Therapeutic effect of tenecteplase on treatment of cerebral arterial thrombosis: a meta-analysis

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Abstract. – OBJECTIVE: To evaluate the clinical efficacy between tenecteplase (TNK) and alteplase (rt-PA). Furthermore, suitable dosage of TNK in cerebral arterial thrombosis treatment was explored.

MATERIALS AND METHODS: The studies met with the predefined selection criteria were selected for the present study. The quality of each study was evaluated by Cochrane quality evaluation. The outcome indexes including early major neurological improvement (MNI), excellent recovery, good recovery, recanalization at 24 hours-complete or partial, symptomatic intracranial hemorrhage, any parenchymal hematoma and deaths were analyzed by using RevMan and Stata statistical software, under a random-effects model or a fixed-effects model. The safety and efficacy between TNK and rt-PA were investigated. Furthermore, the clinical efficacy outcomes between different dosages of TNK were evaluated. Sensitivity analysis was performed to evaluate the reliability.

RESULTS: A total of 6 studies were enrolled for the present study. Compared with the 0.1 mg/kg TNK group, 0.25 mg/kg TNK group had a significantly better MNI (RR = 0.66, 95% CI: [0.49, 0.88], p = 0.005) and excellent recovery (RR = 0.71, 95% CI: [0.53, 0.95], p = 0.02). TNK group achieved an increased MNI (RR = 1.59, 95% CI: [1.08, 2.34], p = 0.02) and a reduced parenchymal hematoma (RR = 0.26, 95% CI: [0.10, 0.71], p = 0.009) than rt-PA group.

CONCLUSIONS: Compared with rt-PA, TNK could better improve the major neurological function. TNK 0.25 mg/kg had a better clinical treatment effect than TNK 0.1 mg/kg.

Key Words:
Tenecteplase, Alteplase, Clinical efficacy, Dosage, Meta-analysis.

Introduction

Cerebral arterial thrombosis (ischemic stroke) is characterized by the sudden loss of blood circulation to some part of the brain, which further leads to the loss of neurologic function[1,2]. Ischemic stroke remains a leading cause of morbidity and mortality worldwide[3]. Systemic thrombolysis with recombinant tissue plasminogen activator is the first therapy that has been proven to be effective in ischemic stroke[4,5]. For a long time, alteplase (rt-PA, recombinant tissue plasminogen activator) has been widely used for the treatment of ischemic stroke[6]. Additionally, thrombolysis with intravenous rt-PA has been proven as an effective treatment for patients with ischemic stroke in various studies[7,8]. Although rt-PA is considered to be safe and effective, it also has several side effects[8]. The increasing use of rt-PA in ischemic stroke has resulted in some complications like lingual angioedema[10]. Thus, novel thrombolytic therapy is needed.

Tenecteplase (TNK), the genetically engineered variant of rt-PA, is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line[11]. A previous study[12] shows that TNK and rt-PA are equivalent for 30-day mortality in clinical therapy. The preclinical study[13] suggests that TNK has a better pharmacological profile than rt-PA. Parsons et al[11] indicate that TNK is associated with significantly better reperfusion and clinical outcomes than rt-PA. However, since the small sample size and lack of large scale of clinical outcomes comparison in previous studies, the effect and safety between TNK and rt-PA are still controversial. Although TNK and rt-PA have the same mechanism of action, the properties of TNK (like rapid single-bolus administration) make it a seemingly more advantageous thrombolytic[14]. Several clinical studies[11,14] have proved the safety, feasibility, and efficacy of TNK in ischemic stroke. However, there are some controversies on the different doses of TNK in clinical treatment. Parsons et al[14] believe

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that 0.1 mg/kg TNK has significant biologic efficacy in acute ischemic stroke. Haley et al[16] indicate that TNK doses of 0.1 to 0.4 mg/kg are safe in ischemic stroke. In the treatment of acute lower-limb ischemia, the TNK 0.25 mg/h and TNK 0.125 mg/h have the similar success and complication rates. Therefore, the effect and safety comparison between TNK and rt-PA based on clinical outcomes are needed to guide the further application of TNK in ischemic stroke treatment.

In the present study, a meta-analysis was performed based on the collection of all TNK-related study on the treatment of ischemic stroke. A comprehensive assessment of clinical treatment effect of TNK would be performed via evaluation of the indexes like neurological function scores, the mortality, the occurrence of intracranial hemorrhage rate and adverse reaction. Furthermore, the optimal dose of TNK was also investigated.

Materials and Methods

Data Sources and Search Strategy

A comprehensive search in bibliographic databases (PubMed, Embase, Cochrane Library) were conducted to identify relevant studies. The searching strategy was "tenecteplase" AND "cerebral infarction" OR "ischemia stroke". The studies were restricted to English publications. The retrieval time for the present study was up to September 2015. Manual searches were used for screening and selection of other eligible studies.

Study Selection

The inclusion criteria for the present meta-analysis were: (1) clinical trial studies of ischemic stroke treated with TNK; (2) at least one of the following outcomes was included: mortality rate, adverse reaction, occurrence of brain ischemia and the neurological functional scores; (3) studies were published in English. Studies with incomplete or unavailable data, or the literature reviews, letters, comments and repeat publications were excluded.

Data Extraction and Quality Assessment

Two investigators independently extracted the information from all selected studies. A consensus on all items was reached via discussion with a third investigator and reexamination. The following data informations were extracted from each eligible study: name of first author, year of publication, study type, country (or area), study time, case characteristics, standard of functional score, the number of cases and age of subjects, and outcomes of the present meta-analysis.

Methodological quality assessment of the included studies were based on the guidelines of Cochrane[17], an official document that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions. The standard criteria of Cochrane were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Outcome Indexes for the Present Meta-Analysis

Efficacy clinical outcomes, imaging efficacy outcomes, and safety outcomes were involved in the evaluation of the present meta-analysis. Efficacy clinical outcomes included: (1) early major neurological improvement (MNI, improvement in acute-24 h National Institutes of Health Stroke Scale score of ≥ 8 points); (2) excellent recovery (modified Rankin Scale score of 0-1 at day 90), and (3) good recovery (modified Rankin Scale score of 0-2 at day 90). Imaging efficacy outcomes referred to recanalization at 24 hours-complete or partial [complete recanalization was defined as normal flow at 24 hours; partial recanalization was defined as any improvement in flow (excepting return to normal)]. Safety outcomes included: (1) symptomatic intracranial hemorrhage (large parenchymal hematoma combined with a significant clinical deterioration of ≥ 4 points on the National Institutes of Health Stroke Scale at 24 hours); (2) any parenchymal hematoma (large or small parenchymal hematoma), and (3) deaths (mortality at 30 days).

Statistical Analysis

Stata 12.0 (STATA, College Station, TX, USA) and RevMan 5.3 statistical software (Cochrane Collaboration, http://ims.cochrane.org/revman) were used for the statistical analysis. Since all the outcomes of this meta-analysis were dichotomous data, the combined effect size was evaluated by the relative ratio (RR) and 95% confidence interval (CI). The tests for heterogeneity were performed using Cochran's Q statistic and I^2 test[18]. The random effects model was applied if significant heterogeneity was found ($p < 0.05$ or $I^2 > 50\%$). Otherwise, the fixed effects model was used if there was no statistical heterogeneity ($p \geq 0.05$ or $I^2 \leq 50\%$). In the comparison of TNK with rt-PA, the sub-group analysis stratified by different doses of TNK was performed. Furthermore, sensitivity analysis via eliminating a study at one time was performed to evaluate the reliability of the present meta-analysis based on Stata 12.0 software.

Results

Included Studies with Their Characteristics

Through database searches and manual searches, the present meta-analysis initially retrieved 192 studies (Figure 1), from which the duplications (n = 56); studies unrelated to the research topics (n = 43); other meta-analysis or reviews (n = 60) were removed. The remaining 33 studies

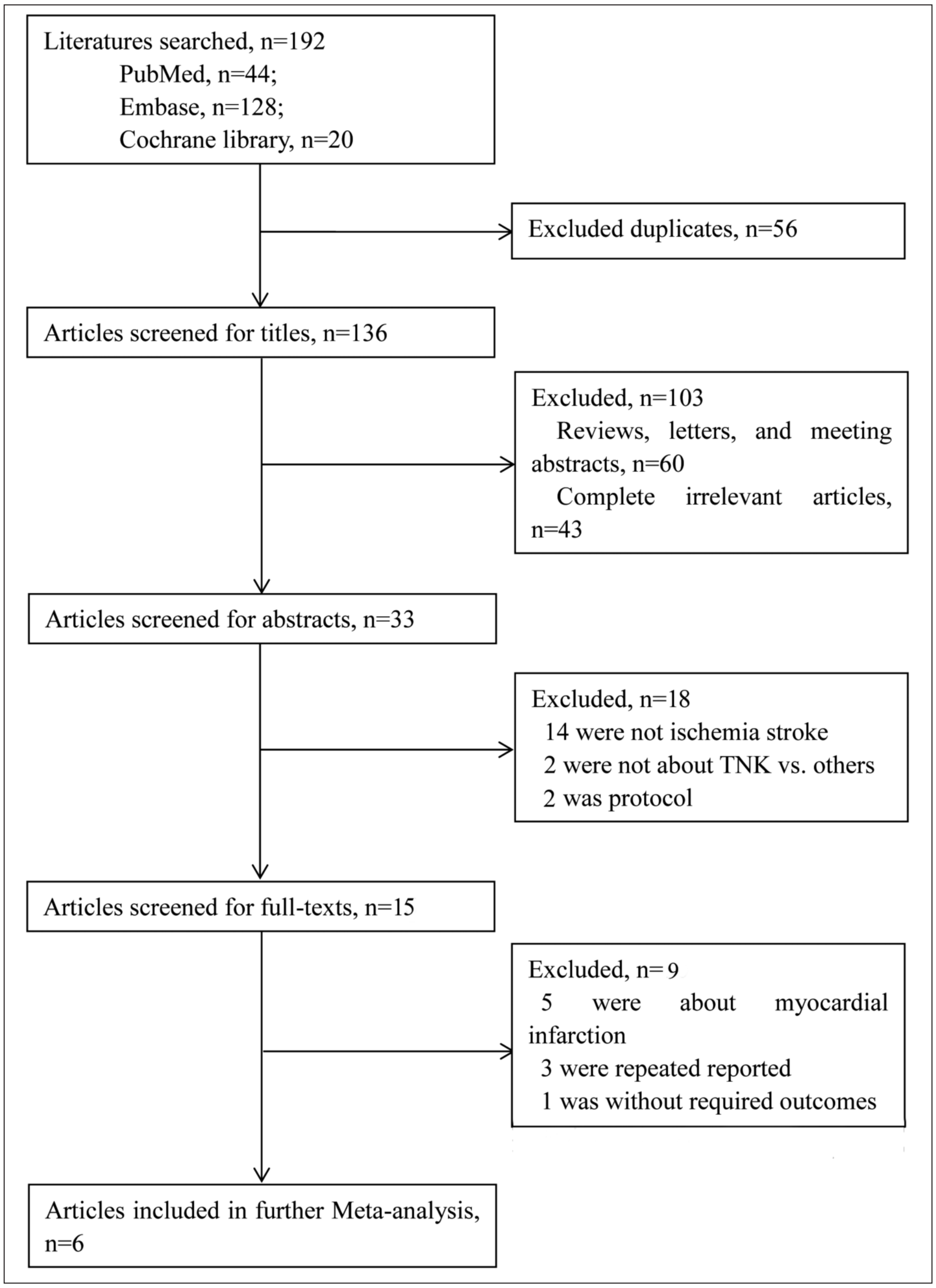

Figure 1. Flow chart of study selection procedure.

were reviewed, and 17 additional studies were excluded via abstract reading due to that they were studies not involving ischemia stroke (n = 14), or not mentioning the comparison of TNK vs. others (n = 2), and that two were just protocols. Subsequently, through full-text reading, the irrelevant studies including studies about myocardial infarction (n = 5), or without the required outcomes (n = 1), or are repeated reported (n = 3), were further excluded. Finally, a total of 6 eligible studies with sufficient data were enrolled for the present meta-analysis[15,19-23].

There were 3 studies concerned the different doses of TNK (0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg), and 5 studies involved in the comparison of TNK and rt-PA. All patients involved in the enrolled studies were diagnosed as ischemia stroke with the neurological functional score criteria of NIHSS (National Institutes of Health Stroke Scale) and mRS (modified Rankin Scale) (Table I). Cochrane quality evaluation result showed that all studies had a high quality except for the high risk of the random sequence generation in Parsons et al[15], as well as the high risk of the blinding of participants and personnel in Huang et al[22] (Figure 2).

Comparison of the Outcomes Between Different Doses of TNK

There were 3 studies[19,21,23] contained the data of comparison for different TNK doses. The heterogeneity in all indexes was not significant ($I^2 < 50\%$ and $p > 0.33$), thus the fixed effect model was adopted. Compared with the 0.1 mg/kg TNK group, the 0.25 mg/kg TNK group gained a significant Early MNI (RR = 0.66, 95% CI: [0.49, 0.88], $p = 0.005$) and excellent recovery (RR = 0.71, 95% CI: [0.53, 0.95], $p = 0.02$) in patients of 0.25 mg/kg TNK group were significant (Figure 3A-B). The good recovery, recanalization at 24 hours complete or partial, symptomatic intracranial hemorrhage, and deaths between two groups were not significant (Figure 3C-F).

Comparison of the Outcomes Between TNK and rt-PA

There were 5 studies[15,20-23] contained the data of comparison between TNK and rt-PA. Due to the significant heterogeneity ($I^2 > 50\%$ or $p < 0.05$) for the outcomes of MNI and recanalization, the random effect model were adopted (Figure 4 A, C). There did not detect any significant heterogeneity ($I^2 < 50\%$ or $p > 0.05$) in other indexes, thus the fixed effect model were selected (Figure 4 B, D-F). Compared with rt-PA group, TNK group achieved a pronounced MNI (95% CI: [1.08, 2.34], RR = 1.59, $p = 0.02$) (Figure 4A) and a reduced parenchymal hematoma (95% CI: [0.10, 0.71], RR = 0.26, $p = 0.009$) (Figure 4E), further suggesting a good improvement of major neurological function and low risk of parenchymal hematoma for TNK in these patients. The excellent recovery (Figure 4B), recanalization at 24 hours complete or partial (Figure 4C), symptomatic intracranial hemorrhage (Figure 4D) and deaths between two groups were not significant (Table II).

Sensitive Analysis

A reverse result was not detected for the combined results after removing any study, indicating that the results of the present meta-analysis were stable.

Discussion

As a new ideal thrombolytic agent, TNK has a longer half-life and higher fibrin specificity than rt-PA[24]. However, a comprehensive analysis based on meta-analysis for TNK is lacked. In this study, a meta-analysis was performed based on all the TNK-related studies on the treatment of ischemic stroke. Compared with rt-PA, TNK could pronouncedly improve major neurological function and lower parenchymal hematoma in patients with ischemic stroke. Compared with 0.1 mg/kg TNK, the 0.25 mg/kg TNK had a better clinical efficacy in MNI and recovery on patients with ischemic stroke.

The accurate dose of TNK is vital for the clinical treatment of thrombosis[25]. A previous study using advanced imaging guidance in an extended time window, indicated that 0.1 mg/kg TNK had significant biologic efficacy in acute ischemic stroke[15]. However, in certain circumstances, the higher dose of TNK (0.25 m/kg) is superior to the lower dose such as exhibiting an absence of serious disability at 90 days[11]. For the recanalization rate, Coutts et al[24] believe that 0.25 mg/kg TNK is superior to 0.1 mg/kg TNK in complete recanalization. A sequential combination of TNK (0.4 mg/kg) led to a complete recanalization of the basilar artery, with a very good clinical outcome[26]. For intracerebral hemorrhage patients, TNK doses of 0.1 to 0.4 mg/kg are safe in ischemic stroke[27]. Hull et al[16] show that treatment

Table I. Characteristics of the included articles.

Study	Study type	Study period	Country	Participants	Function assessment	Group	No. (M/F)	Age, y	White race
Coutts 2015 [18]	Prospective, multicenter, 2-cohort, dose-escalation study	2012.07-2014.07	Canada	Subjects with minor stroke or transient ischemic attack	NIHSS, mRS	TNK-0.1 mg/kg	25 (12/13)	72.3 (21.7)*	23/25
						TNK -0.25 mg/kg	25 (14/11)	70.8 (19.9)	21/25
Georgiadis 2012 [19]	Controlled study	2006.07-2008.11	USA	Patients who received endovascular treatment for acute ischemic stroke	NIHSS, mRS	IA-TNK	33 (18/15)	65 ± 16	29/33
						r-PA/rt-PA	48 (21/27)	69 ± 14	20/48
						Thrombectomy	33 (21/12)	65 ± 13	19/33
Haley 2010 [20]	Multicenter, double-blind, RCT	2006.03-2008.12	USA	Patients with stroke acute ischemic	NIHSS, mRS	TNK -0.1 mg/kg	31 (12/19)	67 ± 19	24/31
						TNK-0.25 mg/kg	31 (16/15)	69 ± 15	26/31
						TNK -0.4 mg/kg	19 (13/6)	68 ± 16	12/19
						rt-PA-0.9 mg/kg	31 (17/14)	72 ± 16	25/31
Huang 2015 [21]	Open-label, blinded endpoint, RCT	2012.01-2013.09	UK	Patients had clinically diagnosed supratentorial acute ischaemic stroke	NIHSS, mRS	TNK-0.25 mg/kg	47 (30/17)	71 ± 13	NA
						rt-PA-0.9 mg/kg	49 (31/18)	71 ± 12	NA
Parsons 2009 [14]	Prospective, non-RCT	2006.01-2007.07	Australia	Patients with ischemic stroke	NIHSS, mRS	TNK-0.1 mg/kg	15	73.0 ± 9.5	NA
						rt-PA-0.9 mg/kg	35	69.4 ± 13.5	NA
Parsons 2012 [22]	Open-label, blinded trial, RCT	2008-2011	Australia	Patients with acute ischemic stroke	NIHSS, mRS	TNK-0.1 mg/kg	25 (13/12)	72 ± 6.9	NA
						TNK-0.25 mg/kg	25 (13/12)	68 ± 9.4	NA
						rt-PA-0.9 mg/kg	25 (12/13)	70 ± 8.4	NA

Abbreviations: TNK: tenecteplase; r-PA: reteplase; rt-PA: alteplase; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; RCT: randomized controlled trial; M: male; F: female; y: years; NA: not available. *Data presented as median.

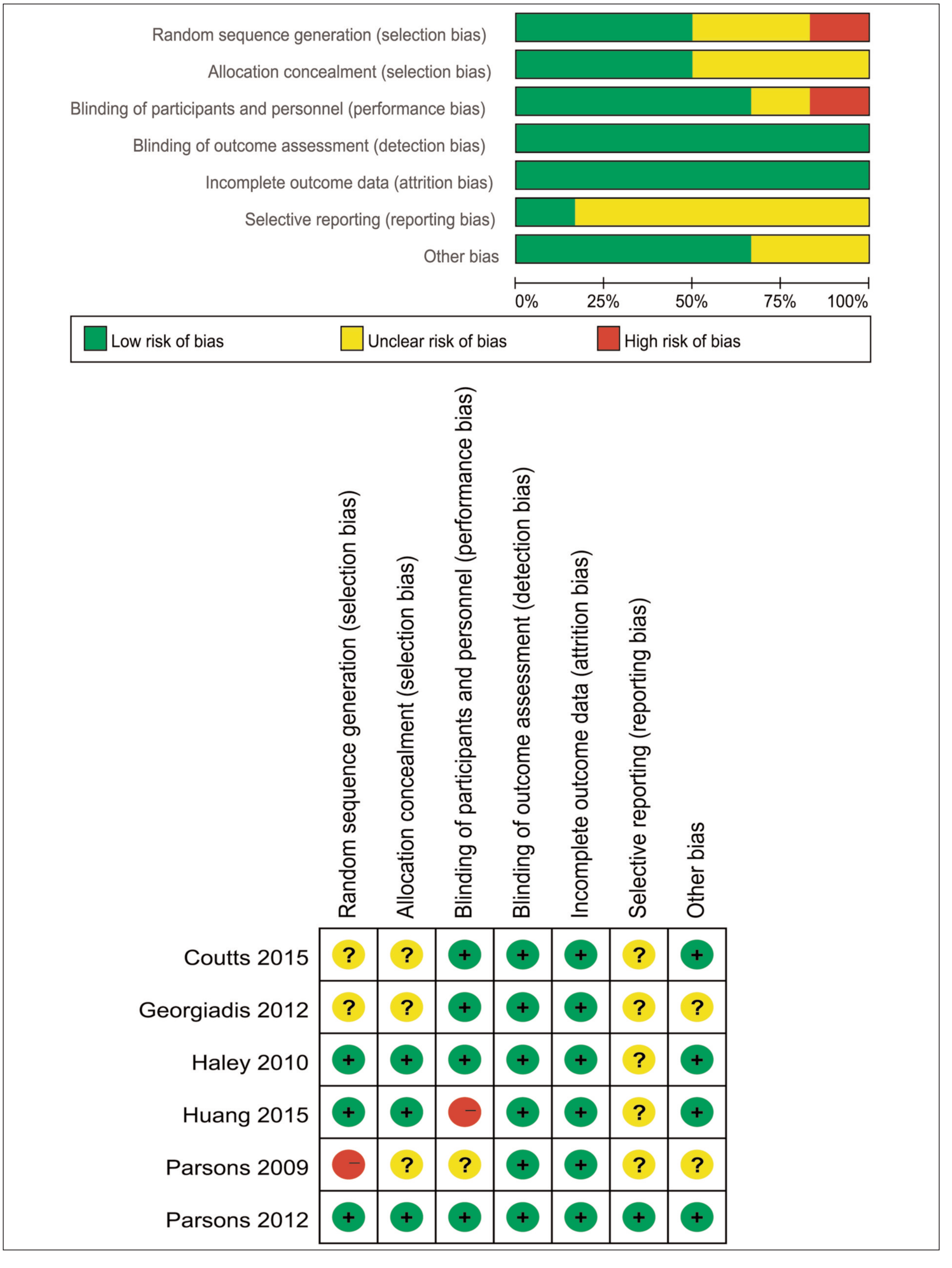

Figure 2. Risk of bias in the present study. The authors' judgements about each risk of bias item presented as percentages across all included studies were listed; +" indicates low risk of bias; "?" represents unclear risk of bias; "–"represents high risk of bias.

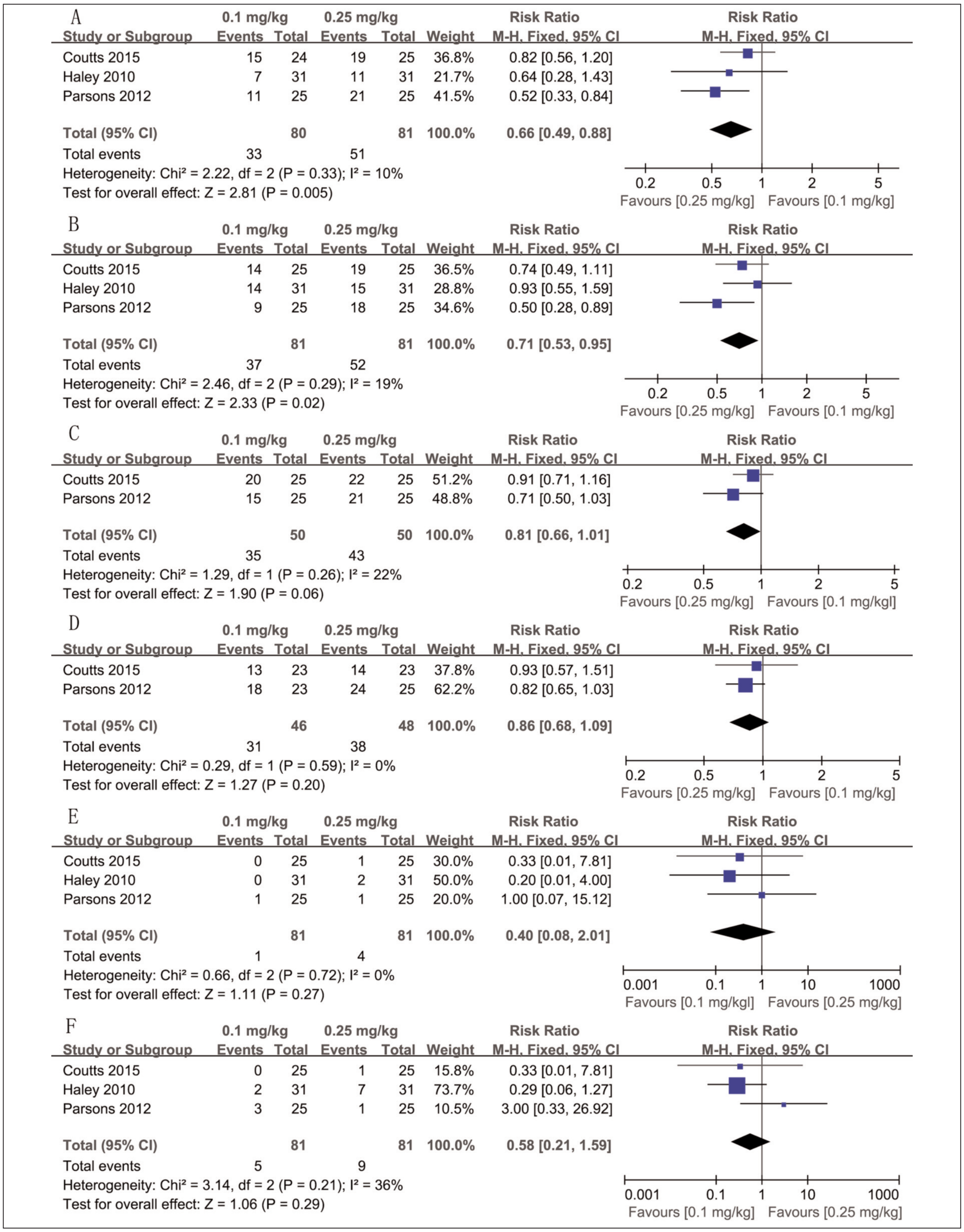

Figure 3. Results of the comparison between different doses of TNK in the present meta-analysis. ***A-F,*** Represent the comparison between 0.1 mg/kg TNK and 0.25 mg/kg TNK in early major neurological improvement, excellent recovery, good recovery, recanalization at 24 hours-complete or partial, symptomatic intracranial haemorrhage and death, respectively. The squares and horizontal line correspond to study-specific RR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled RR and 95% CI. RR: relative risk; CI: confidence interval. TNK: tenecteplase.

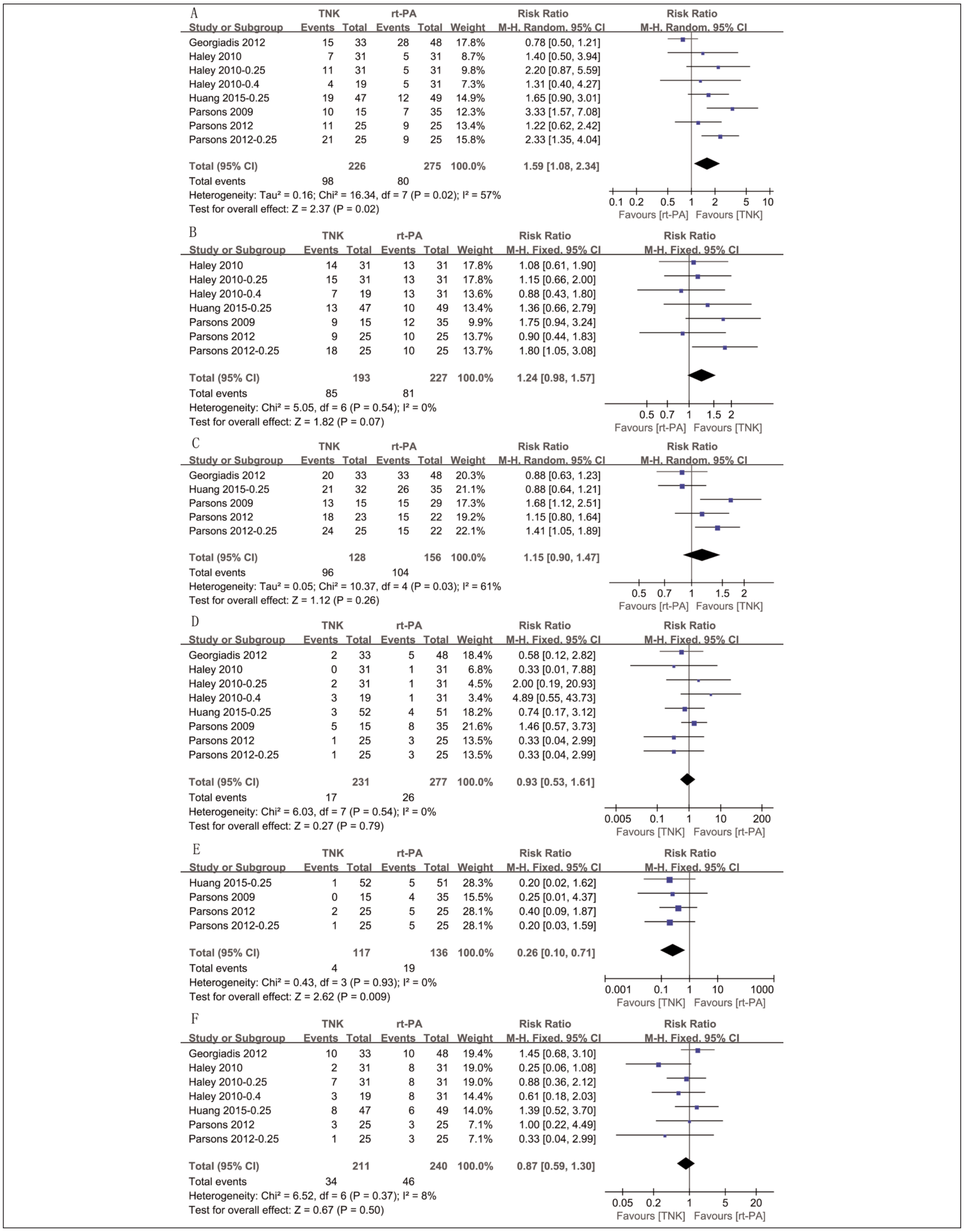

Figure 4. Results of comparison between tenecteplase and alteplase in the present meta-analysis. ***A-F,*** Represent the comparison between TNK and rt-PA in early major neurological improvement, excellent recovery, good recovery, recanalization at 24 hours-complete or partial, symptomatic intracranial haemorrhage and death, respectively. The squares and horizontal line correspond to study-specific RR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled RR and 95% CI. RR: relative risk; CI: confidence interval. TNK: tenecteplase; rt-PA: alteplase.

Table II. Pooled outcomes (TNK vs. rt-PA) and subgroup analyses.

Outcomes	No. of study	No. of participants		Heterogeneity		Model (F/R)	Effect size		p
		TNK	rt-PA	p	I2		RR	95% CI	
MNI-Overall	5	226	275	0.02	57%	R	1.59	[1.08, 2.34]	0.02
TNK-0.1 mg/kg	3	71	91	0.13	51%	R	1.81	[0.93, 3.52]	0.08
TNK-0.25 mg/kg	3	103	105	0.69	0%	F	2.00	[1.37, 2.91]	0.0003
TNK-0.4 mg/kg	1	19	31	–	–	–	1.31	[0.40, 4.27]	0.66
Excellent Recovery-Overall	4	193	227	0.54	0%	F	1.24	[0.98, 1.57]	0.07
TNK-0.1 mg/kg	3	71	91	0.33	0%	F	1.18	[0.82, 1.60]	0.37
TNK-0.25 mg/kg	3	103	105	0.52	0%	F	1.41	[1.00, 1.99]	0.05
TNK-0.4 mg/kg	1	19	31	–	–	–	0.88	[0.43, 1.80]	0.72
Recanalization-Overall	4	128	156	0.03	61%	R	1.15	[0.90, 1.47]	0.26
TNK-0.1 mg/kg	2	38	51	0.17	41%	F	1.36	[1.04, 1.77]	0.02
TNK-0.25 mg/kg	2	57	57	0.03	78%	R	1.12	[0.70, 1.78]	0.63
sIH-Overall	5	231	277	0.54	0%	F	0.93	[0.53, 1.61]	0.79
TNK-0.1 mg/kg	3	71	91	0.34	7%	F	0.91	[0.41, 2.05]	0.83
TNK-0.25 mg/kg	3	108	107	0.55	0%	F	0.74	[0.27, 2.07]	0.57
TNK-0.4 mg/kg	1	19	31	–	–	–	4.89	[0.55, 43.73]	0.16
Any parenchymal hematoma-Overall	3	117	136	0.93	0%	F	0.26	[0.10, 0.71]	0.009
TNK-0.1 mg/kg	2	40	60	0.77	0%	F	0.35	[0.09, 1.37]	0.13
TNK-0.25 mg/kg	2	77	76	0.99	0%	F	0.20	[0.05, 0.87]	0.03
Death-Overall	5	211	240	0.37	8%	F	0.87	[0.59, 1.30]	0.50
TNK-0.1 mg/kg	2	56	56	0.19	41%	F	0.45	[0.17, 1.23]	0.12
TNK-0.25 mg/kg	3	103	105	0.48	0%	F	0.96	[0.52, 1.78]	0.89
TNK-0.4 mg/kg	1	19	31	–	–	–	0.61	[0.18, 2.03]	0.42

Abbreviations: TNK: tenecteplase; rt-PA: alteplase; MNI: Major Neurological Improvement; sIH: symptomatic Intracranial Haemorrhage; F: fixed effect model; R: random effect model; RR: risk ratio; CI: confidence interval.

of acute lower-limb ischemia with TNK infusion at 0.25 mg/h and 0.125 mg/h is associated with similar success and complication rates, and the initial TNK bolus dose should be limited to 1.5 mg, which further indicating that a suitable dose of TNK is important for the clinical application. Furthermore, in the combination therapy (like integrilin and TNK) of acute myocardial infarction, the reduced-dose of TNK leads to faster, more stable ST-segment recovery and improved angiographic flow patterns, compared with full-dose TNK[28]. Double-bolus eptifibatide plus half-dose TNK tended to improve angiographic flow and ST-segment resolution compared with TNK monotherapy[29]. In the present meta-analysis, the 0.25 mg/kg TNK had better clinical efficacy in MNI and recovery compared with 0.1 mg/kg TNK in patients with ischemic stroke. Meanwhile, the differences of safety indexes like symptomatic intracranial hemorrhage and death between 0.1 mg/kg TNK and 0.25 mg/kg TNK were not significant, which further indicated that 0.25 mg/kg TNK would not bring additional adverse effect. Thus, we speculate that 0.25 mg/kg TNK might be a safe and efficacy dose for the monotherapy clinical application of ischemic stroke patients. These observations warrant further confirmation in randomized clinical trials in ischemic stroke.

As the genetically engineered variant of rt-PA, TNK is commonly used to compare with rt-PA on the clinical effect in various situations[30]. A previous study[31] showed that TNK appeared to induce recanalization more rapidly than rt-PA, and thrombolysis that initiated early after the onset of symptoms was associated with remarkably low mortality. Parsons et al[11] demonstrate TNK is associated with significantly better reperfusion and clinical outcomes than rt-PA in patients with stroke who are selected on the basis of CT perfusion imaging. The comparison between TNK and rt-PA based on safety indexes shows that mortality rates remain similar in patients with acute myocardial infarction treated with rt-PA or a single bolus of TNK[32]. Although TNK and rt-PA were equivalent for 30-day mortality, the ease of administration of TNK may facilitate more rapid treatment in and out of hospital[12]. In this meta-analysis, compared with rt-PA, TNK could improve major neurological function and lower parenchymal hematoma in patients with ischemic stroke. Meanwhile, the differences of symptomatic intracranial hemorrhage and death between TNK and rt-PA were not significant. Thus, we believed that for major neurological function improvement and parenchymal hematoma risk reducing, TNK might be a better choice than rt-PA.

The reasons for the significant heterogeneity in our meta-analysis might be: (1) although the same evaluation criteria have been used in different studies, the subjective judgments of patients made by researchers are different; (2) health and living conditions in different areas, as well as differences between different individuals may lead to the heterogeneity. There were some limitations in the present study such as sample sizes and few follow-up data in the enrolled studies, which affected the results. Therefore, further studies with larger sample sizes and long follow-up time are needed to confirm our findings and provide a more accurately representative statistical analysis.

Conclusions

Compared with rt-PA, TNK might improve the major neurological function. The 0.25 mg/kg TNK had a relatively good clinical treatment effect than 0.1 mg/kg TNK. The adverse outcome for different TNK dosage was not significant.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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