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. Current international guidelines recommend that the optimal time for thrombolytic treatment of AIS is within 4.5 h of stroke onset. Several trials have attempted to assess potentially viable brain tissue that allows further extension of the time window for intravenous thrombolysis therapy. For example, the time window for thrombolysis. Furthermore, the MRI perfusion weighted imaging (PWI)/diffusion weighted imaging (DWI) mismatch pattern has been studied as an effective marker of ischemic penumbra. 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.

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. 5.5%; OR 1.39, 95% CI 0.87–2.20).

Conclusions: Use of IVT in patients with extended time window may improve their functional outcomes at 90 days, although IVT may increase the 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). Current international guidelines recommend that the optimal time for thrombolytic treatment of AIS is within 4.5 h of stroke onset. However, previous trials have shown that only 5% to 25% of AIS patients receive rt-PA, 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, 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, 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. 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-
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 \( \mu \)g/kg desmoteplase, 125 \( \mu \)g/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 (\( \leq 70 \) years or >70 years), the NIHSS (\( \leq 10 \) 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 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 NIHSS 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
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 there was a 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 IVT group and 22 of 418 patients (5.3%) in the CG. Meta-analysis of death found that there was no significant difference between the IVT group and the CG (OR, 1.40; 95% CI, 0.82–2.42; P = 0.22) [Figure 6].
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; \( P = 0.08 \)). Subgroup analyses showed that the effects were statistically significant in favorable outcomes when patients were at the age \( \leq 70 \) (\( P = 0.010 \)), NIHSS \( \leq 10 \) (\( P = 0.009 \)), 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 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 |
|-------------------|---------------------|---------------|--------------|-------------------|--------------|
| Michel et al 2012 | IG 6                | 69.5 ± 49     | 3/3          | HTN: 4, DM: 1, AF: 2 | 17.0 ± 14.5  |
|                   | CG 4                | 65.3 ± 52     | 165/89       | HTN: 135, DM: 43, AF: 30 | 6.0 ± 6.0    |
| Thomalla et al 2018 | 254                | 73.7 ± 71     | 36/25        | HTN: 42, DM: 16, AF: 14 | 12.0 ± 10.0  |
| Ringleb et al 2019 | 61                 | 76 ± 79       | 28/30        | HTN: 46, DM: 10, 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 |
|---------------|---------------------------------------------------------------------------------------------|-----------------------------------------------|--------------|
| Michel et al 2012 | Patients with unknown stroke onset, age 18 to 80 years, NIHSS 6 to 22                        | IVT with alteplase 0.9 mg/kg                  | 564.0 min (9.4 h) |
|               | 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 | placebo                                       | 437.5 min (7.3 h) |
| Thomalla et al 2018 | 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) | 10.3 h        |
| Ma et al 2019    | 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 | 432.0 min (7.2 h) |
| Ringleb et al 2019 | 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 | 7.7 h         |

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

| 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).
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 \textit{et al} \(^{[14]}\) randomly assigned...
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. 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 Thrombolysis 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. 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

| Parameters | No. of participants | Studies | IG | CG | P | OR | 95% CI | Heterogeneity P (F) | Model |
|-----------|---------------------|---------|----|----|---|----|--------|-------------------|-------|
| **mRS 0 to 1 at 90 days** |
| Age ≤70 years | 116 | 131/246 | 102/244 | 0.010 | 1.59 | 1.11–2.27 | Random |
| Age >70 years | 217,18 | 63/173 | 49/168 | 0.230 | 1.32 | 0.84–2.09 | Random |
| NIHSS ≤10 | 216,18 | 152/306 | 118/300 | 0.009 | 1.54 | 1.11–2.13 | Random |
| NIHSS >10 | 117 | 40/113 | 33/112 | 0.340 | 1.31 | 0.75–2.30 | Random |
| Time window 4.5 to 9.0 h | 217,18 | 63/173 | 49/168 | 0.230 | 1.32 | 0.84–2.09 | Random |
| Time window >9.0 h | 116 | 131/246 | 102/244 | 0.010 | 1.59 | 1.11–2.27 | Random |
| **mRS 0 to 2 at 90 days** |
| Age ≤70 years | 214,16 | 186/252 | 160/250 | 0.280 | 2.35 | 0.50–11.14 | Random |
| Age >70 years | 217,18 | 85/173 | 73/168 | 0.290 | 1.26 | 0.82–1.93 | Random |
| NIHSS ≤10 | 216,18 | 211/314 | 184/300 | 0.040 | 1.43 | 1.02–2.02 | Random |
| NIHSS >10 | 214,17 | 60/119 | 49/118 | 0.360 | 2.28 | 0.39–13.48 | Random |
| Time window 4.5 to 9.0 h | 217,18 | 85/173 | 73/168 | 0.290 | 1.26 | 0.82–1.93 | Random |
| Time window >9.0 h | 214,16 | 57/260 | 58/255 | 0.340 | 2.01 | 0.21–19.03 | Random |
| **sICH** |
| Age ≤70 years | 214,16 | 5/257 | 1/250 | 0.150 | 4.94 | 0.57–42.59 | Random |
| Age >70 years | 217,18 | 8/173 | 1/168 | 0.060 | 5.52 | 0.94–32.27 | Random |
| NIHSS ≤10 | 216,18 | 6/311 | 1/300 | 0.120 | 4.17 | 0.70–24.97 | Random |
| NIHSS >10 | 214,17 | 7/119 | 1/118 | 0.060 | 7.33 | 0.89–60.59 | Random |
| Time window 4.5 to 9.0 h | 217,18 | 8/173 | 1/168 | 0.060 | 5.52 | 0.94–32.27 | Random |
| Time window >9.0 h | 214,16 | 5/257 | 1/250 | 0.150 | 4.94 | 0.57–42.59 | Random |
| **Death** |
| Age ≤70 years | 214,16 | 10/257 | 3/250 | 0.070 | 3.33 | 0.91–12.26 | Random |
| Age >70 years | 217,18 | 20/173 | 14/168 | 0.320 | 1.44 | 0.70–2.95 | Random |
| NIHSS ≤10 | 216,18 | 17/311 | 7/300 | 0.060 | 2.38 | 0.95–5.95 | Random |
| NIHSS >10 | 214,17 | 13/119 | 10/118 | 0.520 | 1.33 | 0.56–3.16 | Random |
| Time window 4.5 to 9.0 h | 217,18 | 20/173 | 14/168 | 0.320 | 1.44 | 0.70–2.95 | Random |
| Time window >9.0 h | 214,16 | 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.

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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.[137]

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.

**References**

1. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–282. doi: 10.1016/S0140-6736(07)60149-4.

2. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768–774. doi: 10.1016/S0140-6736(04)15692-4.

3. Emberson J, Lees KR, Lyden P, Blackwell I, Albers G, Bluhmki E, et al. Stroke Thrombolysis Trials’ Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5.

4. Khaja AM, Grotta JC. Extending thrombolysis for acute ischemic stroke. Lancet 2007;369:319–330. doi: 10.1016/S0140-6736(07)60154-8.

5. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and clinical implications. Front Neurol 2014;5:35. doi: 10.3389/fneur.2014.00035.

6. Thomalla G, Rossbach P, Rosenkranz M, Siemonsen S, Krützelmann M, Radiology 2010;257:782–792. doi: 10.1148/radiol.10100461.

7. Petkova M, Rodrigo S, Copenheim G, Touzé E, Mas JL, et al. MR imaging helps predict time from symptom onset in patients with acute stroke: implications for patients with unknown onset time. Neurology 2010;75:1040–1047. doi: 10.1212/\( \text{WNL.0b013e3181f39ab6} \).

8. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 h with selection by perfusion imaging. N Engl J Med 2018;378:708–718. doi: 10.1056/NEJMoa1713973.

9. Chemmanur T, Campbell BCV, Christensen S, Nagakane Y, Desmond PM, Bladin CF, et al. EPITHET Investigators. Ischemic diffusion lesion reversal is uncommon and rarely alters perfusion-diffusion mismatch. Neurology 2010;75:1040–1047. doi: 10.1212/\( \text{WNL.0b013e3181f39ab6} \).

10. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. EPITHET Investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Guide Thrombolysis Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008;7:299–309. doi: 10.1016/S1474-4422(08)70044-9.

11. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. IntraVenous desmoteplase in patients with acute ischemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol 2009;8:141–150. doi: 10.1016/S1474-4422(08)70205-9.

12. Hoggins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. 10.1136/bmj.d5928.

13. Kuczyński AM, Marzoughi S, Al-Sultan AS, Colbourne F, Menon BK, van Es AGCM, et al. Therapeutic hypothermia in acute ischemic stroke - a systematic review and meta-analysis. Curr Neurol Neurosci Rep 2020;20:13. doi: 10.1007/s11910-020-01029-3.

14. Michel P, Ntaios G, Reichhart M, Bogousslavsky J, Fieschi C, Kaste M, von Kummer R, Donnan G, Kaste M, Broderick JP, et al. ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768–774. doi: 10.1016/S0140-6736(04)15692-4.

15. Emberson J, Lees KR, Lyden P, Blackwell I, Albers G, Bluhmki E, et al. Stroke Thrombolysis Trials’ Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5.

16. Khaja AM, Grotta JC. Extending thrombolysis for acute ischemic stroke. Lancet 2007;369:319–330. doi: 10.1016/S0140-6736(07)60154-8.

17. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and clinical implications. Front Neurol 2014;5:35. doi: 10.3389/fneur.2014.00035.
resonance imaging-based patient selection. Int J Stroke 2019;14:483–490. doi: 10.1177/1747493019840938.

19. Cortijo E, García-Bermejo P, Calleja AI, Pérez-Fernández S, Gómez R, del Monte JM, et al. Intravenous thrombolysis in ischemic stroke with unknown onset using CT perfusion. Acta Neurol Scand 2014;129:178–183. doi: 10.1111/ane.12160.

20. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al. DEFUSE 2 Study Investigators. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol 2012;11:860–867. doi: 10.1016/S1474-4422(12)70203-X.

21. Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M, et al. Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI. Stroke 1999;30:2043–2052. doi: 10.1161/01.str.30.10.2043.

22. Nogueira RG, Jadhav AP, Haussen DC, Bonafo A, Budzik RF, Bhuva P, et al. DAWN Trial Investigators. Thrombectomy 6 to 24 h after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11–21. doi: 10.1056/NEJMoa1706442.

23. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695–1703. doi: 10.1016/S0140-6736(10)60491-6.

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