

Different doses of tenecteplase vs alteplase in thrombolysis therapy of acute ischemic stroke: evidence from randomized controlled trials

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Background: Recent studies showed inconsistent results of tenecteplase vs alteplase for acute ischemic stroke (AIS) with safety and efficacy.

Methods: A meta-analysis was performed to explore the value of tenecteplase and alteplase in AIS treatment. Medline, Embase, and Cochrane Library from January 2001 to April 2018 were searched for randomized controlled trials (RCTs) with tenecteplase vs alteplase for AIS.

Results: The primary outcomes were early neurological improvement at 24 h and functional outcome at 3 months. We pooled 1,390 patients from four RCTs. Tenecteplase showed a significant early neurological improvement ($P=0.035$) compared with alteplase. In addition, tenecteplase showed a neutral effect on excellent outcome ($P=0.309$), good functional outcome ($P=0.275$), and recanalization ($P=0.3$). No significant differences in safety outcomes were demonstrated. In subgroup analysis, 0.25 mg/kg dose of tenecteplase showed a significantly increased early neurological improvement ($P<0.001$). In serious stroke at baseline (National Institutes of Health Stroke Scale [NIHSS] >12) subgroup, tenecteplase showed a dramatic early neurological improvement ($P=0.002$) and low risks of any intracranial hemorrhage (ICH) ($P=0.027$).

Conclusion: Tenecteplase provided better early neurological improvement than alteplase. The 0.25 mg/kg dose of tenecteplase subgroup specially showed better early neurological improvement and lower any ICH tendency than that of alteplase. In addition, in serious stroke at baseline subgroup, tenecteplase showed a lower risk of any ICH.

Keywords: tenecteplase, alteplase, acute ischemic stroke, early neurological improvement, meta-analysis

Introduction

Acute ischemic stroke (AIS) is a high mortality and high disability disease, the most common stroke subtype, life-threatening illness, with large financial burdens.¹ Alteplase is a thrombolytic drug used primarily to treat AIS and acute myocardial infarction.^{2,3} Alteplase is a second-generation drug, which selectively activates fibrin-bound plasminogen to facilitate thrombolysis and recanalize the occluded blood vessels.⁴ However, intravenous alteplase increases the risk of bleeding, especially intracranial hemorrhage (ICH).⁵ Therefore, many new thrombolytic drugs are currently compared with alteplase on whether these new drugs have better safety and efficacy.⁶⁻⁹ Tenecteplase is one of these new drugs.

Tenecteplase is a multipoint variant of tissue plasminogen activator (t-PA). It is a third-generation fibrinolytic agent and is used clinically for the treatment of thrombolysis. In addition, models of fibrinolysis show that the bolus injection of tenecteplase is better than the infusion of t-PA.¹⁰ Preclinical studies have indicated that tenecteplase has a better thrombolytic effect, faster recanalization, and lower bleeding risk.¹¹

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These beneficial results stimulated enthusiasm for the clinical transformation of the drug to humans.¹² These clinical studies explore whether tenecteplase has better efficacy and safety than alteplase.^{6–9} The Phase IIB/III trial⁶ randomly assigned AIS patients (symptom onset <3 h) to receive fixed doses in 0.1, 0.25, and 0.4 mg/kg. This prematurely terminated clinical trial has demonstrated the potential efficiency in selecting a propitious dose for future study of a new thrombolytic agent for AIS. However, due to the premature interruption of the study, no convincing results can be obtained. A study of a lower weight-adjusted dose of tenecteplase (0.1 and 0.25 mg/kg) in the *New England Journal of Medicine*⁷ selected the patient based on the strict imaging criteria, which showed that tenecteplase had better recanalization and clinical prognosis than alteplase. Another Phase II trial⁸ investigated the efficacy and safety of 0.25 mg/kg tenecteplase for AIS in *Lancet Neurology*. However, the results suggested that tenecteplase and alteplase in neurological and radiological outcomes did not differ. However, it is hoped that there will be larger clinical samples to obtain more exact results for this study. In a recent large sample randomized controlled trial (RCT) study⁹ in *Lancet Neurology*, the clinical efficacy results of tenecteplase (0.4 mg/kg) were not superior to alteplase, and they had a similar safety profile. Because of the lower baseline National Institutes of Health Stroke Scale (NIHSS) scores in this study, further studies are recommended to explore patients with more severe ischemic stroke.

Based on the above results, the efficacy and safety of tenecteplase over alteplase in the treatment of AIS are unclear. Several problems need to be solved, including the optimal dosage of tenecteplase and the efficacy and safety of the two drugs. The meta-analysis pooled data from previous randomized clinical trials to investigate whether the value of tenecteplase treatment for AIS is superior to alteplase in the onset of symptoms and to explore the potential factors that might influence the efficacy and safety of tenecteplase.

Methods

Study protocol

At the beginning of this project, a study protocol was drafted following the Cochrane Collaboration format.¹³

Eligibility criteria

Inclusion criteria were as follows: 1) study type (RCT); 2) language restriction (only English was available); 3) participants (patients with stroke); 4) intervention (tenecteplase or alteplase); and 5) outcomes (excellent and favorable outcomes based on modified Rankin scale [mRS] and early

neurological improvement based on a major neurological improvement [MNI] or NIHSS of ≥ 8 points or an NIHSS score of 0 or 1 at 24 h posttreatment, recanalization, and adverse events). Exclusion criteria were as follows: 1) study types (case reports, case reviews, retrospective studies, and cohort studies) and 2) the intervention of control group (placebo).

Search strategy and information sources

Three major databases, such as Medline, Embase, and Cochrane Library, were systematically searched by two independent authors (NX and ZC). The search strategy of the Medline was the combination of the variables “tenecteplase” OR “alteplase” AND “Stroke”. Searches were limited to clinical trials and matched the titles and abstracts of studies. The search strategy for Embase and the Cochrane Library were similar to that used for Medline. In addition, two investigators (NX and ZC) independently manually screened reference lists from RCTs and systematic reviews to ensure all relevant studies had been included in this study.

Study selection and data collection

All records from the systematic search in the electronic database and reference lists of RCTs and systematic reviews were evaluated by two authors (NX and ZC) independently in accordance with the eligibility criteria as mentioned earlier. After strict selection and evaluation, the data were extracted from the included RCTs as follows: basic information on the included trials, inclusion and exclusion criteria for the participants, study design, and outcome assessments (Table 1).

Outcomes of interest

The primary efficacy outcomes were excellent functional outcomes, which were defined as mRS 0–1 at 3 months. Secondary efficacy outcomes included good functional outcome (mRS 0–2 at 3 months), early neurological improvement at 24 h, which was defined as an improvement on the NIHSS of ≥ 8 points or an NIHSS score of 0 or 1 at 24 h posttreatment and recanalization within 24 h. The primary safety endpoint was ICH, including symptomatic ICH (sICH) and any ICH. sICH was defined as the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)¹⁴ criteria (parenchymal hemorrhage type 2 or remote parenchymal hemorrhage type 2 on 24–48 h noncontrast computed tomography [CT], with the neurological deterioration of ≥ 4 points NIHSS score). Any ICH was defined as any ICH on the follow-up CT postthrombolysis. Secondary safety outcomes included dependence (mRS 3–5) and death rate at

Table 1 Characteristics of the included studies and outcome events

Trials	Haley et al (2010) ⁶ (NCT00252239)	Parsons et al (2012) ⁷ (ACTRN12608000466347)	Huang et al (2015) ⁸ (NCT01472926)	Logallo et al (2017) ⁹ (NCT01949948)
1. Information of the included trials				
Regions	8 centers in Japan	3 centers in Australia	Single center in the UK	13 centers in Norway
Phases	IIB/III	IIB	II	III
Publication	<i>Stroke</i>	<i>New England Journal of Medicine</i>	<i>Lancet Neurology</i>	<i>Lancet Neurology</i>
2. Eligibility criteria and study design				
Inclusion criteria	Acute ischemic stroke; symptom onset <3 h; NIHSS >0; if NIHSS =1, requires significant deficit	Acute ischemic stroke; symptom onset <6 h; NIHSS: 4–24; mRS 0–2; core volume <1/3 of MCA or 1/2 ACA/PCA territory; perfusion volume >120% core and ≥20 mL; occlusion of MCA/ACA/PCA	Acute ischemic stroke; time window <4.5 h; NIHSS 1–25; mRS 0–2	Acute ischemic stroke; symptom onset or awakening with symptoms <4.5 h; age ≥18 years; NIHSS >0
Exclusion criteria	Stroke in previous 3 months; seizures at the onset of stroke	Stroke in previous 3 months; eGFR <15 mL/min; contraindication for MRI	Recent stroke on NCCT; hypodensity of >1/3 of the MCA territory; ASPECT score ≤4; glucose >18 mmol/L; eGFR <30 mL/min; allergy to iodinated contrast	mRS score ≥3; NIHSS cannot be obtained; no arterial occlusion on baseline CT; ICH; SAH; large areas of ischemic; any serious medical illness
Study design	Tenecteplase 0.1, 0.25, and 0.4 mg/kg vs alteplase 0.9 mg/kg	Tenecteplase 0.1 or 0.25 mg/kg or alteplase 0.9 mg/kg	Tenecteplase 0.25 mg/kg (maximum 25 mg) or alteplase 0.9 mg/kg (maximum of 90 mg)	Tenecteplase 0.4 mg/kg (to a maximum of 40 mg) or alteplase 0.9 mg/kg (to a maximum of 90 mg)
3. Outcomes assessments				
Efficacy outcomes	Favorable outcome, 3 months Rankin good and poor and 24 h (MNI)	Reperfusion at 24 h, NIHSS, infarct growth at 24 h, infarct growth at 90 days, complete recanalization at 24 h, complete or partial recanalization at 24 h, MNI	Percentage penumbra at 24–48 h, infarct volume on 24–48 h NCCT, mRS response (30 and 90 days), NIHSS response, excellent (0–1 points of mRS) functional outcome at 30 and 90 days, mean home time by 90 days	Excellent (0–1 points of mRS) functional outcome at 3 months, mRS response, change in NIHSS
Safety outcomes	sICH, asymptomatic ICH, all hemorrhage, major systemic bleeding, and death at 3 months	Large parenchymal hematoma, any parenchymal hematoma, sICH, poor outcome at 90 days and death	Any ICH, any parenchymal hemorrhage type 2, sICH	Any intracranial hemorrhage occurring within 24–48 h, sICH occurring within 24–48 h, and death at 90 days

Abbreviations: ACA, anterior cerebral artery; CT, computed tomography; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; MCA, middle cerebral artery; MNI, major neurological improvement; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; SAH, subarachnoid hemorrhage; sICH, symptomatic ICH.

Day 90. In subgroup analysis, we set the relevant cutoff values that could distinctly affect the effectiveness of tenecteplase or alteplase and stratified the included trials into low (<45%) and high (≥45%) percentage of patients with hypertension, high stroke severity at baseline (NIHSS ≥12), and low stroke severity at baseline (NIHSS <12) (Table 2).

Risk of bias

The risk of bias plot in individual studies was created using the Review Manager 5.2 software. For assessing the risk of

bias of RCTs, we applied uniform criteria of the Cochrane Collaboration, which included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases.

Summary measures and synthesis of results

STATA (version 12.0) was used to assess the data. Dichotomous outcomes were analyzed as the risk ratio (relative risk [RR]; 95% confidence interval [CI]) and calculated using a

Table 2 Subgroup analysis of efficacy and safety outcomes

Subgroup	Efficacy outcomes							
	Excellent functional outcome		Good functional outcome		Early neurological improvement		Recanalization	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
1. Stroke severity at baseline								
NIHSS ≥12	1.30 (0.91, 1.88)	0.154	1.25 (0.69, 2.27)	0.464	1.71 (1.21, 2.43)	0.002	1.13 (0.89, 0.42)	0.322
NIHSS <12	1.03 (0.95, 1.13)	0.480	1.08 (0.82, 1.42)	0.575	1.50 (0.68, 3.33)	0.319	N/A	N/A
2. Hypertension								
N≥45	1.03 (0.94, 1.13)	0.520	1.30 (0.95, 1.77)	0.104	1.07 (0.93, 1.24)	0.332	N/A	N/A
N<45	1.17 (0.91, 1.50)	0.223	1.13 (0.79, 1.61)	0.510	1.83 (1.34, 2.51)	0.000	1.13 (0.89, 0.42)	0.322
Safety outcomes								
sICH		Any ICH		Dependence		Mortality		
RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	
3. Stroke severity at baseline								
NIHSS ≥12	0.38 (0.10, 1.38)	0.140	0.48 (0.25, 0.92)	0.027	0.67 (0.34, 1.34)	0.260	1.01 (0.47, 2.16)	0.981
NIHSS <12	1.29 (0.67, 2.46)	0.447	0.95 (0.68, 1.33)	0.759	1.05 (0.84, 1.31)	0.673	0.90 (0.55, 1.47)	0.668
4. Hypertension								
N≥45	1.15 (0.55, 2.40)	0.702	0.94 (0.65, 1.38)	0.764	1.07 (0.83, 1.38)	0.614	1.12 (0.67, 1.88)	0.668
N<45	0.76 (0.24, 2.46)	0.648	0.63 (0.35, 1.15)	0.132	0.79 (0.52, 1.20)	0.271	0.79 (0.49, 1.29)	0.350

Abbreviations: CI, confidence interval; ICH, intracranial hemorrhage; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; RR, relative risk; sICH, symptomatic ICH.

random effect model. Statistical heterogeneity was estimated by the I^2 statistic as follows: $I^2 < 30\%$ means “low heterogeneity”, $I^2 = 30\%–50\%$ denotes “moderate heterogeneity”, and $I^2 > 50\%$ represents “substantial heterogeneity”. Subgroup analyses were implemented to detect the dose of drug administration and the severity of stroke and hypertension. Sensitivity analysis was used to explore the stability of the consolidated results. Tests were two-tailed, and a P -value of < 0.05 was considered significant for all analyses.

Results

A total of 513 titles and abstracts were identified through Medline, Embase, and Cochrane Library (Figure 1). After removing the duplicates and irrelevant records, 17 full-text articles were assessed for eligibility. Additionally, the following 13 articles were excluded due to the limitation of publication types: three protocol studies, one post hoc analysis, one meta-analysis, seven comments, and eight reviews. Ultimately, four RCTs containing 1,390 patients were included in qualitative synthesis (Figure 1). The main characteristics of the included studies are listed in Table 1.

Outcomes analysis

All four RCTs enrolling 1,390 patients were available for the analysis of efficacy and safety outcomes.

Tenecteplase showed a neutral effect on excellent functional outcome (58.7 vs 55.6% for tenecteplase vs alteplase; RR 1.04; 95% CI: 0.96, 1.14; $P=0.309$; Figure 2A) and good functional outcome (70.8 vs 68.6% for tenecteplase vs alteplase; RR

1.16; 95% CI: 0.89, 1.53; $P=0.275$; Figure 2B). Tenecteplase showed a significantly early neurological improvement at 24 h (40.6 vs 33.9% for tenecteplase vs alteplase; RR 1.52; 95% CI: 1.03, 2.25; $P=0.035$; Figure 2C) compared with alteplase. In addition, tenecteplase showed a neutral effect on recanalization within 24 or 24–48 h (61.8 vs 54.9% for tenecteplase vs alteplase; RR 1.26; 95% CI: 0.53, 3.01; $P=0.3$; Figure 2D). No significant differences in other safety outcomes were demonstrated (Figure 3). These safety outcomes include sICH (3.1 vs 3.2% for tenecteplase vs alteplase; RR 0.99; 95% CI: 0.53, 1.86; $P=0.968$; Figure 3A), any ICH (9.6 vs 11.9% for tenecteplase vs alteplase; RR 0.77; 95% CI: 0.52, 1.15; $P=0.202$; Figure 3B), dependence (21.4 vs 22.7% for tenecteplase vs alteplase; RR 0.89; 95% CI: 0.66, 1.19; $P=0.437$; Figure 3C), and mortality (7.2 vs 8.1% for tenecteplase vs alteplase; RR 0.93; 95% CI: 0.65, 1.33; $P=0.699$; Figure 3D). The heterogeneity of good functional outcome ($I^2=73.1\%$, $P=0.011$; Figure 2B), the early neurological improvement ($I^2=70.3\%$, $P=0.018$; Figure 2C), recanalization within 24 or 24–48 h at 24 h ($I^2=88.6\%$, $P=0.0033$; Figure 2D), and dependence ($I^2=50.2\%$, $P=0.11$; Figure 3C) were apparent. To detect the source of the statistical heterogeneity, sensitivity analysis was performed. The sensitivity analysis showed that all the consolidated results were stable (Figure S1).

Subgroup analysis

A subgroup analysis was performed to examine the influence of tenecteplase dosage, NIHSS score at baseline, and hypertension. Tenecteplase dosage did not influence most

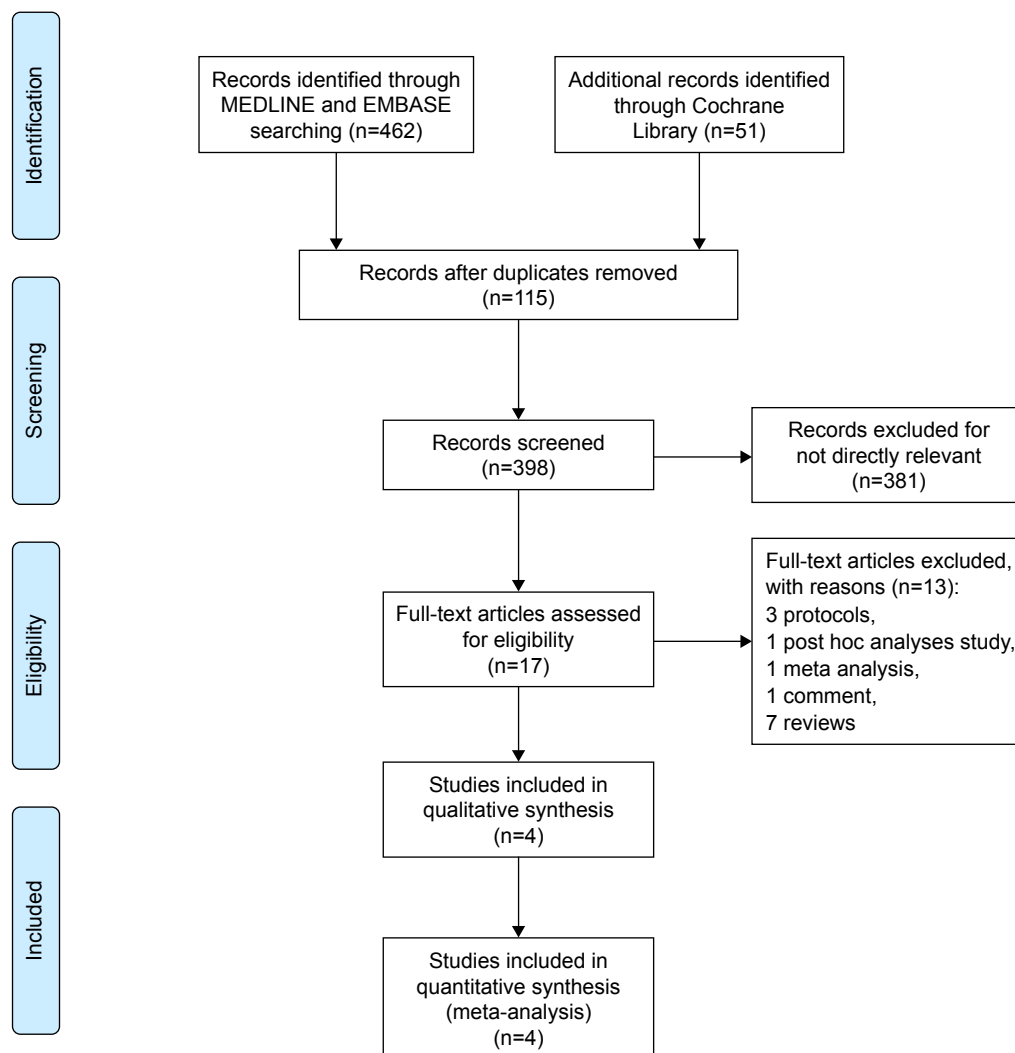


Figure 1 The study search, selection, and inclusion process.

efficacy outcomes (Figure 4-1A–C, 4-2A–C, 4-3A and C and 4-4A and B), except that 0.25 mg/kg dose of tenecteplase showed a significantly increased early neurological improvement (47.2 vs 22.2% for tenecteplase vs alteplase; RR 2.1; 95% CI: 1.43, 3.09; $P < 0.001$; Figure 4-3B). Tenecteplase dosage did not influence safety outcomes (Figure 5), but 0.25 mg/kg dose of tenecteplase subgroup showed a trend for lower risk of any ICH (12.0 vs 22.2% for tenecteplase vs alteplase; RR 0.57; 95% CI: 0.30, 1.06; $P = 0.076$; Figure 5-2B). Serious stroke symptoms at baseline (NIHSS > 12) showed a dramatic early neurological improvement at 24 h (50.0 vs 29.4% for tenecteplase vs alteplase; RR 1.71; 95% CI: 1.21, 2.43; $P = 0.002$; Table 2) but low risks of any ICH (10.8 vs 23.5% for tenecteplase vs alteplase; RR 0.48; 95% CI: 0.25, 0.92; $P = 0.027$; Table 2). In addition, hypertension (number of hypertension patients/total patients $< 45\%$) had an apparent early neurological improvement at 24 h (37.4 vs 20.0% for tenecteplase vs

alteplase; RR 1.83; 95% CI: 1.34, 2.51; $P < 0.001$; Table 2). The sensitivity analysis showed that the different doses of tenecteplase subgroup results were stable (Figure S2).

Risk of bias in included studies

Full details about the risk of bias of the included studies are shown in Figure 6. For allocation concealment, the risk of bias of one trial was unclear, and another trial had a high risk of bias. For the blinding of outcomes assessment, the risk of bias was high in two studies. For incomplete outcome data, the risk of bias was unclear in one study. Apart from these three items, no high or unclear risk of bias was observed in any of the other items.

Discussion

Based on the data gathered from the four published RCTs including 1,390 individuals, our present meta-analysis showed that tenecteplase was superior to alteplase in early

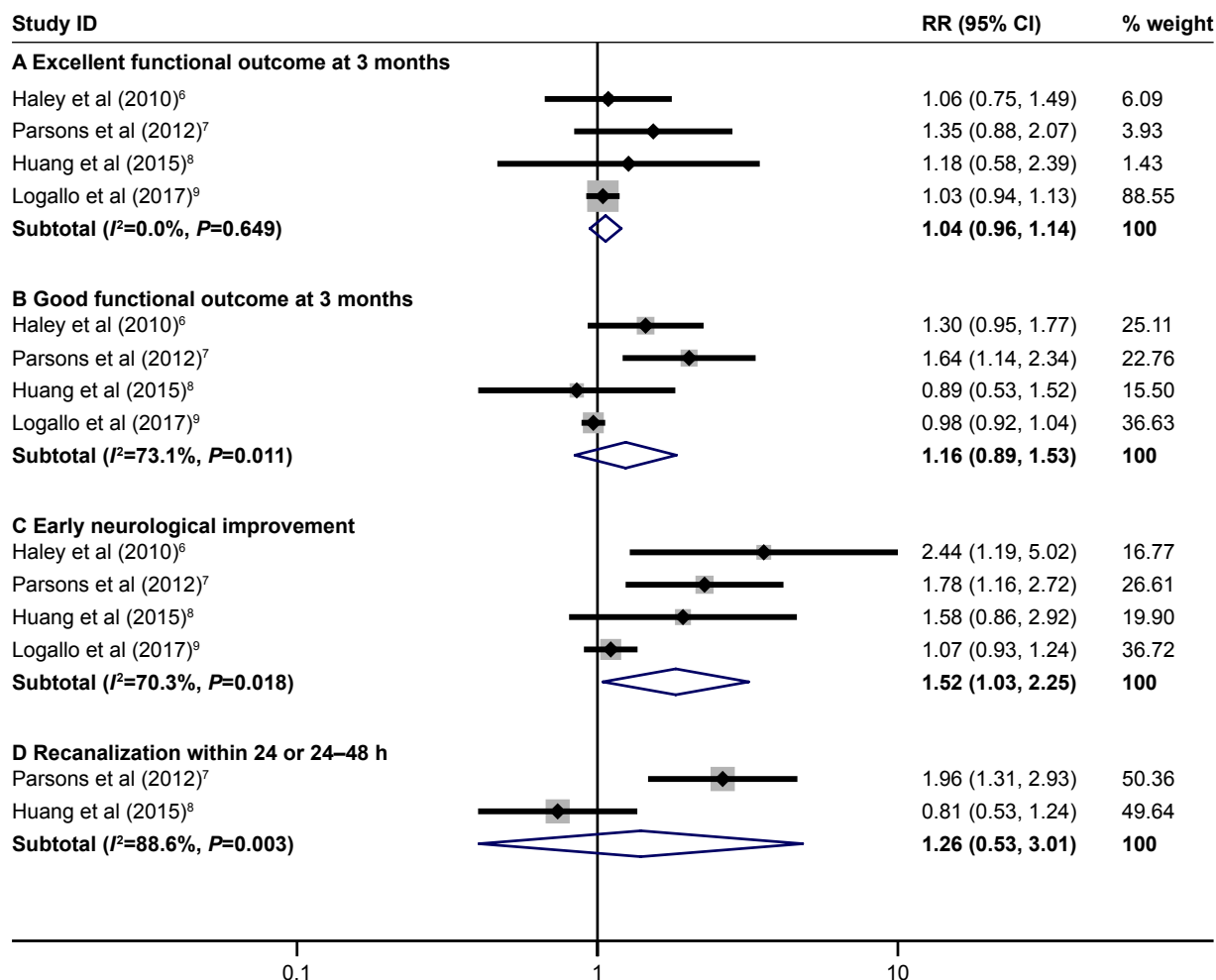


Figure 2 The pooled RR of the efficacy outcomes.

Notes: The black diamond indicates the estimated RR for each RCT. The gray box around each diamond indicates the estimated weight of each RCT, and the extending lines indicate the estimated 95% CI of RR for each RCT. The diamond indicates the estimated RR (95% CI) for all patients together. **(A)** Excellent favorable outcome. **(B)** Good functional outcome. **(C)** Early neurological improvement. **(D)** Recanalization within 24 or 24–48 h. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

neurological improvement. There was no significant difference between tenecteplase and alteplase in other efficacy items and all safety items. Different doses of tenecteplase subgroup analysis showed that the 0.25 mg/kg dose of tenecteplase was significantly better than alteplase in terms of early neurological improvement. Although previous meta-analysis had reached similar conclusions,¹² the number of patients in this meta-analysis was 1,100 more than the number of patients in the previous meta-analysis from four RCT studies. In addition, we not only compared different dose subgroups but also performed NIHSS score at baseline subgroup and percentage of hypertension patients' subgroup analyses to further explore the relevant factors affecting clinical efficacy and safety of tenecteplase and alteplase. Surprisingly, in the subgroup with a higher NIHSS score at

baseline, the risk of any ICH with tenecteplase was lower than that of alteplase.

In the previous meta-analysis,¹² there was a potential correlation between drug dose and ICH risk, but small numbers (19 patients) of high doses (0.4 mg/kg) of tenecteplase did not give credible results. However, the latest RCT study,⁹ 549 patients in the high-dose group of tenecteplase, increased the reliability of the assessment of high-dose subgroup and its influence on ICH risk. Why did the previous study use less high dose of tenecteplase as thrombolytic therapy for AIS? The choice of the early thrombolytic drug dose was often based on the study of small samples.^{15–18} When the higher dose group had more serious complications, the dose study was abandoned. Previous experience had taught us that the use of higher dose of thrombolytic drugs often led

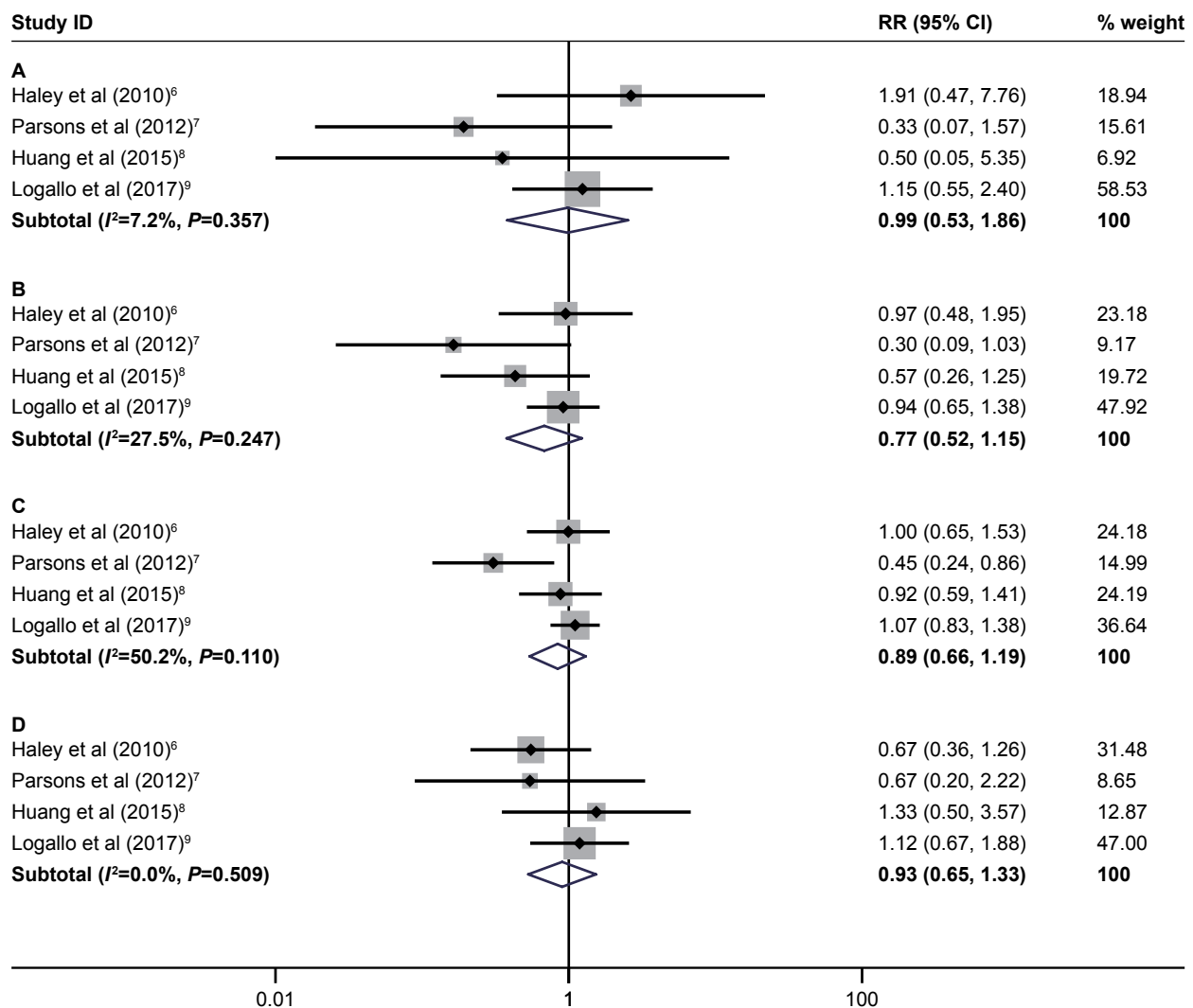


Figure 3 The pooled RR of the safety outcomes.

Notes: The black diamond indicates the estimated RR for each RCT. The gray box around each diamond indicates the estimated weight of each RCT, and the extending lines indicate the estimated 95% CI of RR for each RCT. The diamond indicates the estimated RR (95% CI) for all patients together. (A) sICH. (B) Any ICH. (C) Dependence. (D) Mortality. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; ICH, intracranial hemorrhage; RCT, randomized controlled trial; RR, relative risk; sICH, symptomatic ICH.

to higher risks of ICH.¹⁹ Therefore, doctors are often cautious when using high drug doses with probable serious side effects. However, in the latest large sample RCT⁹ in *Lancet Neurology*, when the high dose of tenecteplase was used, it did not increase the risk of ICH. In addition, there was no significant difference in dependence and mortality after 3 months at AIS.⁹ These new data demonstrated that increasing the dose concentration of tenecteplase did not increase the risk of ICH. This evidence may provide an indicator that high dose of tenecteplase could be used in clinical treatment and has important clinical significance.

Thrombolytic therapy is based on the hypothesis that recanalization of the infarct vessels is for salvageable of

ischemic penumbra.²⁰ Hence, in the treatment of AIS, recanalization is an important indicator of efficacy. In this meta-analysis, we increased the assessment of recanalization but unfortunately only had the study data for the 0.1 and 0.25 mg/kg dose groups. Although Parsons et al's⁷ study supported the possibility that there may be tenecteplase dose-dependent recanalization, there was no study on the high-dose tenecteplase group with recanalization, which means that no result had reached statistical significance. In the latest RCT study included in this meta-analysis,⁹ the study of 0.4 mg/kg dose tenecteplase did not have appropriate clinical data for recanalization, and it was not possible to conclude that high dose of tenecteplase can promote recanalization. In addition,

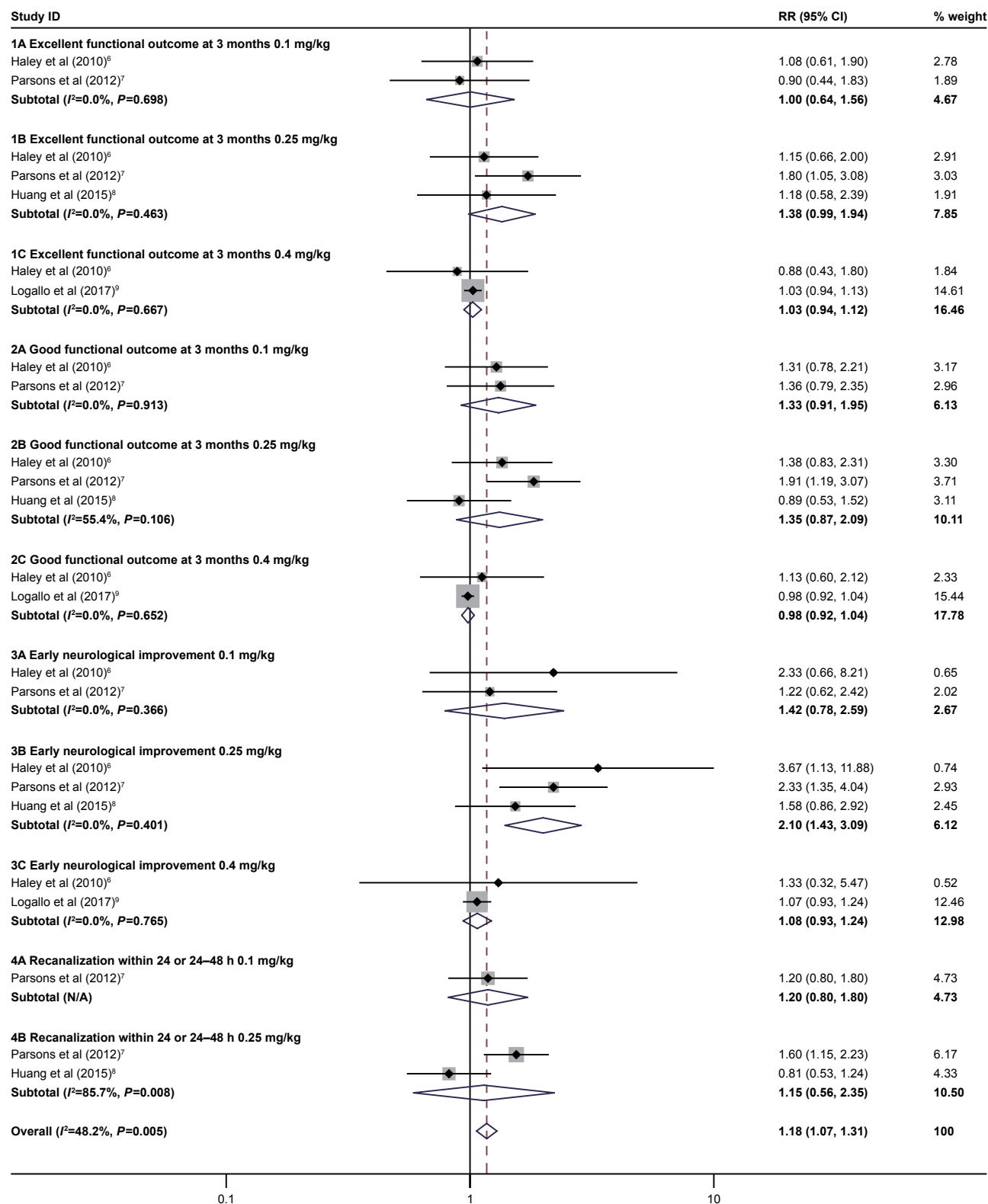


Figure 4 Subgroup analysis of the effect of tenecteplase (all doses) compared with alteplase on efficacy outcomes.

Notes: The black diamond indicates the estimated RR for each RCT. The gray box around each diamond indicates the estimated weight of each RCT, and the extending lines indicate the estimated 95% CI of RR for each RCT. The diamond indicates the estimated RR (95% CI) for all patients together. (1A–C) Excellent functional outcome at 3 months with different doses of tenecteplase. (2A–C) Good functional outcome at 3 months with different doses of tenecteplase. (3A–C) Early neurological improvement with different doses of tenecteplase. (4A and B) Recanalization within 24 or 24–48 h with different doses of tenecteplase. Weights are from random-effects analysis.

Abbreviations: N/A, not applicable; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

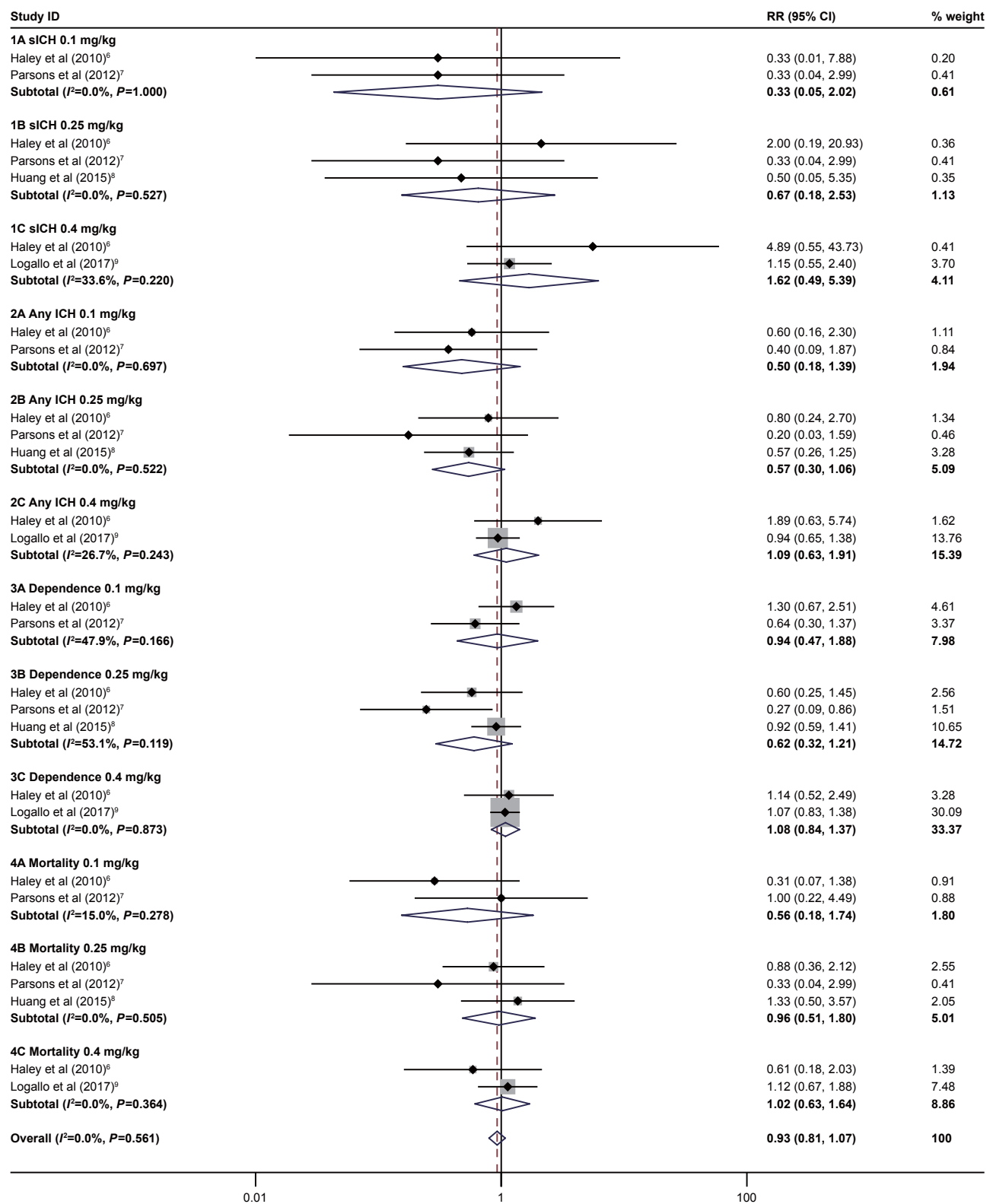


Figure 5 Subgroup analysis of the effect of tenecteplase (all doses) compared with alteplase on safety outcomes.

Notes: The black diamond indicates the estimated RR for each RCT. The gray box around each diamond indicates the estimated weight of each RCT, and the extending lines indicate the estimated 95% CI of RR for each RCT. The diamond indicates the estimated RR (95% CI) for all patients together. (1A–C) sICH with different doses of tenecteplase. (2A–C) Any ICH with different doses of tenecteplase. (3A–C) Dependence with different doses of tenecteplase. (4A–C) Mortality with different doses of tenecteplase. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; ICH, intracranial hemorrhage; RCT, randomized controlled trial; RR, relative risk; sICH, symptomatic ICH.

	Huang et al (2015) ⁸	Parsons et al (2012) ⁷	Logallo et al (2017) ⁹	Haley et al (2010) ⁶	
	+	+	+	+	Random sequence generation (selection bias)
	-	+	+	?	Allocation concealment (selection bias)
	+	+	+	+	Blinding of participants and personnel (performance bias)
	-	+	-	+	Blinding of outcome assessment (detection bias)
	+	?	+	+	Incomplete outcome data (attrition bias)
	+	+	+	+	Selective reporting (reporting bias)
	+	+	+	+	Other bias

+ Low risk of bias
? Unclear risk of bias
- High risk of bias

Figure 6 Risk of bias: a summary table for each risk of bias item for each study.

the latest protocol of clinical RCTs in which tenecteplase vs alteplase also included recanalization indicators.²¹ Therefore, in the further clinical randomized controlled study, the recanalization rate can be considered as an important evaluation index of treatment effectiveness.

This meta-analysis analyzed the safety of tenecteplase and alteplase including sICH, any ICH, dependence, and mortality. In the overall analysis and dose subgroup analysis, there was no statistical difference in the safety of the two drugs. However, the trend of a lower ICH risk was still found at the 0.25 mg/kg dose of tenecteplase than alteplase. Therefore, we conducted further subgroup analysis using different criteria for evaluation. We found that the risk of ICH was significantly lower when tenecteplase was compared with alteplase in the high NIHSS scores at baseline of clinical trials. A higher NIHSS score at baseline means that AIS patients were in more serious condition. This may also mean that in patients with more severe AIS, the risk of ICH with tenecteplase was lower than that of alteplase. At the same time, RCTs of tenecteplase and alteplase can be considered for the inclusion of patients with high NIHSS scores to explore whether the risks of ICH are different in the future. A three-period RCT (NOR-TEST trial⁹) also came to the same conclusion that further trials are needed to establish the efficacy and safety in AIS patients with severe stroke and whether tenecteplase is noninferior to alteplase.

It is unclear whether the tenecteplase reaches the appropriate concentration. Our present meta-analysis showed that the 0.25 mg/kg dose of tenecteplase led to an

increased early neurological improvement ($P < 0.001$) and a trend for lower risk of any ICH ($P = 0.076$). However, the 0.1 and 0.4 mg/kg doses of tenecteplase compared to alteplase did not significantly improve early neurological improvement. The reason is probably that the NIHSS score at baseline of RCT (NOR-TEST trial) including 0.4 mg/kg dose of tenecteplase was low, so even though the recovery of patients was good, the early neurological improvement (NIHSS scores decrease) is not significant. Then, did a high dose of tenecteplase cause a higher risk of ICH? The current study of high dose of tenecteplase (0.4 mg/kg dose) did not increase the risk of ICH in patients. In addition, increasing the dose of tenecteplase may increase the chance of recanalization. Nevertheless, due to the lack of relevant data, it is impossible to draw a firm conclusion. The current evidence tends to support the use of 0.25 mg/kg of tenecteplase, which provided better early neurological improvement and less bleeding propensity than alteplase. Therefore, the latest protocol of RCT, the dose of tenecteplase is still 0.25 mg/kg.²¹ As mentioned earlier, further clinical randomized controlled studies cannot ignore the patients of high NIHSS score at baseline with high-dose tenecteplase vs alteplase in clinical controlled trials.

Present meta-analysis still has several limitations that should be noted. First, we performed this analysis based on limited data. Only four published RCTs with 1,390 patients were pooled to test the efficacy and safety of tenecteplase for AIS with different doses. Second, different RCT studies lacked uniform research indicators such as different doses of

tenecteplase and disease severity in patients in these trials. In particular, the NOR-TEST trial used high doses of tenecteplase and had a large sample size compared to other RCTs in relatively mild strokes. The data for all patients may be imbalanced and over-dominated by a single large trial with specific protocol conditions. Therefore, the NOR-TEST trial caused a certain degree of bias to the conclusions. However, we used different doses of subgroup analysis to reduce the bias. In addition, the NOR-TEST trial was a randomized, open-label, blinded endpoint trial from 13 centers, which is more better fit to the real situation. Third, only one RCT study was a Phase III clinical trial; hence, this meta-analysis lacked more comprehensive, multicenter, large-sample randomized controlled clinical trials. Finally, in NOR-TEST⁹ clinical study, the AIS patients were milder and more people were lost to follow up, which reduced the detection of outcome differences in intent-to-treat analysis.

Conclusion

The present meta-analysis indicated that tenecteplase provided better early neurological improvement than alteplase. The 0.25 mg/kg dose of tenecteplase subgroup especially showed better early neurological improvement and lower any ICH tendency than alteplase. In addition, in serious stroke at baseline subgroup, tenecteplase showed a lower risk of any ICH. These data provide guarantees for further researches on tenecteplase in AIS.

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Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

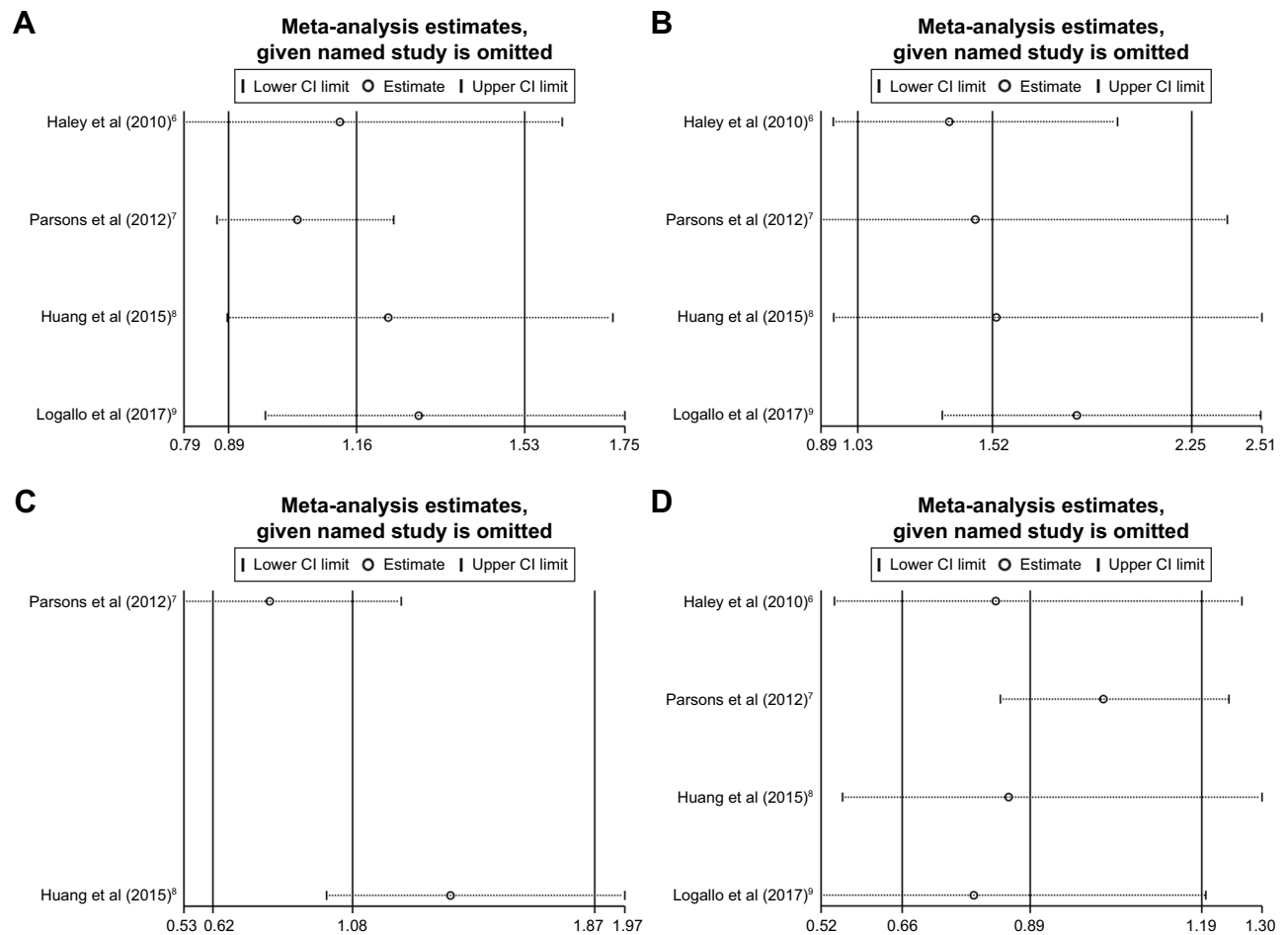


Figure S1 The sensitivity analysis showed that all of the consolidated results were stable.

Notes: (A) A sensitivity analysis of good functional outcome from four RCTs. (B) A sensitivity analysis of early neurological improvement from four RCTs. (C) A sensitivity analysis of recanalization within 24 h from two RCTs. (D) A sensitivity analysis of dependence from four RCTs.

Abbreviations: CI, confidence interval; RCTs, randomized controlled trials.

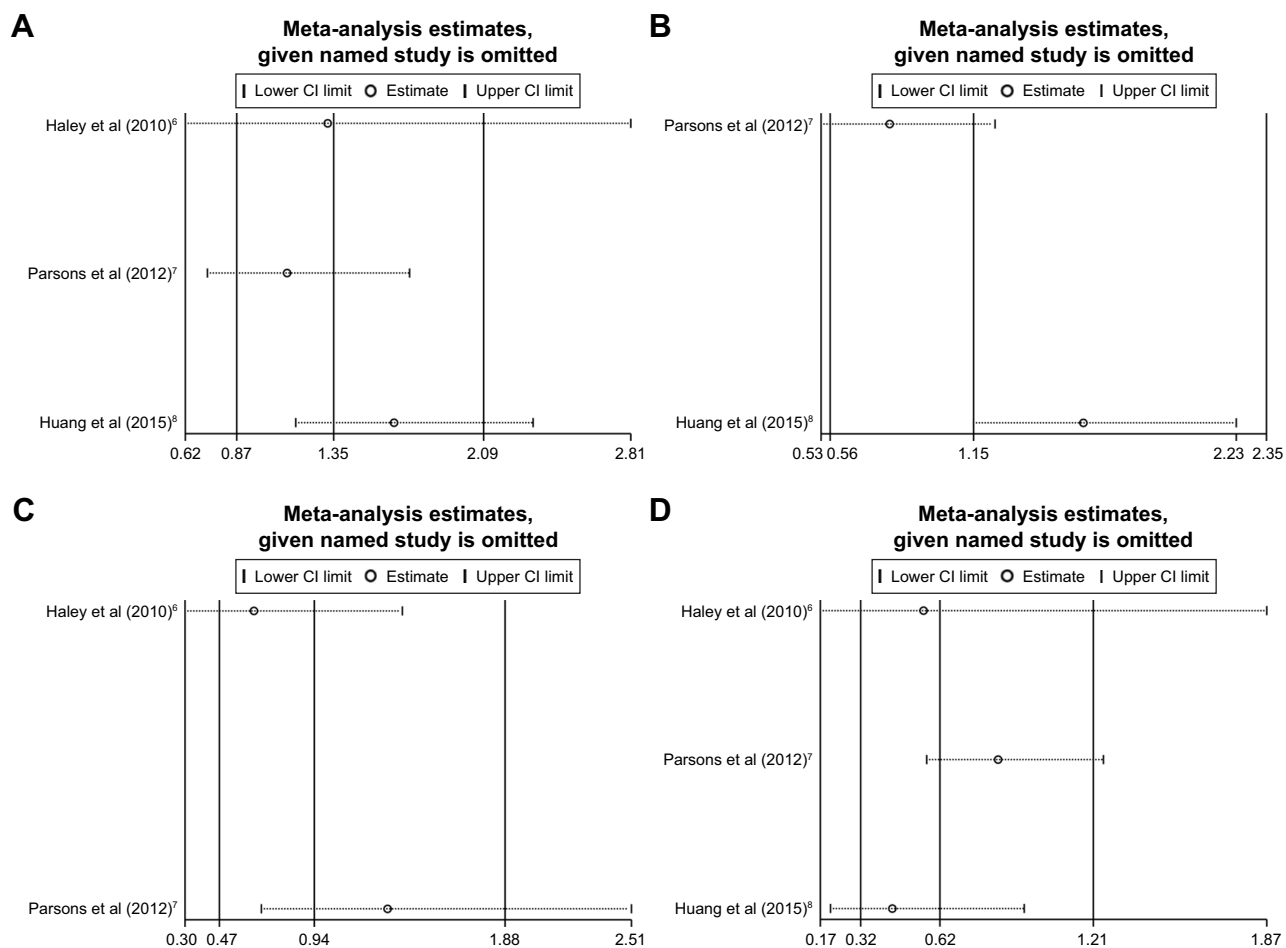


Figure S2 The sensitivity analysis showed that the different doses of tenecteplase subgroup results were stable.

Notes: (A) A sensitivity analysis of good functional outcome with 0.25 mg/kg subgroup from three RCTs. (B) A sensitivity analysis of recanalization with 0.25 mg/kg from two RCTs. (C) A sensitivity analysis of dependence with 0.1 mg/kg subgroup from two RCTs. (D) A sensitivity analysis of dependence with 0.25 mg/kg subgroup from three RCTs.

Abbreviations: CI, confidence interval; RCTs, randomized controlled trials.

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