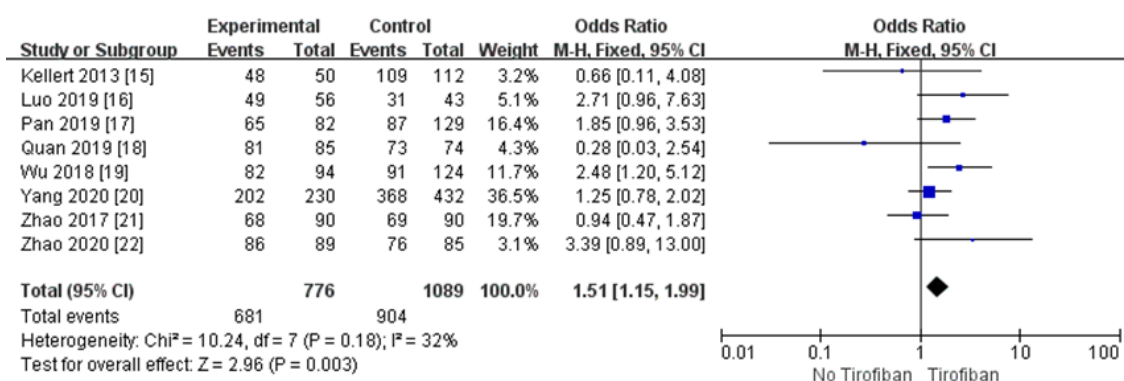
**Figure 9.**

A: L'Abbé heterogeneity test plot for bleeding. B: Funnel plot for bleeding

Meta-analysis of recanalization

The OR of recanalization of AIS treated with tirofiban was 1.51, and 95% CI was (1.15, 1.99), $I^2 = 32\%$, $P = 0.18$. The OR values revealed low heterogeneity among

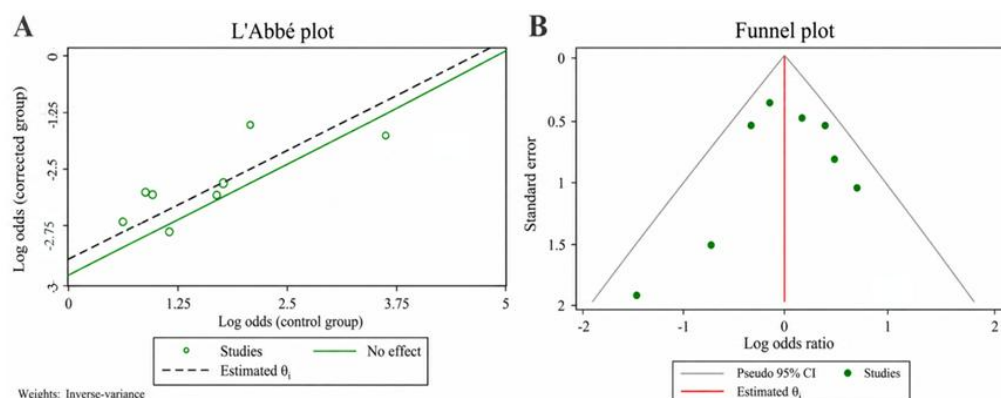
groups for recanalization. The lowest and the highest OR was 0.28 (95% CI = (0.03, 2.54)) and 2.71 (95% CI = (0.96, 7.63)), respectively (Figure 10).

**Figure 10.**

Forest plot of recanalization

Figure 11A indicates the heterogeneity test plot of recanalization after tirofiban treatment, showing that there was little heterogeneity gap across studies. Figure 11B suggests that the risk of bias across studies

was small. Therefore, tirofiban was better than no tirofiban for AIS in terms of recanalization.

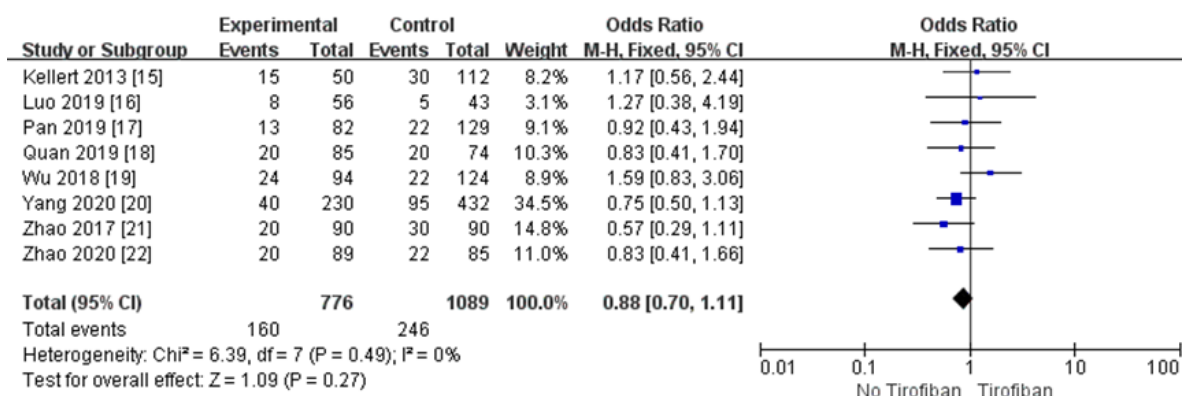
**Figure 11.**

A. L'Abbé heterogeneity test plot for recanalization. B: Funnel plot for recanalization

Meta-analysis of mortality

The OR for mortality in AIS treated with tirofiban was 0.88, and 95% CI was (0.70, 1.11), $I^2 = 0.00\%$, $P = 0.49$. OR revealed no heterogeneity among groups

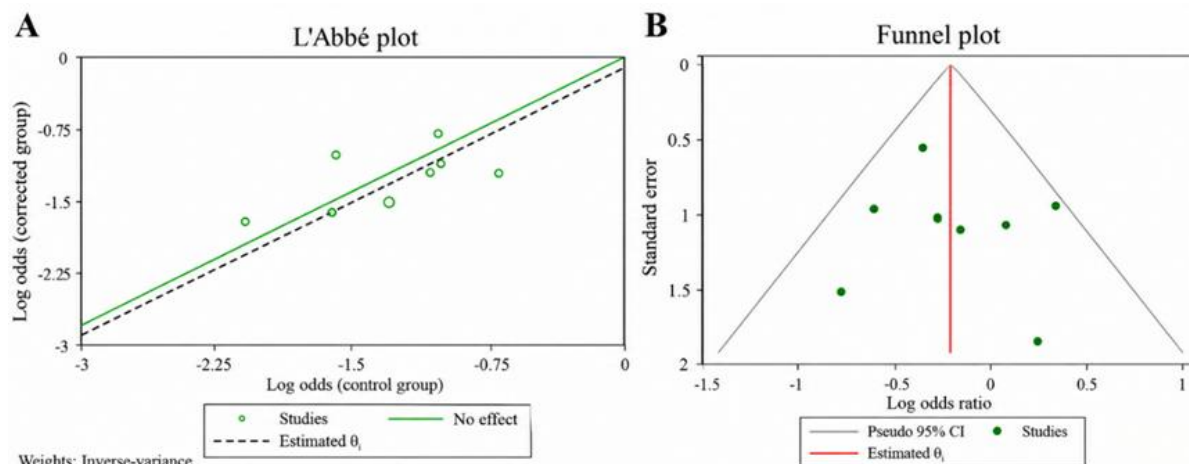
for mortality after treatment. The lowest and the highest OR was 0.57 (95% CI = (0.29, 1.11)) and 1.59 (95% CI = (0.83, 3.06)), respectively (Figure 12).

**Figure 12.**

Forest plot for mortality

Figure 13A shows a heterogeneity test plot for mortality in AIS after tirofiban treatment, showing little heterogeneity gap across studies. Figure 13B indicates

that the risk of bias across studies was small. Therefore, tirofiban was associated with lower mortality in AIS than no tirofiban.

**Figure 13.**

A: L'Abbé heterogeneity test plot for mortality. B: Funnel plot for mortality

Reliability test

The summary results using different analysis models differed slightly, indicating good stability of the papers included. Model analysis such as funnel asymmetry linear regression analysis also supported that the specificity was in good agreement with sensitivity verification.

AIS is a common disease in clinical practice, which endangers people's physical and mental health. The main causes of AIS are atherosclerotic rupture of intracranial feeding arteries and thrombosis. Platelet aggregation takes an active part in the process of thrombosis, and therefore, antiplatelet therapy is beneficial in reducing thromboembolism, restoring intracranial arterial blood flow, and hemoperfusion of brain

tissue (23-26). Antiplatelet agents have been widely used to treat atherosclerotic diseases, including AIS and acute coronary syndrome. Although the use of aspirin and clopidogrel for anti-platelet aggregation has become a routine treatment for AIS patients, the therapeutic effect remains poor, reaching as many as 4 - 30% of resistant to clopidogrel according to studies (27-29). Traditional antiplatelet drugs such as aspirin and clopidogrel inhibit platelet aggregation through cyclooxygenase and adenosine diphosphate, and other molecular pathways are not affected by these drugs, resulting in activation of glycoprotein IIb/IIIa receptors, which is considered to be the final pathway of platelet aggregation and thrombosis (30).

Utilized in percutaneous coronary intervention for AIS patients, glycoprotein IIb/IIIa receptor antagonists can prevent platelet aggregation and thrombosis by blocking fibrinogen binding receptor reversibility. However, its use in stroke is limited due to the risk of hemorrhagic transformation. Tirofiban has inferior molecular weight and half-life to abciximab and eptifibatide, and no immunogenicity, thus being widely recognized in cerebrovascular disease therapy (31, 32). Nevertheless, using tirofiban for endovascular treatment in AIS remains controversial. Some hold that tirofiban increases the risk of bleeding, leading to adverse outcomes (33). In contrast, others suggested that tirofiban can enhance functional outcome and post-operative recanalization rate without causing more hemorrhagic complications, which is consistent with the present results (34). Tirofiban also inhibits the inflammatory response other than platelet aggregation and reduces reperfusion injury by suppressing inflammatory expressions, which may help the functional prognosis of AIS patients. Thrombus retrieval usually enables recanalization of large vessels; however, many ruptured small emboli may occlude distal small vessels spontaneously. Intraoperative tirofiban usage can lead to dissolved small emboli, reduced occurrence of small vessel occlusion, and enhanced long-term prognosis. The dissolution of small emboli may be the key to improve the prognosis of patients with stent removal for tirofiban.

The results showed that tirofiban was more effective than no tirofiban in the treatment of AIS; tirofiban was better in terms of good prognosis and recanalization; tirofiban was not different from no tirofiban in terms of bleeding; and tirofiban was associated with lower mortality than no tirofiban. In addition, some studies were of low quality, which may cause bias. Therefore, larger, high-quality randomized controlled trials are needed to confirm differences in total blood transfusion, blood loss between the experimental and control groups.

Conclusions

The relevant literatures on AIS after tirofiban treatment were collected for meta-analysis to investigate the efficacy and safety of tirofiban treatment for AIS. In general, tirofiban was more effective than no tirofiban; tirofiban improved prognosis and recanalization rate, did not significantly improve bleeding events, and reduced mortality. Of course, there are inevitable certain defects. The drug concentration is not uniform in the included clinical trials. Some studies have not been included in this meta-analysis due to few randomized controlled trials and different outcome indicators, leading to reduced evidence level. Subsequently, more indicators will be collected to compare different drug concentrations in detail and provide established results for clinical treatment.

Acknowledgement

Not applicable.

Funding

Not applicable.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article. The other data generated in the present study may be requested from the corresponding author.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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