Original article

Effects of Tenecteplase on vascular recanalization, clinical prognosis and safety evaluation in patients with acute ischemic stroke: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess the effect and safety of Tenecteplase (TNK) on vascular recanalization, clinical prognosis, and safety in patients with acute ischemic stroke (AIS). **Methods:** PubMed, EMBASE, ScienceDirect, Cochrane Library, China National Knowledge Infrastructure (CNKI), China VIP Database, Wanfang Database and China Biomedical Literature Database (CBM) online database were searched for case-control trials in patients with AIS treated with TNK and alteplase. Between January 2010 and the present, the search period was limited. The data were collected separately by two researchers, and a meta-analysis of the collected data was conducted by RevMan5.3 statistical software using the Cochrane Handbook 5.3 standard for assessing bias risk. **Results:** Finally, 5 clinical control studies were contained. The total number of samples collected was 1569. In order to determine the improvement rate of early neurological function following treatment, an analysis of meta-analyses was conducted. Based on the fixed effect model analysis, the study group showed a noticeable improvement in early neurological function ($P<0.05$). To determine the reperfusion rate after thrombolysis for 24 hours, an analysis of meta-analyses was conducted. The fixed effect model analysis indicated that the reperfusion rate of the study group after 24 hours of thrombolysis was noticeably higher ($P<0.05$). To determine the proportion of cases with a Modified Rankin Scale (mRS) score ≤ 1 point 90 days after thrombolysis, an analysis of meta-analyses was conducted. Using the fixed effect model analysis, no statistically noticeable differences were found in the proportion of cases with 90dmRS score ≤ 1 after treatment ($P>0.05$). To determine the rate of symptomatic intracranial hemorrhage, an analysis of meta-analyses was conducted. There exhibited no statistically noticeable difference in the rate of symptomatic intracranial hemorrhage after treatment ($P>0.05$). To determine the incidence of bleeding, an analysis of meta-analyses was conducted. In effect model analysis, bleeding incidence after treatment was not noticeably different from baseline ($P>0.05$). To determine the mortality rate, an analysis of meta-analyses was conducted. No statistical difference was found in the mortality rate after treatment ($P>0.05$). Some of the distributions were asymmetric, suggesting that in the contained literature, a certain publication bias was present, which could be explained by the heterogeneity of studies and the small number of papers contained. **Conclusion:** TNK can noticeably enhance the early neurological function of patients with AIS, effectively improve the recanalization rate of blood vessels, promote the prognosis of patients, and do not increase the incidence of adverse events. The treatment deserves to be popularized in clinics. Study and follow-ups with higher methodological quality and a longer intervention period are required to achieve a greater degree of verification.

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Keywords: Tenecteplase, AIS, Revascularization, Clinical prognosis

Introduction

Acute ischemic stroke (AIS) is one of the diseases with the highest morbidity in humans [1, 2], accounting for 60-70% of stroke events (including hemorrhagic and ischemic stroke), with high morbidity and mortality. In accordance with statistics, about 17 million people in the world are suffering from AIS every year. In China, the mortality rate has surpassed cancer and cardiovascular disease, becoming the largest in China. In the United States, this is the fourth most common cause of death. AIS is not only a threat to the lives of patients, but also easy to relapse. Many patients are disabled after the onset of the disease and need long-term rehabilitation care. It can also be said to be a devastating disease, which will cause the survival tragedy of patients. The prevention, control and treatment of cerebrovascular disease has always been a priority for neurologists, as the number of patients with this type of disease is increasing day by day due to ageing and environmental factors.

It is well documented that neurological deficits caused by an ischemic stroke can negatively impact a patient's life ability and quality of life. Efforts should be made to improve patients' prognoses promptly and effectively. Intravenous thrombolysis is a more effective measure for the treatment of AIS, and it is in a cornerstone position [3, 4]. The time window for thrombolytic

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therapy is generally influenced by the time of stroke onset and the location and severity of cerebrovascular obstruction. The effectiveness of thrombolytic agents relies on various factors, containing the age of the patient with thrombosis, the specificity of the thrombolytic agent, and the presence and half-life of neutralizing antibodies [5].

Clinically, the intravenous thrombolytic drugs used have also undergone a renewal [6]. The first generation is a non-selective thrombolytic drug, which is characterized by consumption of fibrinogen (FIB) in the blood of the whole body and is prone to bleeding, such as Streptokinase (SK), urokinase (UK). SK has been eliminated in thrombolytic therapy due to severe side effects such as allergic reactions. However, the half-life of the drug is short, and the possibility of re-embolization caused by AIS is high. At present, it is mainly used in AIS with an onset time window within 6 hours. Due to its low price, it is relatively easy to be accepted by the public in developing countries, but the side effects are also noticeable. The second generation of selective thrombolytic drugs is represented by alteplase, which can act on fibrin-bound FIB, but does not produce fibrinolytic effect on free FIB in the blood. There is no systemic fibrinolysis, and the risk of bleeding is reduced. It is currently the most widely used thrombolytic drug in clinical treatment of AIS with proven efficacy and safety [7]. The third generation is mainly based on Reteplase (RPA) and Tenecteplase (TNK) [8], which is an upgrade of the previous two generations of thrombolytic drugs, among which TNK is a type of DNA modification of t-PA. It has a half-life of 20-24 minutes, a 14-fold increase in fibrin specificity and an 80-fold increase in anti-plasminogen activator inhibitor-1 (PAI-1) capacity. These characteristics provide enhanced thrombolytic capacity, with excellent safety [9].

Several previous clinical research results have preliminarily confirmed the effectiveness and safety of TNK for AIS within 4.5 hours of onset, and it is not inferior to t-PA[10].

Studies have reached different conclusions, and there is a large variation in the designs, as well as a wide range of evaluation indicators. An evaluation indicator that demonstrates the effectiveness of a document or the enhancement of an evaluation indicator illustrates the role of TNK in acute ischemic injury. There is no convincing evidence that this approach makes a significant difference in stroke patients' care, and high-quality research needs to be conducted before recommending it. Therefore, the importance of further relevant studies and more authoritative scientific studies are essential for demonstrating TNK's value in AIS management. In this study, the results of several independent similar studies were systematically, quantitatively, and comprehensively analyzed through meta-analysis to evaluate the effects of TNK on revascularization and clinical prognosis of AIS patients and to provide further guidance for its clinical application[11].

Research contents and methods

The sources and Retrieval methods of documents

The following databases were searched: the PubMed database, EMBASE, ScienceDirect, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), the China VIP Database, the Wanfang Database, and the China Biomedical Literature Database (CBM).

The relevant Chinese and foreign periodicals, conference papers, degree papers, news, manual search contents were supplied by the method of literature tracing. The data of case-control trials in patients with AIS treated with TNK and alteplase were harvested. Literature search was performed with the key words, such as AIS; vascular recanalization; clinical prognosis; safety evaluation; Tenecteplase from January 2010 to now.

Literature inclusion and exclusion criteria

Literature inclusion criteria

(1) Type of study: all the case-control trials when treating patients with AIS with TNK and alteplase. (2) Subjects: patients with AIS within 6 hours of onset with arterial occlusion confirmed by CT angiography of the head or neurological deficits (NIHSS score ≥ 1) assessed by the National Institutes of Health Stroke Scale (NIHSS). In addition, the patient lived independently before the stroke and agreed to intravenous thrombolysis. The diagnostic criteria of AIS refer to the related literature [14]. (3) Intervention: alteplase was used for the control group, whereas TNK was used for the study group; (4) More than one of the following outcome indexes was reported: 1) early neurological function improvement rate; 2) reperfusion rate after 24 hours of thrombolysis; 3) mRS score 90 days; 4) symptomatic intracranial hemorrhage rate; 5) bleeding incidence; 6) mortality.

Literature exclusion standard

(1) Neither a case-control nor a cohort study was conducted. (2) It was impossible to utilize the data due to an incomplete data report. (3) From the most recent research, repeated studies were taken. (4) It was not possible to evaluate the study's curative effect. (5) Review of related literature. (6) Clinical cases.

Quality evaluation and data extraction

1) bias risk assessment contained in this research: our assessment of the effectiveness of the study was conducted using Cochrane System Review Manual 5.3's bias risk assessment tool.

2) Literature screening and data extraction: In addition to screening literature and gathering data independently, two researchers assessed quality of results and crossed-checked the findings. There should be discussions and a resolution of disagreements, or a third researcher should be asked to weigh in on the judgment as well. Managing and extracting research data was done. Incomplete data in the literature should be contacted by the writer. As a result of data extraction, the following information was collected: (1) basic information: author, publication date, cases; (2) intervention: scheme, course of treatment; (3) outcome indicators: early neurological function improvement rate, 24-hour reperfusion rate after thrombolysis, 90-day mRS score, symptomatic intracranial hemorrhage rate, hemorrhage incidence, mortality and other indicators.

Statistical processing

It was the RevMan5.4 software that was provided by the Cochrane Collaboration Network for Meta-Analysis. The early neurological function improvement rate, reperfusion rate after 24 hours thrombolysis, the proportion of cases with 90dmRS score ≤ 1 after treatment, symptomatic intracranial hemorrhage rate, hemorrhage incidence and mortality rate were input into RevMan5.4 for analysis. Relative risk (RR) was adopted as the effect index, and 95% confidence interval (CI) was calculated. Firstly, the $\chi 2$ test was detected heterogeneity. If $P > 0.05$ and $I^2 < 50\%$, we considered the study to be homogeneous, allowing us to collect the revised influence model for meta-analysis. If $P < 0.05$ and $I^2 \geq 50\%$, the combination effect was needed to judge the homogeneity, then the random-effect model was selected. Meta-analysis would not be conducted if $P < 0.05$ and the heterogeneity

sources were impossible to determine. Instead, descriptive analysis would be carried out.

Results and analysis

Literature retrieval results and basic inclusion conditions

A computerized database search found 983 articles, and 611 articles were obtained after excluding duplicates. Based on the titles and abstracts of the literature, 427 articles were identified. 104 articles were obtained, excluding irrelevant studies. The next step was to review the full text and exclude 99 articles with incomplete data and no primary outcome measures. A total of 1569 samples from the five clinically controlled studies were finally contained for meta-analysis. An overview of the literature screening graph can be found in Figure 1, and a list of the basic characteristics of the literature can be found in Table 1.

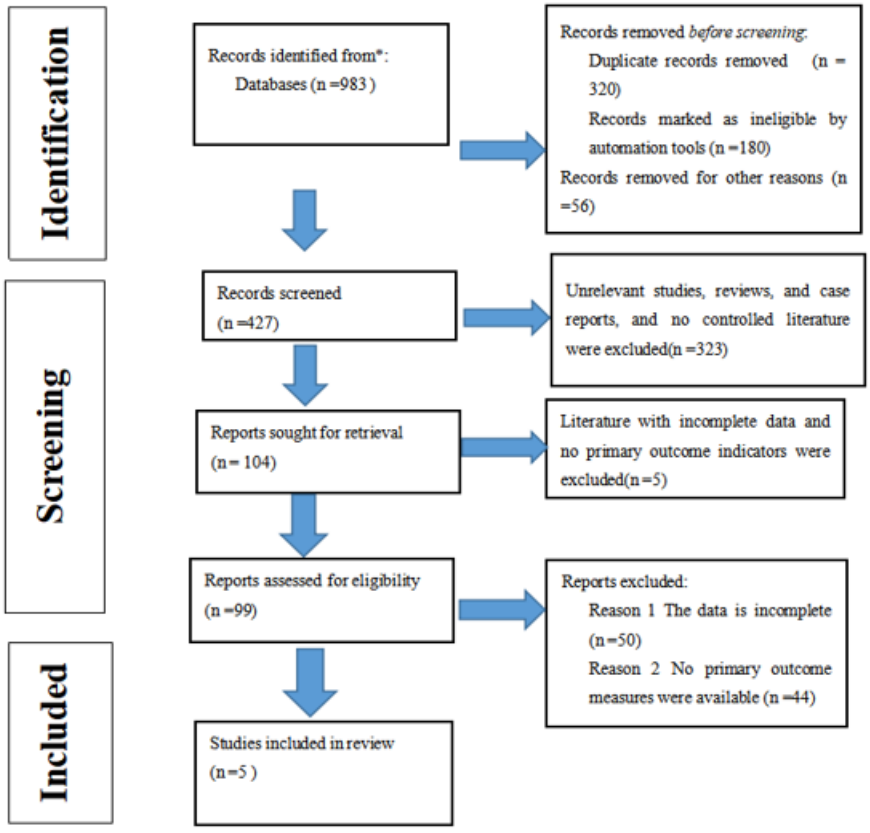

Figure 1: Illustration of literature screening

Table 1 **Basic characteristics of literature**

Include the literature	Year of publication	Sample size		Intervention measures		Research start time	Treatment time window	Outcome index
		Control group	Research group	Control group	Research group			
Parsons[12]	2012	25	50	Alteplase	Tenecteplase	2008-2011	＜6h	①②③④⑤⑥
Huang [13]	2015	49	47	Alteplase	Tenecteplase	2012-2013	＜4.5h	①②③④⑤⑥
Logalllo [14]	2017	551	549	Alteplase	Tenecteplase	2012-2016	＜4.5h	①③④⑤⑥
Qiaoyulin [15]	2018	49	47	Alteplase	Tenecteplase	2015-2016	＜4.5h	①③④⑤⑥
Campbell [16]	2018	101	101	Alteplase	Tenecteplase	2015-2017	＜4.5h	②③④⑤⑥

Note: ①Early neurological function improvement rate; ②Reperfusion rate after 24 hours of thrombolysis; ③90-day modified Rankin scale (mRS) score; ④Symptomatic intracranial hemorrhage rate; ⑤Incidence of bleeding; ⑥Death rate.

Quality assessment of literature-based methodologies

In this meta-analysis study, the six case-control literatures contained. All literature described detailed interventions and study duration. Only one article described the randomization method; no literature described in detail the number or reasons for blinding or the loss to follow-up. In accordance with the analysis of Jadad scale, the score of high-quality literature was ≥ 3

and that of low-quality literature was ≤ 2. As shown in Figs. 2 and 3, the risk bias analysis was conducted.

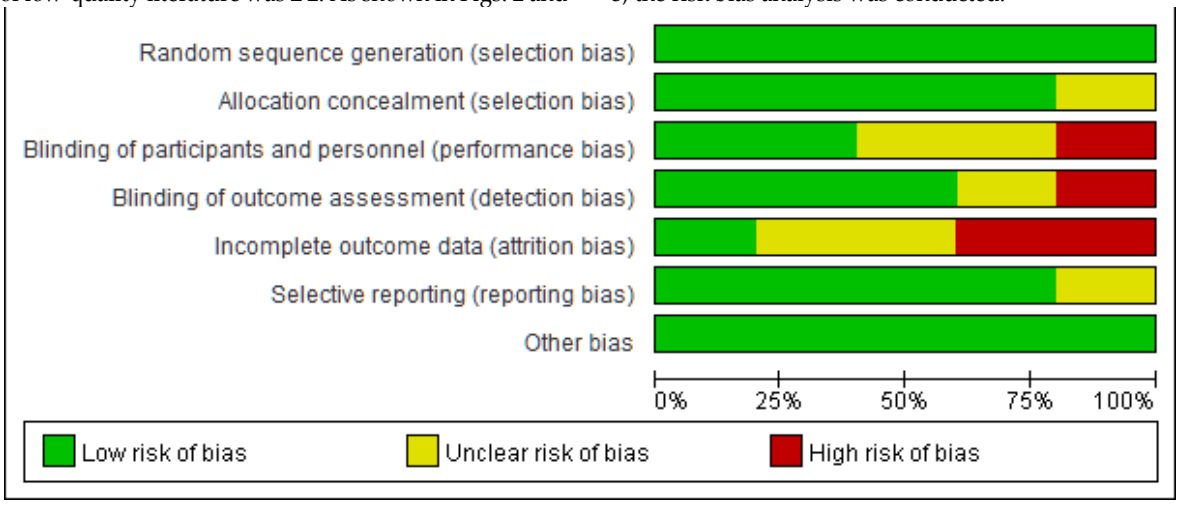

Figure 2: risk bias chart

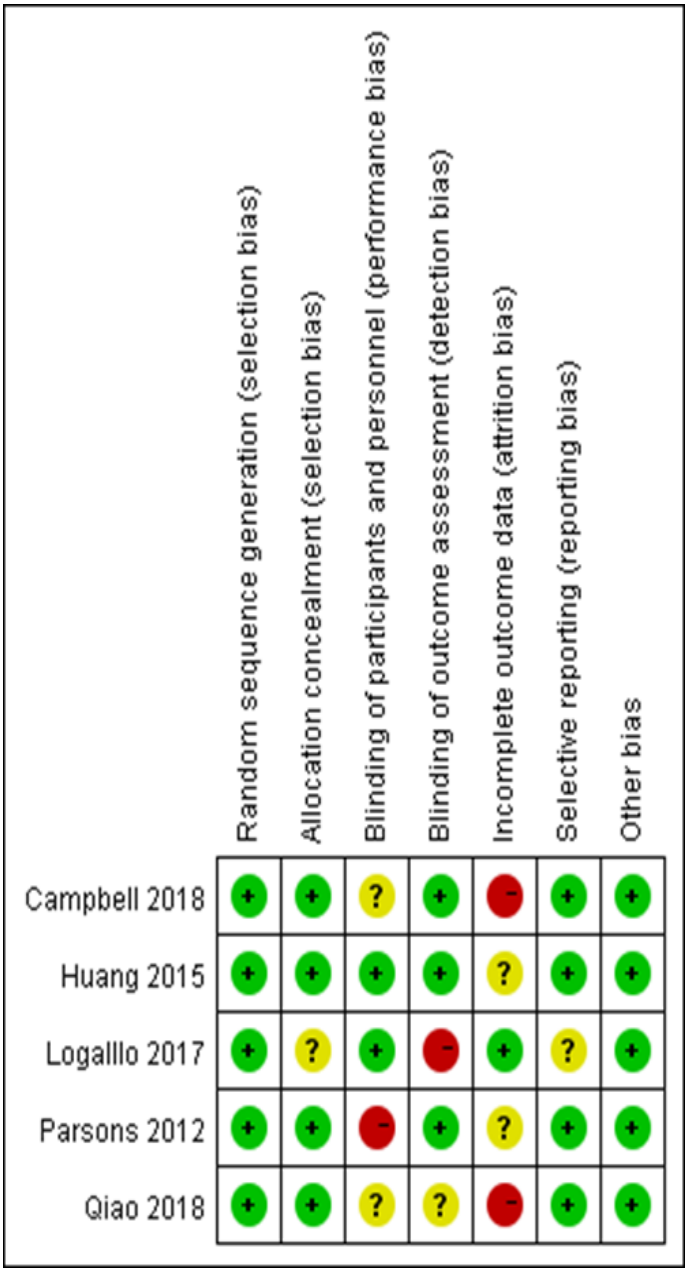

Figure 3: summary chart of risk bias

Meta-analysis results

Early neurological function improvement rate

This study contained 5 clinical control studies with 1569 samples. The early neurological function improvement rates of the two groups after treatment were analyzed. Using the heterogeneity test, we found that: Chi^2=6.74, df=4, P=0.15, I^2=41%. The results showed that data contained in the research were evidently heterogeneous. In the study group, the early improvement rate of neurological function was remarkably higher based on the fixed effect model analysis (Fig. 4, P<0.05).

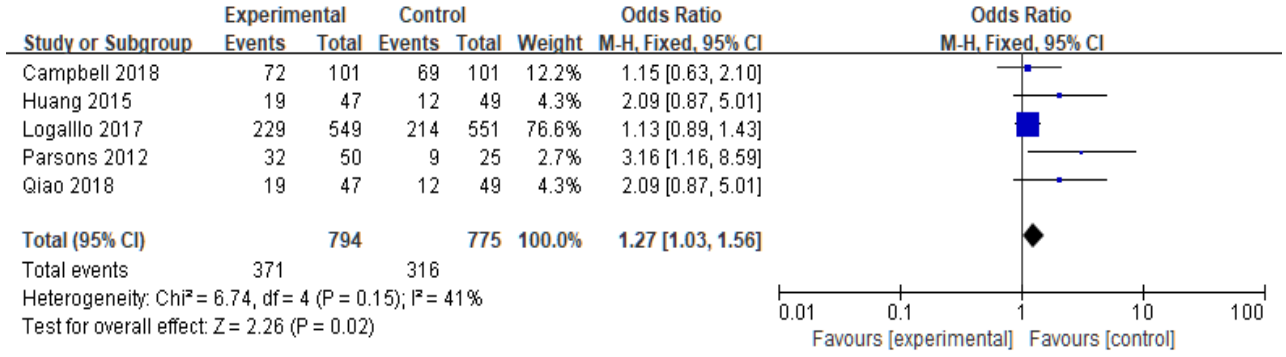

Figure 4: Forest analysis map of comparison of early neurological function improvement rates

Reperfusion rate after 24 hours of thrombolysis

The reperfusion rates after 24 hours of thrombolysis were analyzed by meta. Using the heterogeneity test, we found that: Chi^2=1.26, df=2, P=0.53, I^2=0%, showing that data contained in the research was evidently heterogeneous. After 24 hours of thrombolysis, the fixed effect model analysis indicated that the study group's reperfusion rate was noticeably higher (P<0.05, Fig.5).

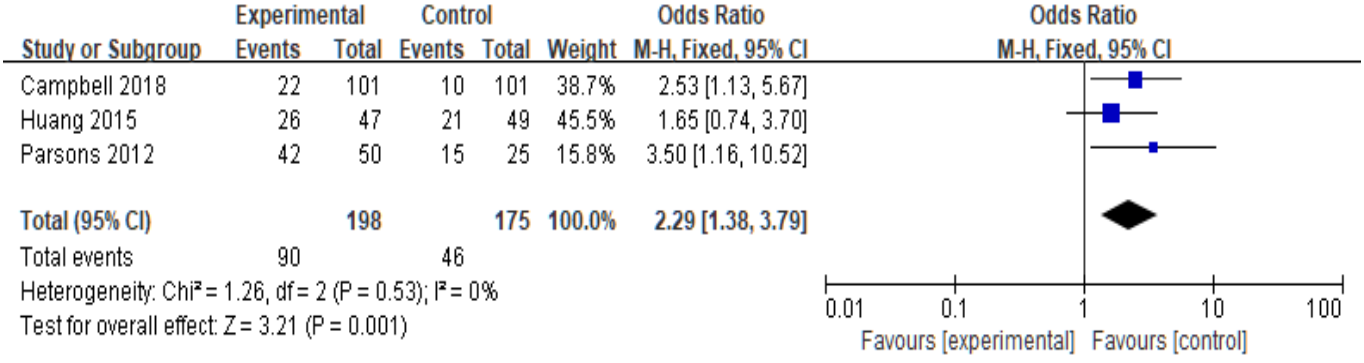

Figure 5: Forest analysis map of the reperfusion rate of the two groups after 24 hours of thrombolysis

The modified Rankin scale (mRS) score ≤ 1 90 days after thrombolysis

To determine the proportion of cases with a mRS score ≤ 1 point 90 days after thrombolysis, an analysis of meta-analyses was conducted. Using the heterogeneity test, we found that: Chi^2=2.04, df=4, P=0.73, I^2=0%, showing that data contained in the research were evidently heterogeneous. Using the fixed effect model analysis (Fig. 6), there exhibits no statistically noticeable difference in the proportion of cases with 90dmRS score ≤ 1 after treatment (P>0.05). It suggested that there exhibited no statistically noticeable difference between TNK and Alteplase about improving the prognosis of patients.

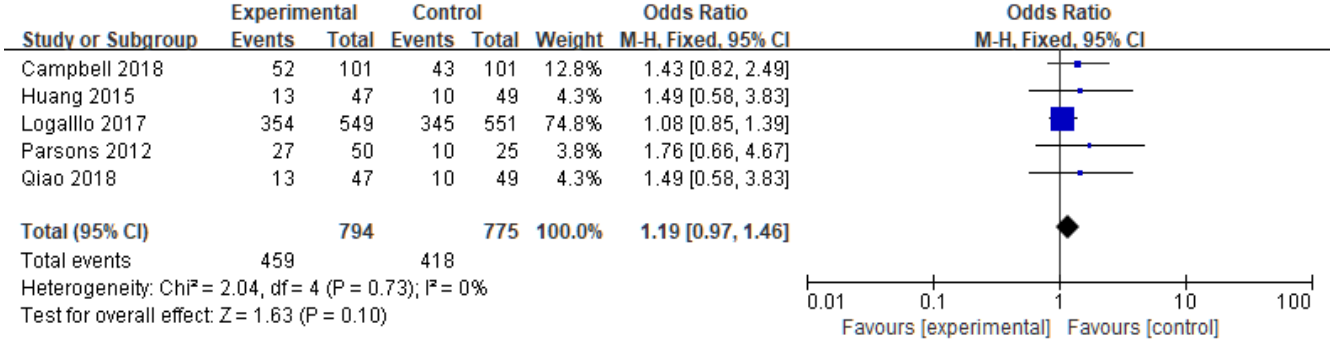

Figure 6: Forest analysis map with 90dmRS score ≤ 1

Symptomatic intracranial hemorrhage rate

The symptomatic intracranial hemorrhage rates were analyzed by meta. Using the heterogeneity test, we found that: Chi^2=1.87, df=4, P=0.76, I^2=0%. The results indicated that data contained in the research were evidently heterogeneous, which was analyzed by fixed effect model (Fig. 7).

After treatment, there exhibited no noticeable difference in the rate of symptomatic intracranial hemorrhage (P>0.05).

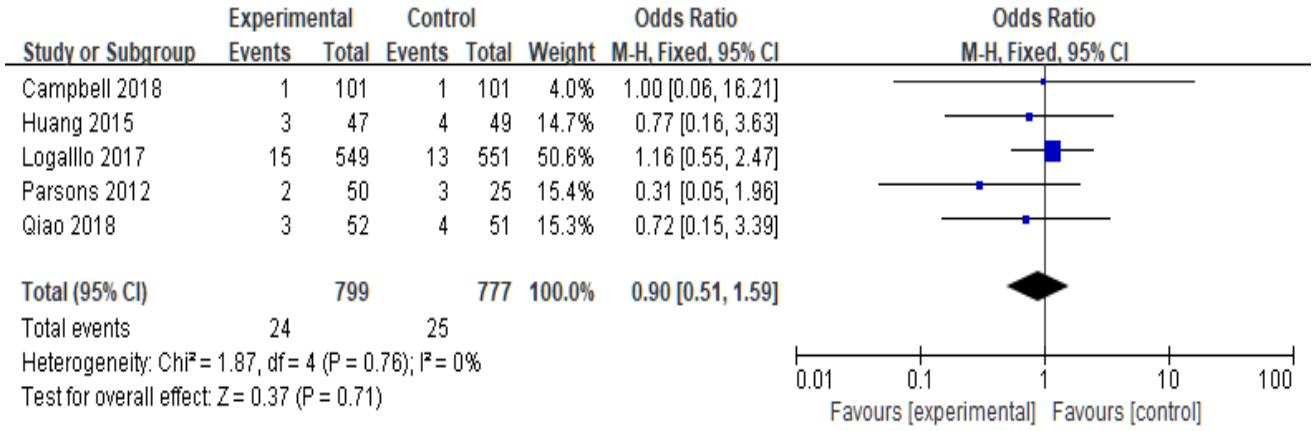

Figure 7: Forest analysis map of the comparison of symptomatic intracranial hemorrhage rates

Incidence of bleeding

The incidence of bleeding was the subject of a meta-analysis. From the results of the heterogeneity test, it could be seen that Chi^2=30.54, df=4, P<0.0001, I^2=87%. It indicated that data contained in the research were evidently heterogeneous. No statistical difference was found in the incidence of bleeding after treatment based on the random effect model (P>0.05, Fig.8).

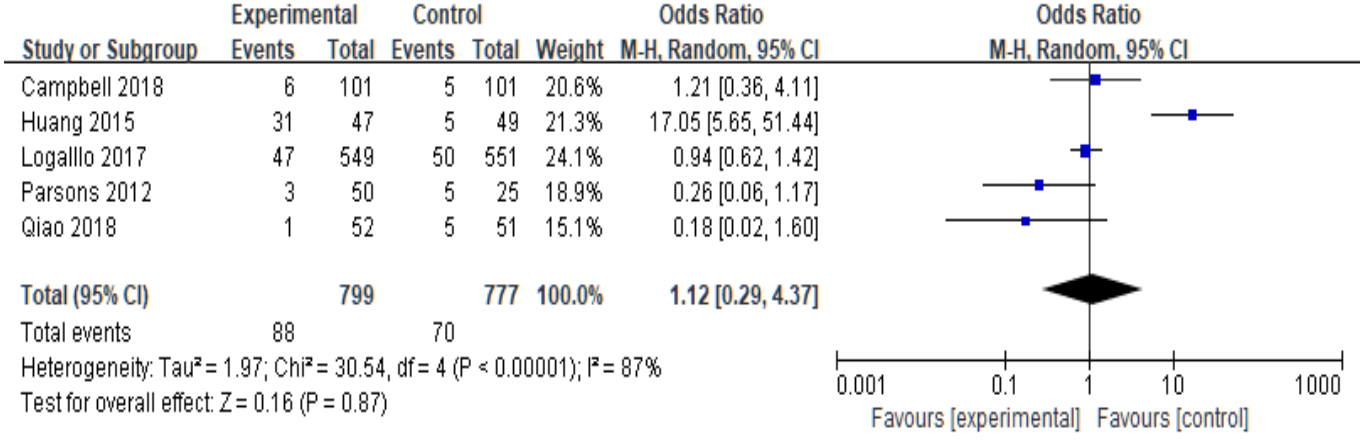

Figure 8: Forest analysis map of the comparison of bleeding incidence

Death rate

In this study, 1569 samples were used in five clinical controlled studies contained. Mortality rates were subjected to meta-analysis. Using the heterogeneity test, we found that: Chi^2=3.94, df=4, P=0.41, I^2=0%, showing that data contained in the research were evidently heterogeneous.

The fixed effect model analysis suggested no statistical difference was found in the mortality rate after treatment (P>0.05, Fig.9).

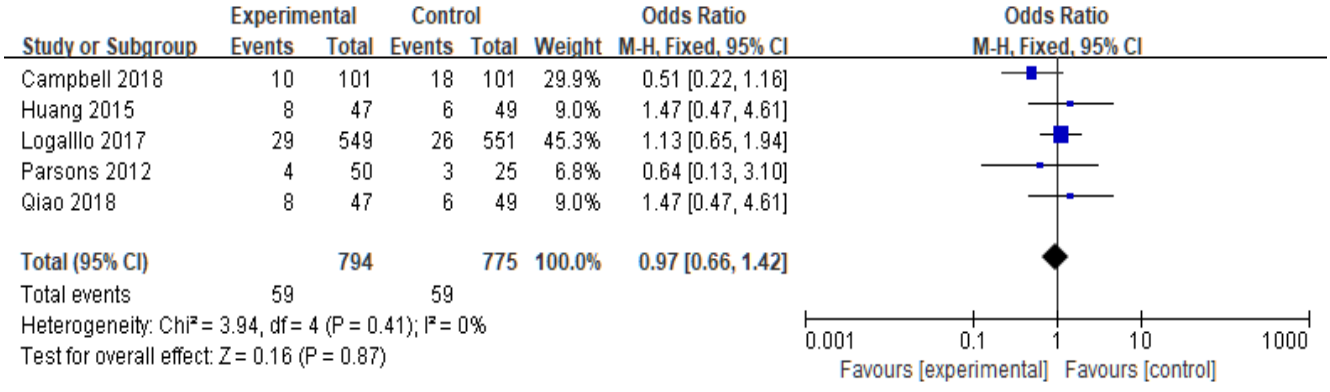

Figure 9: Forest analysis map of comparison of mortality

Publication bias analysis

The funnel chart was drawn based on the early neurological function improvement rate after treatment, the reperfusion rate after 24 hours of thrombolysis, the proportion of cases with 90dmRS score ≤ 1, the symptomatic intracranial hemorrhage rate, the hemorrhage incidence rate and the mortality rate. The publication bias analysis was carried out (Fig.10-15). According to the funnel charts, publishing bias was detected due to the diversity of studies and the limited number of cases included in the literature, with only a few asymmetries.

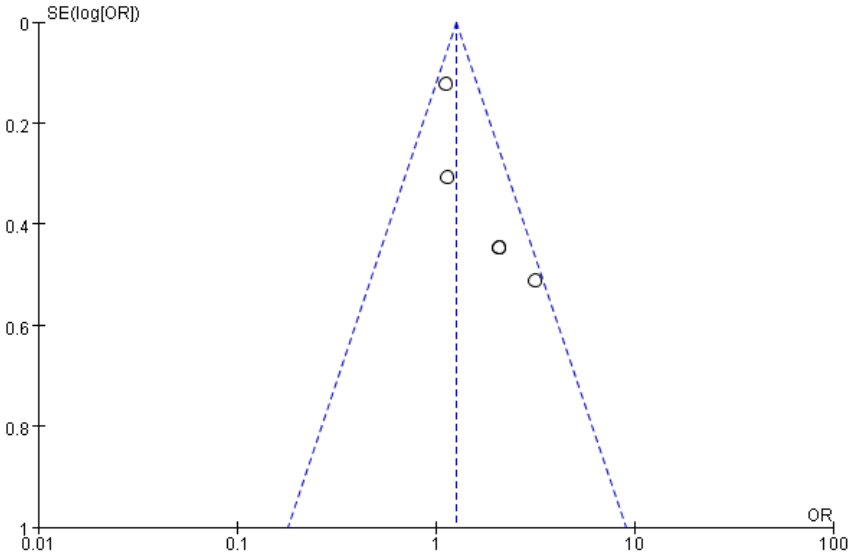

Figure 10: Funnel chart based on early neurological function improvement rate

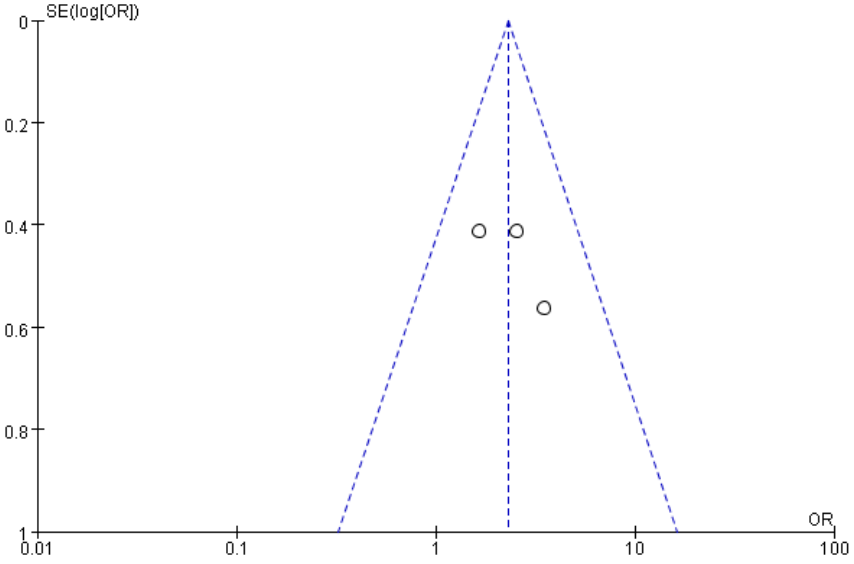

Figure 11: Funnel chart based on reperfusion rate after thrombolysis for 24 hours

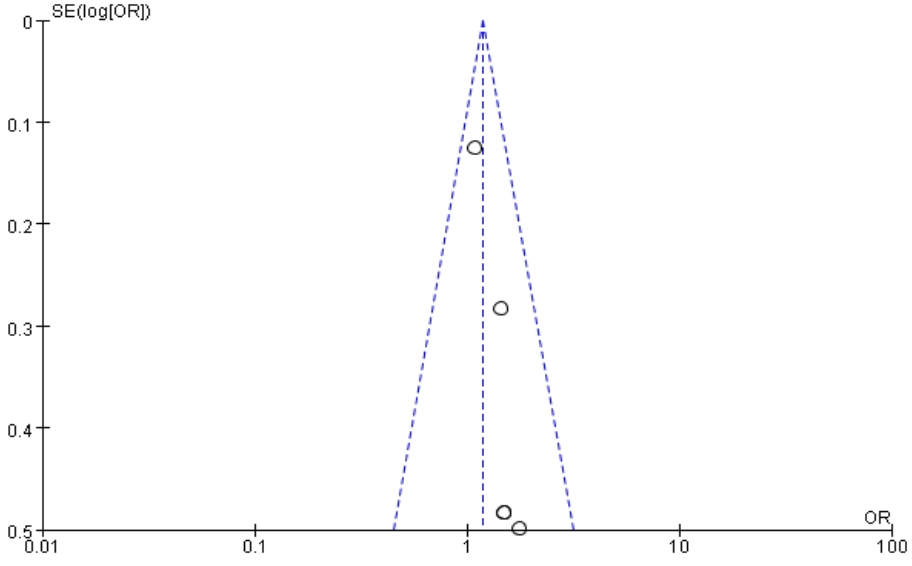

Figure 12: Funnel chart based on 90dmRS score ≤ 1

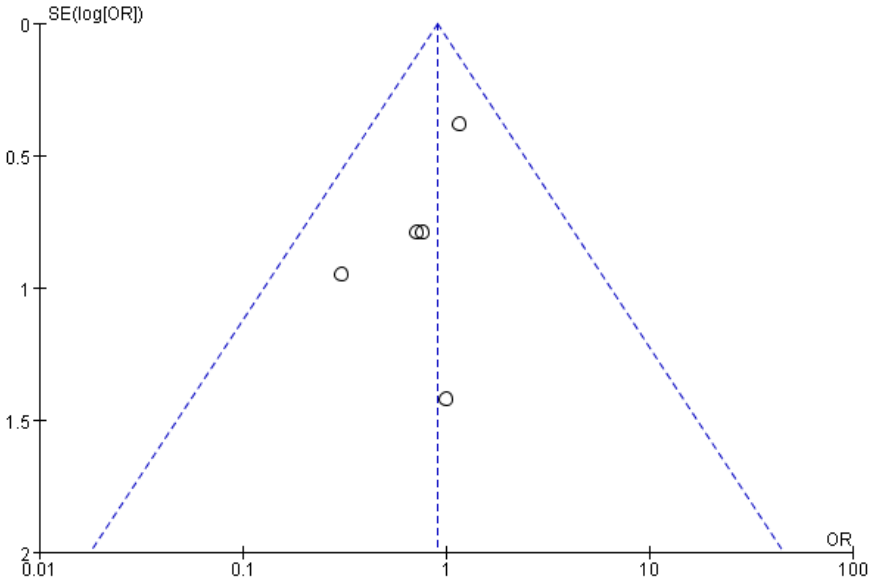

Figure 13: Funnel chart based on symptomatic intracranial hemorrhage rate

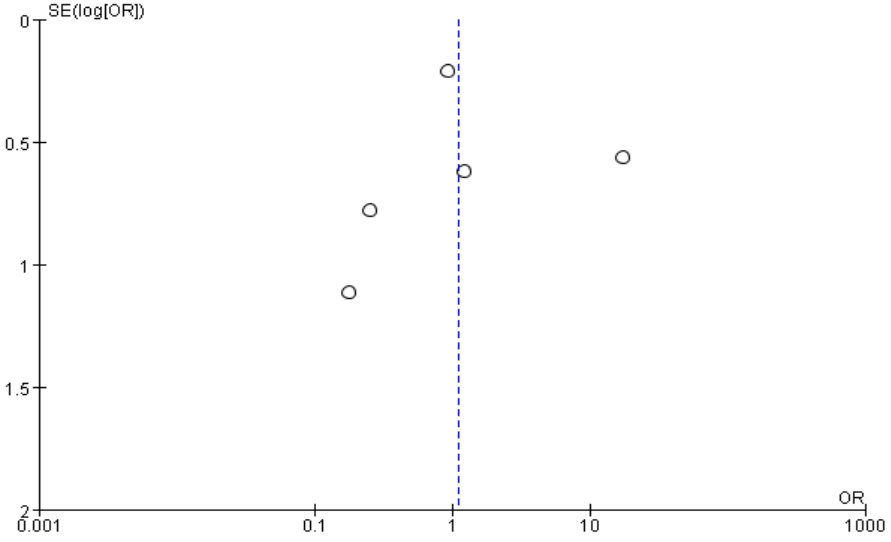

Figure 14: Funnel chart based on the incidence of bleeding

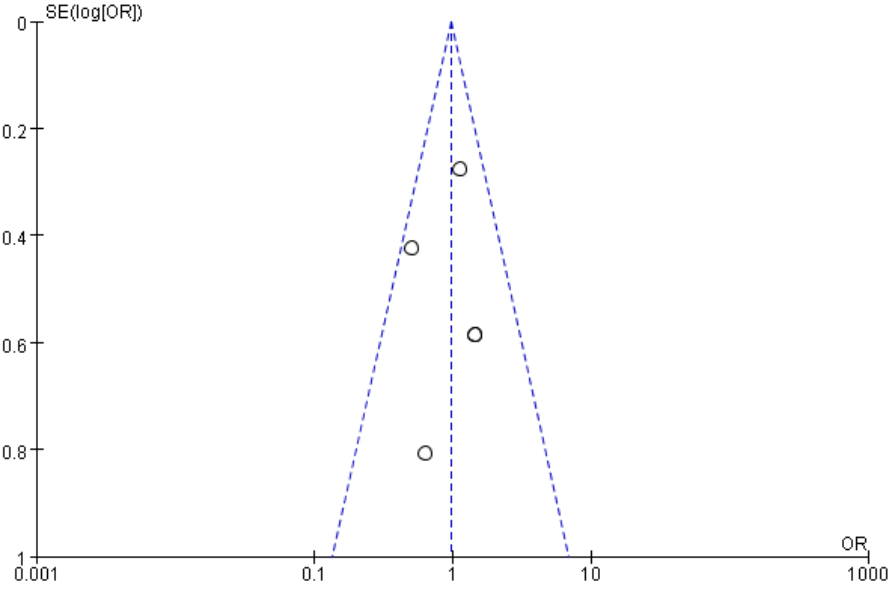

Figure 15: Funnel chart based on mortality

Analysis and discussion

Stroke is a common clinical cerebrovascular disease, and ischemic stroke is the main type of new stroke [20] accounting for 70% and 80% of all strokes. In the early stages of the disease, timely restoration of blood supply to the lesion can effectively reduce neuronal damage in the lesion area. If the patient is not treated promptly, the lesion can cause irreversible neuronal damage, which may eventually lead to disability or even death [17, 18]. In patients with ischemic stroke, early effective recanalization of cerebrovascular therapy is of great importance for both patients and clinics. Thrombolysis is the main method of recanalization and occlusion of blood vessels in the early clinical stage. After ischemic stroke symptoms first appear in 4.5 hours, intravenous thrombolysis has proven to be effective in treating it. Currently, alteplase is the only drug approved in most countries for treating AIS [12, 19]. Using cDNA from endogenous tissue plasminogen activator, human melanoma cells synthesize alteplase, a recombinant tissue plasminogen activator. There are five domains of this 527-amino acid glycoprotein including fibronectin finger, human epidermal growth factor, kringle1, kringle2 and serine protease. By binding to fibrin in thrombi, alteplase activates fibrin-bound plasminogen into active plasmin, which initiates fibrinolysis locally. As a result of its fast elimination by the liver, alteplase has a fast half-life in the plasma that is less than 5 minutes.

Moreover, the PADI-1 inhibitor can irreversibly inactivate alteplase. Notably, alteplase noticeably increases the rate of dissolution of emboli zed vessels. However, it has a limited effect on fibrinolysis, with a revascularization rate of less than 50% and a risk of conversion to intracranial hemorrhage [16, 20]. Because the half-life of alteplase is short, and its therapeutic effect can be reduced with time, so it is bioengineered to produce TNK. The presence of a three-amino acid substitution in the tissue structure, which binds fibrin with greater specificity, effectively reduces the activity of plasminogen activator inhibitors and therefore has a more potent fibrinolytic effect. A glycosylation site was added at the 103 site of asparagine substituted threonine, and a high mannose side chain was reduced at aspartic acid substituted glutamine 117 site, so the clearance rate of TNK in plasma was slowed down and the half-life was prolonged. Its antithrombotic effect was also prolonged [25-26].

Recent study has shown that the severity of early onset of ischemic stroke patients and the degree of neurological impairment are closely related to the prognosis of patients [21]. There is a development process between early reversible ischemic injury of brain tissue and irreversible infarction. Therefore, effective improvement of cerebral vascular blockage and timely improvement of cerebral blood perfusion during this period will greatly enhance the short-term prognosis of patients. There were 1,569 samples included in five clinical controlled studies with the results of this meta-analysis. The early neurological function improvement rate after treatment, the reperfusion rate after 24 hours of thrombolysis, and the number of cases with a 90dmRS score of ≤1 after thrombolysis were compared. The enhancement rate of early neurological function and reperfusion rate after 24 hours of thrombolysis in the study group were noticeably higher. It is advised that compared with alteplase, the use of TNK can noticeably enhance the early neurological improvement rate of patients and the reperfusion rate after 24 hours of thrombolysis, which can successfully promote the prognosis of patients. The reason for this analysis is that the distribution volume of TNK after entering the human body is basically the same as the plasma volume, and it is metabolized by the liver. It enhances the therapeutic effect in the patient's body, restoring blood perfusion to the ischemic area, effectively reducing the severity of the patient's condition, improving the degree of neurological damage and ultimately improving the patient's prognosis [22, 23]. There was a meta-analysis of human hemorrhage incidence, mortality, and symptomatic intracranial hemorrhage based on safety data. The analysis indicated that no statistical difference was found in the rate of symptomatic intracranial hemorrhage, incidence of hemorrhage and mortality after treatment. This has indicated that TNK does not noticeably increase the risk of adverse events in patients with AIS while improving early neurological function and prognosis. Due to the long half-life of TNK, it mainly targets the fibrin in the thrombus, so it has a strong affinity and action on the fibrin in the thrombus, while it has a strong action on the fibrin in the thrombus. The impact of fibrin in the system is small, so it can effectively reduce the bleeding risk of patients after intravenous thrombolysis and mechanical thrombectomy.

Conclusion

To sum up, TNK intravenous thrombolysis for AIS can effectively remove intravascular thrombus and restore blood perfusion to ischemic brain tissue, thereby achieving limited relief of brain tissue and neurological damage in the focal area and thus improving prognosis. This therapeutic option is therefore worth promoting. Limitations of this study include the following: 1) the inclusion and exclusion criteria were stringent, and the small final literature did not allow for a more detailed subgroup analysis of the heterogeneity of the studies; 2) the inconsistent criteria for the inclusion of treatment and outcome indicators across studies may have affected the reliability of the results. Follow-up studies by scholars are required and more high-quality case-control trials are needed to validate.

Reference

[1] A. Li and Y. Liu, "Reminiscence therapy serves as an optional nursing care strategy in attenuating cognitive impairment, anxiety, and depression in acute ischemic stroke patients," *Irish Journal of Medical Science (1971-),* pp. 1-8, 2021.

[2] G. S. Silva and R. G. Nogueira, "Endovascular treatment of acute ischemic stroke," *Continuum: Lifelong Learning in Neurology,* vol. 26, no. 2, pp. 310-331, 2020.

[3] V. Saini, L. Guada, and D. R. Yavagal, "Global epidemiology of stroke and access to acute ischemic stroke interventions," *Neurology,* vol. 97, no. 20 Supplement 2, pp. S6-S16, 2021.

[4] W. J. Powers *et al.*, "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,* vol. 50, no. 12, pp. e344-e418, 2019.

[5] P. M. Rothwell, A. Algra, Z. Chen, H.-C. Diener, B. Norrving, and Z. Mehta, "Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials," *The lancet,* vol. 388, no. 10042, pp. 365-375, 2016.

[6] M. C. Schroeder *et al.*, "Generating Practice-Based Evidence in the Use of Guideline-Recommended Combination Therapy for Secondary Prevention of Acute Myocardial Infarction," *Pharmacy,* vol. 10, no. 6, p. 147, 2022.

[7] A. Sharobeam, B. Jones, D. Walton-Sonda, and C. J. Lueck,

"Factors delaying intravenous thrombolytic therapy in acute ischaemic stroke: a systematic review of the literature," *Journal of neurology,* vol. 268, pp. 2723-2734, 2021.

[8] S. J. Warach, A. N. Dula, and T. J. Milling Jr, "Tenecteplase thrombolysis for acute ischemic stroke," *Stroke,* vol. 51, no. 11, pp. 3440-3451, 2020.

[9] E. Y. Ucar, "Update on thrombolytic therapy in acute pulmonary thromboembolism," *The Eurasian journal of medicine,* vol. 51, no. 2, p. 186, 2019.

[10] H. Wei, B. Fu, C. Yang, and M. Huang, "The efficacy and safety of intravenous thrombolysis with tenecteplase versus alteplase for acute ischemic stroke: a systematic review and meta-analysis," *Neurological Sciences,* pp. 1-11, 2023.

[11] A. M. Burgos and J. L. Saver, "Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials," *Stroke,* vol. 50, no. 8, pp. 2156-2162, 2019.

[12] M. Parsons *et al.*, "A randomized trial of tenecteplase versus alteplase for acute ischemic stroke," *New England Journal of Medicine,* vol. 366, no. 12, pp. 1099-1107, 2012.

[13] X. Huang *et al.*, "Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study," *The Lancet Neurology,* vol. 14, no. 4, pp. 368-376, 2015.

[14] N. Logallo *et al.*, "Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial," *The Lancet Neurology,* vol. 16, no. 10, pp. 781-788, 2017.

[15] Qiao Yulin, Xiang Wenqiang, Wang Lei, and Wang Zhaohui, "Thrombolysis study of tenaiplase and Alteplase in patients with AIS," *Journal of brain and Neurological Diseases,* vol. 26, no. 7, pp. 444-450, 2018.

[16] B. C. Campbell *et al.*, "Tenecteplase versus alteplase before thrombectomy for ischemic stroke," *New England Journal of Medicine,* vol. 378, no. 17, pp. 1573-1582, 2018.

[17] E. Eskioglou, M. Huchmandzadeh Millotte, M. Amiguet, and P. Michel, "National Institutes of Health Stroke Scale zero strokes: immeasurable but not innocent," *Stroke,* vol. 49, no. 12, pp. 3057-3059, 2018.

[18] C.-H. Chen *et al.*, "Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure," *Hypertension,* vol. 27, no. 2, pp. 168-175, 1996.

[19] K. Alhadid, L. Oliveira, and M. R. Etherton, "Intravenous Thrombolytics in the Treatment of Acute Ischemic Stroke," *Current Treatment Options in Cardiovascular Medicine,* vol. 25, no. 1, pp. 15-28, 2023.

[20] J. P. Ho, "Acute ischemic stroke: emergency department management after the 3-hour window," *Emergency Medicine Practice,* vol. 23, no. Suppl 6, pp. 1-33, 2021.

[21] D. Kuriakose and Z. Xiao, "Pathophysiology and treatment of stroke: present status and future perspectives," *International journal of molecular sciences,* vol. 21, no. 20, p. 7609, 2020.

[22] P. J. Hand, J. Kwan, R. I. Lindley, M. S. Dennis, and J. M. Wardlaw, "Distinguishing between stroke and mimic at the bedside: the brain attack study," *Stroke,* vol. 37, no. 3, pp. 769-775, 2006.

[23] S. M. Ma Lihua, Yuan Pingyao, Wang Manxia, "Meta analysis of intravenous thrombolysis with tinipase when treating AIS. ," *Chinese Journal of Cerebrovascular Diseases,* vol. 15, no. 10, pp. 534-542, 2018.