Intravenous thrombolysis for acute ischemic stroke with extended time window

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Abstract

Background: Intravenous thrombolysis (IVT) is an effective way for treating acute ischemic stroke (AIS). However, its effects have not been established among AIS patients with unclear stroke symptoms or with stroke onset for >4.5 h.

Methods: We searched PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials and Google Scholar databases for randomized controlled trials that compared IVT (IVT group) and placebo or usual care (control group [CG]) in AIS patients with disease onset for >4.5 h. The outcomes of interest included the favorable functional outcome (defined as modified Rankin Scale [mRS] scores 0–1) at 90 days, the functional independence (defined as mRS scores 0–2) at 90 days, proportion of patients with symptomatic intracerebral hemorrhage (sICH) and death at 90 days. We assessed the risk of bias using the Cochrane tool. Pre-specified subgroup analyses were performed by age (≤70 years or >70 years), National Institute of Health Stroke Scale (NIHSS, ≤10 or >10) and time window (4.5–9.0 h or >9.0 h).

Results: Four trials involving 848 patients were eligible. The risk of bias of included trials was low. Patients in the IVT group were more likely to achieve favorable functional outcomes (45.8% *vs.* 36.7%; OR 1.48, 95% CI 1.12–1.96) and functional independence (63.8% *vs.* 55.7%; OR 1.43, 95% CI 1.08–1.90) at 90 days, but had higher risk of sICH (3.0% *vs.* 0.5%; OR 5.28, 95% CI 1.35–20.68) at 90 days than those in the CG. No significant difference in death at 90 days was found between the two groups (7.0% *vs.* 4.1%; OR 1.80; 95% CI 0.97–3.34).

Conclusions: Use of IVT in patients with extended time window may improve their functional outcomes at 90 days, although IVT may induce increased risk of sICH. Care of these patients should well balance the potential benefits and harms of IVT.

Keywords: Intravenous thrombolysis; Acute ischemic stroke; Time window; Meta-analysis

Introduction

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) represents an important treatment option for acute ischemic stroke (AIS).[1,2] Current international guidelines recommend that the optimal time for thrombolytic treatment of AIS is within 4.5 h of stroke onset.[3] However, previous trials have shown that only 5% to 25% of AIS patients receive rt-PA,[4] mainly due to the restriction to the 4.5 h treatment window.

Previous trials showed that stroke patients had significant imaging changes within a few hours of disease progression, but the imaging changes may also appear several days later, suggesting that the time window is not fixed but a dynamic evolution process under multiple conditions,[5] which could provide a potential time window for treatment. In addition, with the progress of modern testing technology, magnetic resonance imaging (MRI) can be used to evaluate the onset of stroke time. Its main imaging feature is acute ischemic lesion detected by diffusion-weighted imaging (DWI), but it is not visible in fluid attenuated inversion recovery (FLAIR) imaging,[6,7] which is likely to be a potentially safe and effective therapeutic time window for thrombolysis. Furthermore, the MRI perfusion weighted imaging (PWI)/DWI mismatch pattern has been studied as an effective marker of ischemic penumbra.[6-9] Therefore, for patients with PWI/DWI mismatch, it seems that early reperfusion can be achieved from the perfusion-diffusion MRI, and better recovery can be achieved.

Several trials have attempted to assess potentially viable brain tissue that allows further extension of the time window for intravenous thrombolytic therapy. For exam-

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ple, a placebo-controlled randomized trial suggested that for stroke patients treated at 3 to 6 h after onset, alteplase reperfusion was associated with less infarct growth, better neurofunctional prognosis and better functional prognosis.[10] In a randomized, placebo-controlled, double-blinded trial, patients were given 90 μg/kg desmoteplase, 125 μg/kg desmoteplase or placebo at a known time of stroke after the onset of symptoms, confirming that the intravenous treatment with desmoteplase did not show benefit from deaminase administered 3 to 9 h after the onset of stroke.[11] Therefore, this study aimed to assess the effects of IVT on stroke patients with extended time windows or with unclear symptom onset.

Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement to report this study.

Eligibility criteria

We included a study it was a randomized controlled trial (RCT) that compared the use of IVT (IVT group) and placebo or usual care (control group [CG]) among AIS patients with unclear symptom onset or extended time window (i.e., >4.5 h). The eligible study should also have reported the following outcomes: patients with mRS scores 0 to 1 and mRS scores 0 to 2 at 90 days, as well as incidence of symptomatic intracerebral hemorrhage (sICH) and death. We excluded a report if it was a trial without using IVT of alteplase; or an abstract, a review article and expert opinion paper.

The titles and abstracts of searched reports were initially screened independently by two reviewers to identify potentially eligible trials. Then, the full texts were further screened for final eligibility. Any disagreements were resolved by discussion or by consulting a third reviewer.

Search strategy

We searched the following databases from the inception up to April 2021: PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The MeSH terms and free texts regarding the keywords were used for developing the search strategy, including acute ischemic stroke OR stroke OR AIS, IV rt-PA OR intravenous lysis OR thrombolysis. We also searched Google Scholar and reviewed the reference lists of included trials. No language or region restrictions were applied.

Risk of bias assessment

The risk of bias of included trials was independently evaluated by two reviewers using the Cochrane Risk of Bias tool.[12] This tool contained seven items, including sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective reporting, and other biases. The overall assessment of included study was assessed as low, high, or unclear risk of bias.

Outcome measures

The outcomes included the favorable functional outcome (defined as mRS scores 0–1) at 90 days, functional independence (defined as mRS scores 0–2) at 90 days, proportion of patients with mRS scores between sICH and death at 90 days.

Data extraction

Two reviewers independently extracted data from eligible trials, and any disagreements were resolved through discussion. These included baseline characteristics of eligible trials, including author, year of publication, average age, sample size and comorbidities, such as diabetes and hypertension. The mean duration of extended window therapy in both treatment and control groups and doses of thrombolytic drugs were documented. The outcomes about National Institute of Health Stroke Scale (NIHSS), mRS scores 0 to 1, mRS scores 0 to 2, death and sICH after treatment were collected.

Data synthesis

Statistical analysis of the meta-analysis was performed using RevMan 5 software (Version 5.2, the Cochrane Collaboration). For dichotomous data, the random-effects Mantel-Haenszel method was used to estimate the odds ratio (OR) and 95% confidence interval (CI) Statistical heterogeneity was assessed by the chi-square test and I^2 statistics.[13]

Pre-specified subgroup analyses were conducted to evaluate the benefits for patients by age (≤70 years or >70 years), the NIHSS (≤10 or >10) and time window (4.5–9 h or >9 h). Funnel plots of mRS scores 0 to 1, mRS scores 0 to 2 and sICH at 90 days, and the incidence of death were used to test publication bias.

Results

Search results

The flow diagram was summarized [Figure 1]. A total of five trials were finally evaluated.[14-18] After reading the full text, only four RCTs[14,16-18] involving 848 patients met the inclusion criteria.

All the included trials were published in the English language between 2012 and 2019; 430 patients in the IVT group and 418 patients in the CG were included. The sample size of trials ranged from 6 to 254. IVT interventions were included in the four trials,[14,16-18] and all of include patients in the IVT group were treated with alteplase 0.9 mg/kg. The mean time window in the IVT group was 7.2 to 10.3 h and 7.3 to 10.4 h in the CG. The average NISHSS scores in the IVT group was 6 to 17 and 6 to 14.5 in the CG. Tables 1 and 2 showed baseline characteristics for the included trials.

The quality assessment

Table 3 summarizes the bias risk for the trial and this result shows a lower bias risk for all four included RCTs. Publication bias was assessed for mRS scores 0 to 1, mRS scores 0 to 2, sICH and death, all at 90 days. The graphs
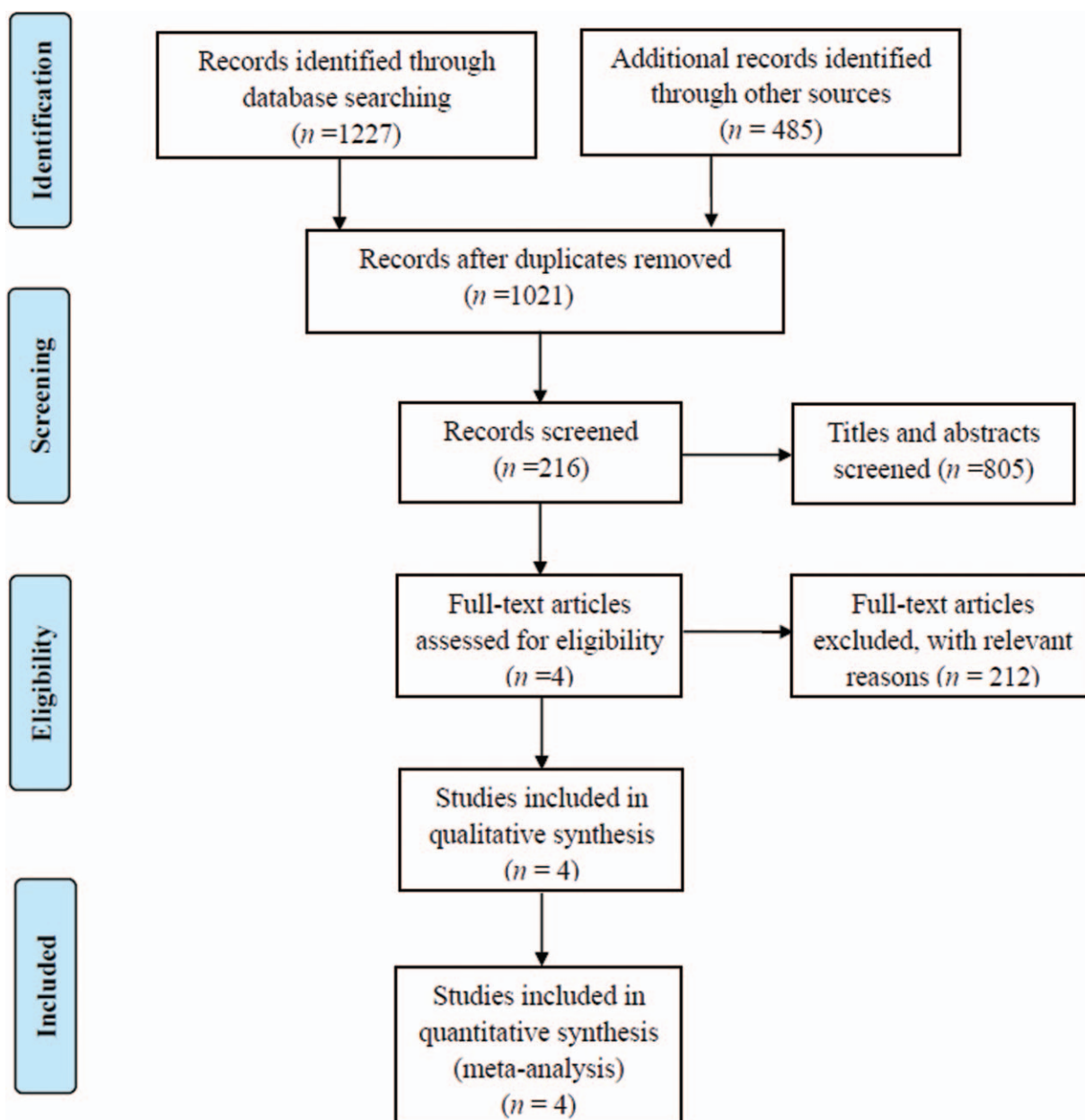
Figure 1: Flow diagram of search process of the studies on intravenous thrombolysis for acute ischemic stroke with extended time window.

were generally symmetric and showed a low likelihood of publication bias [Figure 2].

mRS scores 0 to 1 at 90 days

Three trials[16-18] reported mRS scores 0 to 1 at 90 days, including 192 of 419 patients (45.8%) in the IVT group and 151 of 412 patients (36.7%) in the CG. Meta-analysis of data regarding mRS 0 to 1 scores at 90 days found that significant difference between the IVT group and the CG (OR, 1.48; 95% CI, 1.12–1.96; $P = 0.006$) [Figure 3].

mRS scores 0 to 2 at 90 days

Four trials[14,16-18] reported relevant data regarding mRS 0 to 2 scores at 90 days, including 271 of 425 patients (63.8%) in the IVT group and 233 of 418 patients (55.7%) in the CG.

Meta-analysis of mRS 0 to 2 scores at 90 days found that there was a significant difference between the IVT group and the CG (OR, 1.43; 95% CI, 1.08–1.90; $P = 0.02$) [Figure 4].

Symptomatic intracerebral hemorrhage

Four trials[14,16-18] reported relevant data regarding the incidence of sICH, including 13 of 430 patients (3.0%) in the IVT group and 2 of 418 patients (0.5%) in the CG. Meta-analysis of sICH found that the IVT group had higher rates than the CG (OR, 5.28; 95% CI, 1.35–20.68; $P = 0.02$) [Figure 5].

Death

Four trials[14,16-18] reported relevant data regarding the incidence of death, including 30 of 430 patients (7.0%) in the

Table 1: Characteristics of included trials on comparison between intravenous thrombolysis and control group.

Studies	No. of Participants		Age (y)		Sex (M/F), n		Medical history, n		Median NIHSS	
	IG	CG	IG	CG	IG	CG	IG	CG	IG	CG
Michel et al 2012[14]	6	6	69.5	49	3/3	3/3	HTN: 4, DM: 1, AF: 2	HTN: 1, DM: 0, AF: 0	17.0	14.5
Thomalla et al 2018[16]	254	249	65.3	65.2	165/89	160/89	HTN: 135, DM: 43, AF: 30	HTN: 131, DM: 39, AF: 29	6.0	6.0
Ma et al 2019[17]	113	112	73.7	71.0	59/54	66/46	AF: 46	AF: 36	12.0	10.0
Ringleb et al 2019[18]	61	58	76	79	36/25	28/30	HTN: 42, DM: 16, AF: 14	HTN: 42, DM: 12, AF: 16	10.0	9.0

IG: intravenous thrombolysis group; No.: number; y: years; M: male; F: female; CG: Control group; HTN: Hypertension; DM: Diabetes mellitus; AF: Atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale.

Table 2: Characteristics of included trials on comparison between intravenous thrombolysis and control group.

Studies	Included clinical criteria	Intervention methods		Time windows	
		IG	CG	IG	CG
Michel et al 2012[14]	Patients with unknown stroke onset, age 18 to 80 years, NIHSS 6 to 22 at the start of treatment, hemispheric stroke syndrome, Pre-stroke mRS = 0 to 1 and Barthel index≥95, CT-to-treatment interval (<60 min), et al	IVT with alteplase 0.9mg/kg	placebo	564.0 min (9.4 h)	437.5 min (7.3 h)
Thomalla et al 2018[16]	Patients with clinical signs of acute stroke, ages 18 to 80 years, and had been able to carry out usual activities. Patients either recognized stroke symptoms on awakening or could not report the timing of the onset of symptoms (e.g., as a result of aphasia or confusion). Patient was last known to be well had to be more than 4.5 h, et al	IVT with alteplase 0.9 mg per kilogram of body weight (with 10% administered as a bolus and the remainder by infusion during a 60 min	placebo	10.3 h	10.4 h
Ma et al 2019[17]	Patients were at least 18 years; had excellent functional status before enrollment (defined by a score of <2 on the mRS 0 to 6, had a stroke with a clinical severity score at presentation of 4 to 26 on the NIHSS, on which scores range from 0 to 42, with higher scores indicating greater deficit, et al	IVT with alteplase 0.9 mg per kilogram of body weight [maximum, 90 mg], administered as a 10% bolus and 90% infusion over 1 h	placebo	432.0 min (7.2 h)	450.0 min (7.5 h)
Ringleb et al 2019[18]	Patients with AIS could be included if treatment could be started within 4.5 to 9 h after symptom onset. Patients who woke up with stroke symptoms could be included if the mean between time last seen well and symptom recognition was between these limits	IVT alteplase 0.9 mg/kg (maximum 90 mg), given as 10% of total dose bolus over 1 min, then the remaining 90% as an infusion over 60 min.	placebo	7.7 h	7.3 h

IG: intravenous thrombolysis group; CG: Control group; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography.

IVT group and 17 of 418 patients (4.1%) in the CG. Meta-analysis of the incidence of death found that there was no significant difference between the IVT group and the CG (OR, 1.80; 95% CI, 0.97–3.34; $P = 0.08$) [Figure 6].

Subgroup analysis

Subgroup analyses were performed to investigate the difference in effects by age (≤70 years or >70 years),

NIHSS (≤10 or >10), and time windows (4.5–9.0 or >9.0). Subgroup analyses showed that the effects were statistically significant in favorable outcomes when patients were at the age≤70 ($P = 0.010$), NIHSS≤10 ($P = 0.009$), or with time windows>9 h ($P = 0.010$). However, no significant differences were found in terms of sICH and death in terms of age, NIHSS, and time windows in the subgroup analysis [Table 4].

Table 3: Quality assessment of included randomized controlled trials on comparison between intravenous thrombolysis and control group.

Studies	Level of evidence	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Michel et al 2012[14]	I	Yes	Yes	Yes	No	Unclear	Unclear
Thomalla et al 2018[16]	I	Yes	Yes	Yes	Yes	Yes	Yes
Ma et al 2019[17]	I	Yes	No	No	Unclear	Unclear	Unclear
Ringleb et al 2019[18]	I	Yes	Yes	Yes	Yes	Yes	Unclear

Yes: (low risk of bias), No: (high risk of bias), Unclear:(unclear risk of bias).
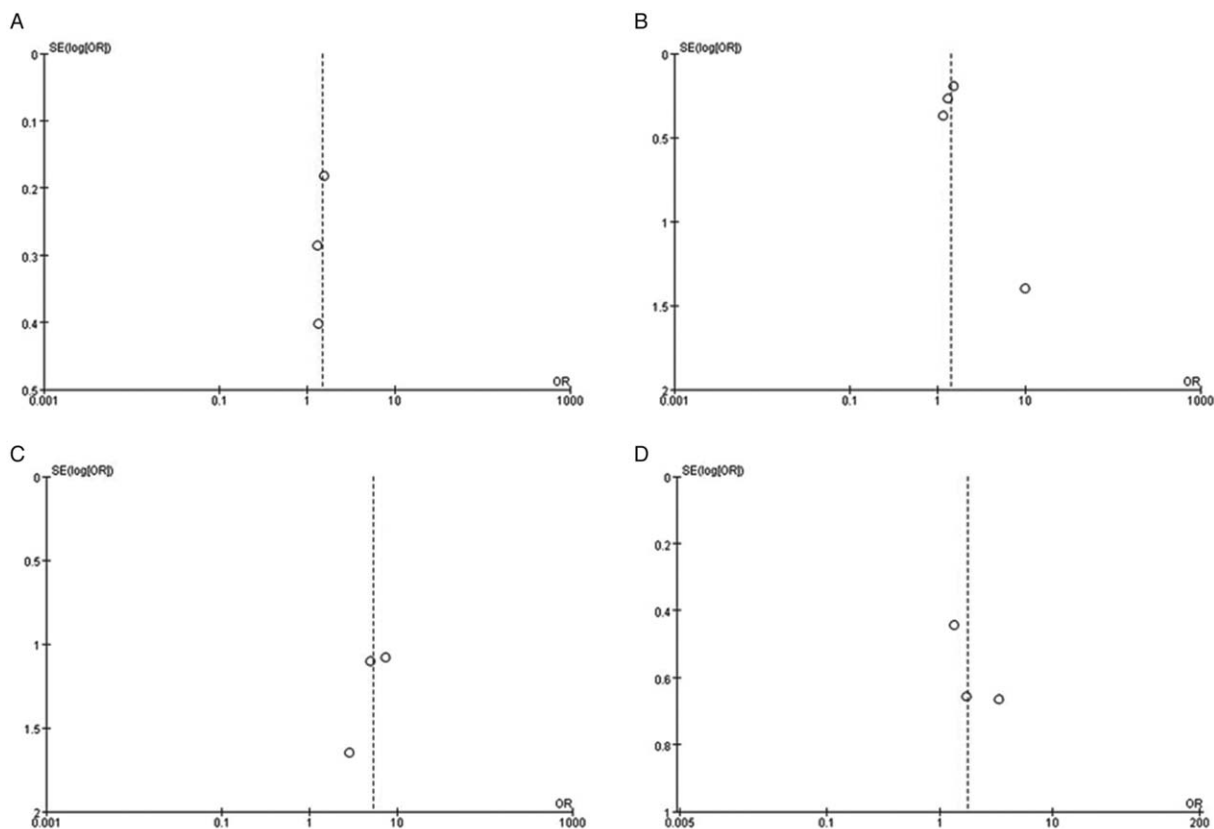
Figure 2: Publication bias of included trials on intravenous thrombolysis for acute ischemic stroke with extended time window. (A) Publication bias of mRS scores 0 to 1 at 90 days; (B) publication bias of mRS scores 0 to 2 at 90 days; (C) publication bias of sICH; (D) publication bias of death. mRS: modified Rankin scale; SE: standard error; OR: odds ratio.

Discussion

IVT was the main therapeutic method for AIS patients. However, the majority of AIS patients did not know the exact time of symptom onset or had already exceeded the optimal treatment window. Due to the narrow time window of traditional treatment, IVT is limited in its wide application.

As previous trials have reported, for acute ischemic lesions detected by DWI but not seen on FLAIR imaging, these results suggest that patients were likely to be within a safe and effective therapeutic time window for thrombolysis.[10,19] Some trials also confirmed that the PWI/DWI mismatch pattern has been used as a marker of ischemic penumbra, suggesting that up to 44% of patients still have a PWI/DWI mismatch even 18 h after symptom onset;[20,21] Therefore, the purpose of this systematic review and meta-analysis was to assess IVT in AIS patients with unclear stroke symptoms or >4.5 h after stroke and to improve functional outcome with CT perfusion or perfusion-diffusion MRI compared with placebo.

The results of this meta-analysis confirmed that IVT was beneficial for patients with stroke lasting >4.5 h, and this treatment method can effectively improve the clinical functional outcome of patients compared with placebo. Our findings were also consistent with recent individual
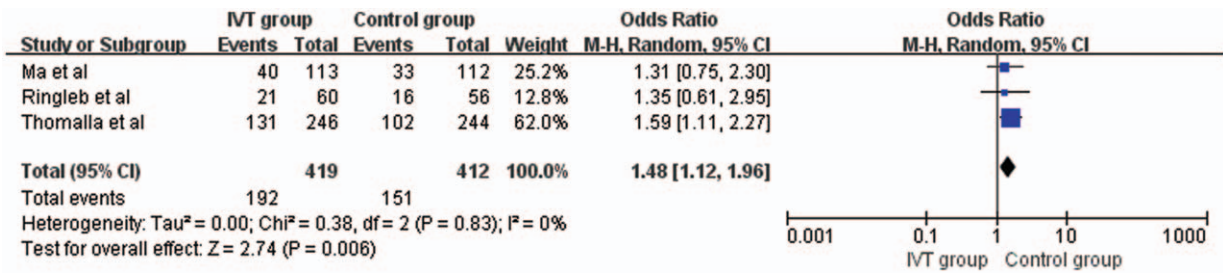
Study or Subgroup	IVT group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ma et al	40	113	33	112	25.2%	1.31 [0.75, 2.30]
Ringleb et al	21	60	16	56	12.8%	1.35 [0.61, 2.95]
Thomalla et al	131	246	102	244	62.0%	1.59 [1.11, 2.27]
Total (95% CI)		419		412	100.0%	1.48 [1.12, 1.96]
Total events	192		151			

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)

Figure 3: Funnel plots of mRS scores 0 to 1 at 90 days. IVT: Intravenous thrombolysis; mRS: modified Rankin scale; M-H: Mantel-Haenszel; CI: confidence interval.

Study or Subgroup	IVT group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ma et al	56	113	48	112	29.5%	1.31 [0.77, 2.22]
Michel et al	4	6	1	6	1.1%	10.00 [0.65, 154.40]
Ringleb et al	29	60	25	56	15.3%	1.16 [0.56, 2.41]
Thomalla et al	182	246	159	244	54.1%	1.52 [1.03, 2.24]
Total (95% CI)		425		418	100.0%	1.42 [1.07, 1.90]
Total events	271		233			

Heterogeneity: Tau² = 0.00; Chi² = 2.46, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)

Figure 4: Funnel plots of mRS scores 0 to 2 at 90 days. IVT: Intravenous thrombolysis; mRS: modified Rankin scale; M-H: Mantel-Haenszel; CI: confidence interval.
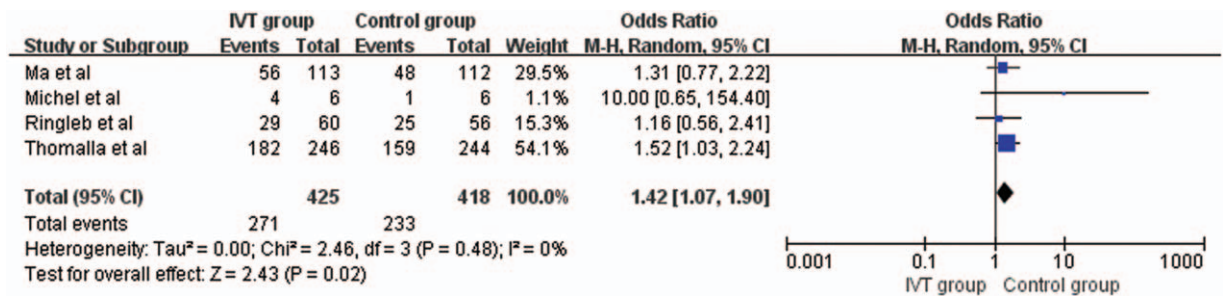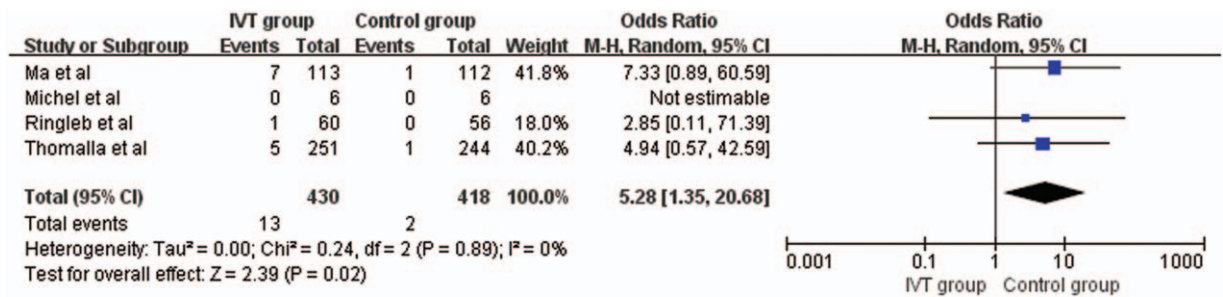
Study or Subgroup	IVT group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ma et al	7	113	1	112	41.8%	7.33 [0.89, 60.59]
Michel et al	0	6	0	6		Not estimable
Ringleb et al	1	60	0	56	18.0%	2.85 [0.11, 71.39]
Thomalla et al	5	251	1	244	40.2%	4.94 [0.57, 42.59]
Total (95% CI)		430		418	100.0%	5.28 [1.35, 20.68]
Total events	13		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)

Figure 5: Funnel plots of sICH. IVT: Intravenous thrombolysis; sICH: symptomatic intracerebral hemorrhage; M-H: Mantel-Haenszel; CI: confidence interval.

Study or Subgroup	IVT group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ma et al	13	113	10	112	52.6%	1.33 [0.56, 3.16]
Michel et al	0	6	0	6		Not estimable
Ringleb et al	7	60	4	56	24.0%	1.72 [0.47, 6.22]
Thomalla et al	10	251	3	244	23.4%	3.33 [0.91, 12.26]
Total (95% CI)		430		418	100.0%	1.75 [0.93, 3.29]
Total events	30		17			

Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%
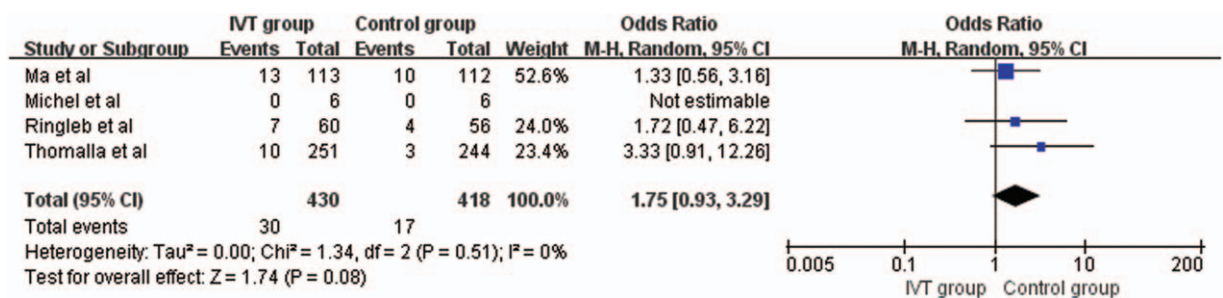Test for overall effect: Z = 1.74 (P = 0.08)

Figure 6: Funnel plots of Death. IVT: Intravenous thrombolysis; M-H: Mantel-Haenszel; CI: confidence interval.

patient data. WAKE-UP investigators[16] performed a multicenter trial in which all patients had ischemic lesions visible on MRI DWI, with no hypersignal in FLAIR, suggesting that stroke occurred within approximately 4.5 h, and these patients were randomly assigned to receive IVT therapy ($n = 254$) and to receive placebo ($n = 249$). The results demonstrated that in AIS patients with unknown onset time, IVT therapy by a mismatch between DWI and FLAIR areas could achieve significantly better functional outcomes. Michel et al[14] randomly assigned

Table 4: Clinical results of subgroup analyses on comparison between intravenous thrombolysis and control group.

Parameters	Studies	No. of participates IG	No. of participates CG	P	OR	95% CI	Heterogeneity P (I^2)	Model
mRS 0 to 1 at 90 days								
Age ≤70 years	1[16]	131/246	102/244	**0.010**	1.59	1.11–2.27	–	Random
Age >70 years	2[17,18]	61/173	49/168	0.230	1.32	0.84–2.09	0.96 (0)	Random
NIHSS ≤10	2[16,18]	152/306	118/300	**0.009**	1.54	1.11–2.13	0.71 (0)	Random
NIHSS >10	1[17]	40/113	33/112	0.340	1.31	0.75–2.30	–	Random
Time window 4.5 to 9.0 h	2[17,18]	61/173	49/168	0.230	1.32	0.84–2.09	0.96 (0)	Random
Time window >9.0 h	1[16]	131/246	102/244	**0.010**	1.59	1.11–2.27	–	Random
mRS 0 to 2 at 90 days								Random
Age ≤70 years	2[14,16]	186252	160/250	0.280	2.35	0.50–11.14	0.18 (44%)	Random
Age >70 years	2[17,18]	85/173	73/168	0.290	1.26	0.82–1.93	0.79 (0)	Random
NIHSS ≤10	2[16,18]	211/314	184/300	**0.040**	1.43	1.02–2.02	0.52 (0)	Random
NIHSS >10	2[14,17]	60/119	49/118	0.360	2.28	0.39–13.48	0.15 (51%)	Random
Time window 4.5 to 9.0 h	2[17,18]	85/173	73/168	0.290	1.26	0.82–1.93	0.79 (0)	Random
Time window >9.0 h	2[14,16]	57/260	58/255	0.540	2.01	0.21–19.03	0.09 (66%)	Random
sICH								Random
Age ≤70 years	2[14,16]	5/257	1/250	0.150	4.94	0.57–42.59	–	Random
Age >70 years	2[17,18]	8/173	1/168	0.060	5.52	0.94–32.27	0.63 (0)	Random
NIHSS ≤10	2[16,18]	6/311	1/300	0.120	4.17	0.70–24.97	0.78 (0)	Random
NIHSS >10	2[14,17]	7/119	1/118	0.060	7.33	0.89–60.59	–	Random
Time window 4.5 to 9.0 h	2[17,18]	8/173	1/168	0.060	5.52	0.94–32.27	0.63 (0)	Random
Time window >9.0 h	2[14,16]	5/257	1/250	0.150	4.94	0.57–42.59	–	Random
Death								Random
Age ≤70 years	2[14,16]	10/257	3/250	0.070	3.33	0.91–12.26	–	Random
Age >70 years	2[17,18]	20/173	14/168	0.320	1.44	0.70–2.95	0.74 (0)	Random
NIHSS ≤10	2[16,18]	17/311	7/300	0.060	2.38	0.95–5.95	0.48 (0)	Random
NIHSS >10	2[14,17]	13/119	10/118	0.520	1.33	0.56–3.16	–	Random
Time window 4.5 to 9.0 h	2[17,18]	20/173	14/168	0.320	1.44	0.70–2.95	0.74 (0)	Random
Time window >9.0 h	2[14,16]	10/257	3/250	0.070	3.33	0.91–12.26	–	Random

IG: intravenous thrombolysis group; CG: Control group; mRS: modified Rankin Scale; sICH: symptomatic intracerebral; NIHSS: National Institute of Health Stroke Scale; h: hour; OR: odds ratio; CI: confidence interval.

stroke patients occurring in the middle cerebral artery territory to alteplase venous thrombolysis, with an average last proof of well-being time point of 564 min (9.4 h), or placebo, and an average last proof of well-being of 437.5 min (7.3 h), and the results showed that thrombolytic therapy is feasible in patients with unknown stroke. Kate et al[15] reported patients were treated with tenecteplase at a median of 9.6 h after symptom onset with a range of 5.1 to 23.7 h and supported the feasibility of tenecteplase treatment in patients with 4 to 24 h of ischemic penumbral onset. In addition, we also performed subgroup analysis through different ages, NIHSS scores, and time windows and demonstrated that patients in the IVT group had better favorable functional outcomes at age ≤70 years, NIHSS ≤10, and time windows >9 h than the patients in the CG. Therefore, the above results may support the effective improvement of the clinical function of patients treated with IVT without knowing the onset of stroke symptoms or >4.5 h.

Previous studies have also reported higher rates of brain hemorrhage in patients treated with IVT therapy because it appears to be driven by bleeding that occurs primarily in patients with target mismatches. In this meta-analysis, we found that the incidence of sICH was also higher in the IVT

group than that in the CG. The results were similar to those obtained in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) of alteplase therapy initiated within 3 to 6 h after stroke,[10] and they were also consistent with the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial[22] and the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial[8] in extended time windows. Additionally, the analysis of subgroup results showed that the proportion of sICH in NIHSS >10 was also higher. However, Lees et al[23] performed a randomized thrombolytic trial and found that there was no convincing evidence to support the risk of severe or fatal symptomatic bleeding with late thrombolytic recanalization. Notably, the subgroup analysis in this meta-analysis also confirmed that the incidence of sICH was not statistically significant at 4.5 to 9 h or >9 h with IVT therapy. Currently, the main objection to late IVT therapy in AIS patients is that rt-PA may lack efficacy, which may be due to greater resistance to recanalization by ischemic tissue or occlusive arteries.

The major findings of this study did receive meaningful conclusions. The meta-analysis found that there was

significant difference in mRS scores 0 to 1 at 90 days (OR, 1.48; 95% CI, 1.12–1.96; $P = 0.006$) and mRS scores 0 to 2 at 90 days (OR,1.43; 95% CI, 1.08–1.90; $P = 0.02$) between the IVT group and the control group. However, we also confirmed that there were no significant differences in sICH in terms of age, NIHSS, and time windows in subgroup analysis. Additionally, there was no significant difference in the proportion of AIS patients who died between the IVT and control groups; however, it should be recognized that there was a clear overall beneficial effect due to the reduced incidence of death in the control group. In this meta-analysis, the absence of mortality benefit from IVT therapy was consistent with the trial of alteplase therapy 4.5 to 9 h after stroke onset.[17]

There were several limitations in this meta-analysis. First, the number of included studies and sample sizes was relatively small, showing the need for more careful and scientifically designed trials in the future. Second, in this meta-analysis, inconsistent mismatch estimation methods and clinical inclusion criteria were different in most of the trials, and central trials from different regions could potentially influence the results. For example, we reviewed the four included trials and found that only Michel et al[14] reported stroke patients in the middle cerebral artery region, while the remaining three trials did not know the exact circulatory region of stroke. Therefore, it is not clear whether patients with anterior circulation were included. Third, although the subgroup analysis was performed according to age, NIHSS, and time window, this analysis was limited by incomplete sample size, information, and data. Finally, we reviewed the four included trials and found that only Michel et al[14] reported stroke patients in the middle cerebral artery region, while the remaining three trials did not know the exact circulatory region of stroke. Therefore, it is not clear whether patients with anterior circulation were included. Fourth, the subgroup analysis of the heterogeneity about the population, such as sex, personal and/or family history of stroke, the large vessel occlusion and hypertension, and/or diabetes, were not performed due to sampling-size limitations. Thus, multicentral, large sample size trials require further discussion of the heterogeneity of different patients in the future.

Conclusion

This meta-analysis of the current literature indicates that although IVT therapy increased the incidence of sICH in stroke patients with unknown onset time or more than 4.5 h, extended time window therapy was still effective in improving functional outcomes at 90 days. Future trials with large sample sizes need to further confirm this result.

Conflicts of interest

None.

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