Efficacy and safety of thrombolytic therapy for stroke with unknown time of onset: a meta-analysis

Ruo-lin Zhu (vivian520179@126.com)
The First Affiliated Hospital of Anhui Medical University
Jing Xu
The First Affiliated Hospital of Anhui Medical University
Cheng-juan Xie
The First Affiliated Hospital of Anhui Medical University
Ying Hu
The First Affiliated Hospital of Anhui Medical University
Kai Wang
The First Affiliated Hospital of Anhui Medical University

Research Article

Keywords: Efficacy, safety, thrombolysis, unclear-onset stroke, meta-analysis

Posted Date: January 10th, 2019

DOI: https://doi.org/10.21203/rs.2.205/v1

Abstract

Background and Purpose: Recombinant tissue plasminogen activator (rt-PA) is one of the most effective therapies available for patients with known-onset stroke (KOS). Whether rt-PA treatment would improve functional outcomes in patients with stroke with unknown time of onset (UTOS) is undetermined. We aimed to systematically assess the efficacy and safety of thrombolysis for UTOS patients in this meta-analysis.

Methods: A systematic literature search of Medline, Embase and Cochrane Library was conducted. We considered the relevant data comparing thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients or thrombolyzed UTOS patients vs. thrombolyzed KOS patients. Treatment efficacy and safety were measured according to modified Rankin Scale scores of 0-2 (mRS 0-2), and the presence of spontaneous intracerebral hemorrhage (SICH) or mortality at 90 days respectively.

Results: A total of 12 studies with 3,084 patients from both clinical trial and database registries meeting the inclusion criteria were included in the meta-analysis. All the patients had an ischemic lesion that was assessed by imaging including computed tomography (CT) or magnetic resonance imaging (MRI). Among these studies, 7 compared the thrombolytic efficacy in thrombolyzed UTOS patients with that in non-thrombolyzed UTOS patients (mRS 0-2: odds ratio (OR)=1.65, 95% CI 1.19-2.27, P=0.002), and 8 studies compared thrombolyzed UTOS patients with thrombolyzed KOS patients (mRS 0-2: OR=0.87, 95% CI 0.66-1.15, P=0.26). The incidence of SICH was higher in thrombolyzed UTOS patients than in non-thrombolyzed UTOS patients (OR 3.07, 95% CI 1.12-8.43, P=0.03), but there was no difference between thrombolyzed UTOS patients and thrombolyzed KOS patients (OR=1.10, 95% CI 0.55-2.22, *P*=0.79) at 90 days. Mortality was not different between thrombolyzed UTOS patients and non-thrombolyzed UTOS patients (OR=1.14, 95% CI 0.46-2.83, *P*=0.77) or between thrombolyzed UTOS patients and thrombolyzed KOS patients (OR=0.68, 95% CI 0.40-1.16, *P*=0.15).

Conclusions: Compared with non-thrombolyzed patients, imaging-guided thrombolysis for UTOS patients had significantly favorable outcomes and more intracranial hemorrhage at 90 days.

Keywords: Efficacy, safety, thrombolysis, unclear-onset stroke, meta-analysis

Introduction

Acute ischemic stroke (AIS) is the fourth leading cause of mortality and accounted for 5.6% of deaths in the United States in 2007.[1] Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is the standard treatment for AIS within 4.5 hours of onset.[2] Previous studies have reported that despite an increased incidence of symptomatic intracerebral hemorrhage, patients with AIS treated with rt-PA within 4.5 hours of the onset of symptoms have significantly improved clinical outcomes at 90 days (no symptoms or nondisabling symptoms).[3, 4] However, the efficacy and safety of rt-PA thrombolysis have

not been established for cases in which this treatment is administered more than 4.5 hours after the onset of symptoms.[5]

Thrombolytic therapy is currently applied in only 10% of AIS patients, even though there is a high prevalence of stroke.[6] Approximately 25% of patients with AIS become aware of their neurological deficits upon awakening (“known-onset stroke”, KOS), while in another quarter of stroke patients, the time of symptom onset is not known (“stroke with an unknown time of onset”, UTOS), frequently because stroke symptoms are unwitnessed during daytime (“daytime-unwitnessed stroke”) or recognized merely when the patient wakes from sleeping (“wake-up stroke”).[2, 7, 8] These patients are ineligible for thrombolysis and are generally excluded from most trials of AIS treatments because of the uncertain time of symptom onset (“time window”); however, some studies have shown similar clinical features and imaging characteristics, such as Alberta Stroke Program Early Computed Tomography Scores (ASPECTS), between UTOS and KOS patients with an onset of symptoms within 3 hours.[9]

Several reports have shown differences in early computed tomography (CT) findings between UTOS and KOS patients, but no differences in all the other important baseline clinical, etiological and other neuroimaging findings have been described.[10-12] These findings imply that there may be a considerable number of UTOS patients who may benefit from thrombolytic therapy. Indeed, numerous articles have previously reported better clinical outcomes and similar side effects, including spontaneous intracerebral hemorrhage (SICH) and mortality, in UTOS patients treated with thrombolysis than in UTOS patients who were not treated with thrombolysis;[13, 14] however, such a correlation has not been found in other studies.[12, 15-17]

The latest attempt to include UTOS patients in an early acute stroke treatment trial was the MRI-based thrombolysis in wake-up stroke trial.[2] This trial was stopped after the recruitment of 503 of a planned 800 patients with a superiority of thrombolysis in the rt-PA group (mRS 0-1 in 53.3% patients) to the placebo group (mRS 0-1 in 41.8% patients) at 90 days, even though there were numerically more intracranial hemorrhages in patients in the rt-PA group than in patients in the placebo group at 90 days. However, no definitive conclusions have been reached to date. In this study, a comprehensive meta-analysis was performed to evaluate the efficacy and safety of thrombolytic therapy for the management of UTOS patients.

Methods

As this study is a meta-analysis, ethical approval was not required. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines.[18] The authors declare that all supporting data are available within the article and its online-only Data Supplement.

Search strategy

A digital computerized search of Medline (PubMed), EMBASE (Ovid), and the Cochrane Central Register was conducted on May 25, 2018 for controlled trials. A combination of the following terms was used: “stroke”, “stroke with unknown time of onset”, “unknown onset stroke”, “unclear-onset stroke”, “wake up stroke”, “stroke on awakening”, “acute ischaemic stroke” AND “recombinant tissue plasminogen activator”, “alteplase”, “rt-PA”, “thrombolysis”, “thrombolyzed”, “reperfusion”, and “recanalization”. There was a limitation with regard to language in that we only considered English publications, but the year of publication was not limited (online-only Data Supplement). In addition, the citations were reviewed to search for relevant original studies, and an electronic search alert was set to cover recent studies. Finally, references from prior systematic reviews/meta-analyses as well as abstracts from major stroke meetings were screened for related studies.

Inclusion and exclusion criteria

All relevant data from clinical trials or database registries comparing thrombolysis between UTOS patients who were treated with rt-PA thrombolysis (“thrombolyzed UTOS patients”) vs. UTOS patients who were not treated with rt-PA thrombolysis (“non-thrombolyzed UTOS patients”) or thrombolyzed UTOS patients vs. KOS patients who were treated with standard thrombolysis (“thrombolyzed KOS patients”) were eligible for inclusion. A study was included based on the following criteria: (1) The study included UTOS patients who underwent intravenous or intra-arterial thrombolysis with rt-PA; (2) A matching control group was defined as UTOS patients who were not treated with rt-PA thrombolysis or KOS patients who were treated with standard thrombolysis; (3) The efficacy of thrombolysis was measured by clinical outcomes as assessed by the modified Rankin Scale (mRS) at 90 days, and the safety was measured by the 3-month mortality and occurrence of SICH after thrombolysis; (4) Primary safety endpoints including SICH confirmed by imaging and/or death were reported; and (5) The study was a complete paper published in English. Studies that met the following criteria were excluded: (1) letters, case reports, reviews or preclinical studies; (2) studies describing a repeated analysis or duplicate data; and (3) studies lacking key information for further analysis.

Trial selection and data extraction

A total of 5,412 references were identified by the literature search. All the references were evaluated by 2 independent investigators (RL Zhu, J Xu), and the decision to include a study was made by consensus.

The full-text versions of all publications that potentially qualified for the review were scanned and assessed in detail based on the inclusion and exclusion criteria. From each study, we extracted the following using a predesigned extraction sheet: publication information (first author's name, publication year, and study design), population features (gender and mean age of participants, sample size, intervention and comparisons, histology, and primary endpoint), clinical characteristics (transient ischemic attack, atrial fibrillation, coronary heart disease, hypertension, diabetes mellitus, NIH Stroke Scale [NIHSS], and admission time after the first abnormality found [AT]), and endpoints (symptomatic intracranial hemorrhage and/or death).

Statistical analysis

We used the DerSimonian and Laird random-effects models to conduct this meta-analysis for dichotomous data. Comparisons were made between thrombolyzed UTOS patients and non-thrombolyzed UTOS patients or thrombolyzed UTOS patients and thrombolyzed KOS patients. The pooled odds ratios (ORs) and 95% confidence intervals (95% CI) of mRS scores of 0-2 for a response to rt-PA thrombolysis were estimated, and the incidences of SICH and death after thrombolysis treatment were also assessed for each study. The heterogeneity across studies was evaluate using the chi-squared test and qualified by I^2 statistics. I^2 values were calculated to assess the heterogeneity effects caused by a proportion of between-study variability, and a statistic of 0% indicated no observed heterogeneity, while a larger value indicated increasing heterogeneity. The likelihood of publication bias was assessed graphically by generating a funnel plot. All of the statistical analyses were performed using Review Manager (RevMan, version 5.3.5, Nordic Cochrane Center, Copenhagen, Denmark). Two-sided P values of 0.05 were considered statistically significant.

Results

Search results and methodological assessment

The flowchart of the literature search is shown in Figure 1. From 10,362 titles and/or abstracts, 286 articles were selected for full-text review after duplicates were removed, and 85 studies were variable after screening using the predefined inclusion and exclusion criteria. Finally, a total of 12 studies published between 2008 and 2018 with 3,084 patients were included in the meta-analysis.[2, 12-17, 19-23] All the patients had an ischemic lesion that was visible on imaging including noncontrast-enhanced computed tomography (NCCT), computed tomography perfusion imaging (CTP), or magnetic resonance imaging (MRI). The clinical and imaging criteria for the use of thrombolytic treatment for patients in individual studies is demonstrated in Table.

Atrial fibrillation was present at baseline in 11.6-60.0% of the patients, and previous stroke was diagnosed in 6.9-40.8% of the patients. Four studies were retrospective trials,[12-14, 21] the remaining 8 were prospective studies,[2, 15-17, 19, 20, 22, 23] and one trial was stopped early due to funding cessation without an interim analysis of trial data.[2] Among these articles, the efficacy of thrombolytic treatment was compared between thrombolyzed UTOS patients and non-thrombolyzed UTOS patients in 7 studies,[2, 12-17] while the efficacy of thrombolytic treatment for thrombolyzed UTOS patients was compared with that of thrombolyzed KOS patients in 8 studies.[13, 15-17, 19, 21-23] (Table I in the online-only Data Supplement).

To guide our methodological assessment of the included studies, we adopted Hayden's criteria for a quality assessment of prognostic studies to evaluate the potential bias of the included studies.[24] The results revealed that all 12 trials had adequate randomization. Two studies were considered low quality, with a score of less than 7, and the other 9 studies were considered moderate or high quality (Table II in the online-only Data Supplement).

Efficacy analysis

mRS scores of 0-2 were used to measure the efficacy of thrombolysis for treating UTOS patients. Seven studies including 1,088 patients examined the efficacy of rt-PA thrombolysis based on mRS 0-2 for thrombolyzed UTOS patients compared with non-thrombolyzed UTOS patients. A favorable outcome (mRS 0-2) was obtained in 52.56% (36.76-72.05%) of thrombolyzed UTOS patients and 41.07% (14.29-63.05%) of non-thrombolyzed UTOS patients. The overall analysis demonstrated that the pooled OR was 1.65 (95% CI 1.19-2.27, P=0.002), and heterogeneity testing revealed that I^2 was 17% (P_{hetero}=0.30) (Figure 2A and Figure I-A in the online-only Data Supplement).

Eight studies including 1,759 patients evaluated the efficacy of rt-PA thrombolysis according to mRS 0-2 for UTOS patients compared with KOS patients. A favorable outcome was obtained in 44.44% (32.14-62.96%) of thrombolyzed UTOS patients and 48.54% (25.00-67.13%) of thrombolyzed KOS patients. The meta-analysis resulted in a pooled OR of 0.87 (95% CI 0.66-1.15, P=0.33) with low heterogeneity (I^2=0%, P_{hetero}=0.81) (Figure 2B and Figure I-B in the online-only Data Supplement).

Safety analysis

Seven studies including 1,080 patients were analyzed to evaluate the occurrence of SICH after thrombolytic treatment in thrombolyzed UTOS patients and non-thrombolyzed UTOS patients in this

meta-analysis. The prevalence of SICH was significantly higher in UTOS patients after rt-PA thrombolytic treatment than in UTOS patients not treated with thrombolysis (OR 3.07, 95% CI 1.12-8.43, P=0.03). There was a very low degree of heterogeneity among these studies (I^2=0%, P_{hetero}=0.62) (Figure 3A). The incidence of SICH within 90 days was reported in 9 studies in both thrombolyzed UTOS patients and thrombolyzed KOS patients after rt-PA thrombolysis. None of the studies showed a significant difference in the incidence of SICH within 90 days between UTOS and KOS patients after thrombolysis (OR=1.04, 95% CI 0.52-2.07, *P*=0.92), and the heterogeneity across the studies was very low (I^2=0%, P_{hetero}=0.99) (Figure 3B).

Six studies reported mortality within 90 days. None of the studies revealed a significant difference between UTOS patients and KOS patients after rt-PA thrombolysis (OR=1.14, 95% CI 0.67-1.92, *P*=0.64), and there was a moderate degree of heterogeneity among these studies (I^2=48%, P_{hetero}=0.09) (Figure 3C). Similarly, in 6 studies that reported mortality after thrombolysis, there was no difference between UTOS patients and KOS patients (OR=0.62, 95% CI 0.37-1.05, *P*=0.07) and a low degree of heterogeneity among the included studies (I^2=0%, P_{hetero}=0.46) (Figure 3D).

Discussion

Standard thrombolysis has been well demonstrated to improve the rate of favorable outcomes in AIS patients within a restricted time window.[25, 26] However, no specific therapeutic options are available for one-quarter of AIS patients (UTOS patients) since the time window of stroke in these patients cannot be determined. AIS patients have wide variations in the severity and range of symptoms, and consequently, they have diverse functional outcomes. In UTOS patients, even though the symptoms are unwitnessed during daytime or occur during sleep, these patients might still have salvageable brain tissue despite the extended time window. Thrombolytic treatment for these patients, based on strict imaging guidance, initiated up to more than 10 hours after the last known neurological normal time appeared to be safe and resulted in better functional outcomes than placebo, according to data from the WAKE-UP trial.[2] Therefore, the onset time of stroke does not provide decisive information for the use of thrombolytic therapy for UTOS patients.[20]

To the authors' knowledge, this is the first systematic meta-analysis to comprehensively evaluate the efficacy and safety of rt-PA thrombolysis for UTOS patients compared to patients who are not treated with thrombolysis and to thrombolyzed KOS patients. The results presented here suggest that rt-PA thrombolysis may lead to more favorable outcomes in UTOS patients than in non-thrombolyzed UTOS patients. In addition, treatment with rt-PA may have a similar efficacy in UTOS patients to that of standard thrombolysis in KOS patients within a restricted time window. The functional outcomes at 90 days based on mRS scores of 0-2 were more favorable among UTOS patients who received rt-PA than in patients who

received placebo treatment. With respect to safety, rt-PA thrombolysis resulted in SICH at 90 days slightly more frequently in UTOS patients than in non-thrombolyzed patients. More importantly, the rates of SICH and mortality in patients treated with rt-PA did not differ from those in patients treated with standard thrombolysis within the restrictive time window of 4.5 hours. These findings suggest that, guided by imaging, more UTOS patients can be effectively and safely treated with thrombolysis, which was a comparable result to those of previous studies.[2, 13, 14] Considering that UTOS patients have been traditionally excluded from thrombolysis, our findings have important implications in clinical practice.

There were no common clinical or imaging inclusion criteria among the 12 included articles. The time windows of thrombolysis ranged widely with different intervals from the last seen normal time (LSN) and the first found abnormality time (FAT), while the imaging criteria included in the meta-analysis varied from NCCT alone, to CTP, MRI or a combination of the two. The variety of inclusion criteria inevitably led to potential heterogeneity that cannot be demonstrated in the heterogeneity detection. Additionally, the difference in definitions of SICH resulted in a varied occurrence of SICH, which may also contribute to the heterogeneity in this meta-analysis. Finally, among the included studies in the meta-analysis, one study (WAKE-UP trial) enrolled fewer patients than anticipated before discontinuation of funding.[2] Since a trend toward a higher rate of death in the alteplase group may have become significant with a larger sample size, the lesser sample size might limit the interpretation of the findings on the safety of thrombolysis. Therefore, the data should be interpreted carefully, even though low heterogeneity was obtained in the efficacy and safety analysis.

Although this study shows the potential benefits of rt-PA treatment for UTOS patients, it is not without limitations. First, only 12 studies met the predefined inclusion criteria and were included in the final meta-analysis. In addition, these included studies were almost all single-center studies with a small number of patients, and only 2 multicenter studies were included.[2, 21] However, after a comprehensive literature search covering 3 databases was performed and eligible studies were selected by two different investigators according to strict inclusion criteria, most of the included studies had moderate-to-high quality. Therefore, we believe that it is reasonable to draw conclusions from this meta-analysis. Second, since the UTOS patients selected for thrombolytic treatment had more disabling strokes than did untreated patients, there was inevitably selection bias in assessing the efficacy and safety of rt-PA for UTOS patients. Third, combined treatment with rt-PA and urokinase was used in a proportion of the enrolled patients in one early study.[21] Additionally, the patients were administered intra-arterial thrombolysis or a combined treatment with both intravenous and intra-arterial thrombolysis in 3 studies.[13, 14, 21] Due to the insufficient number of related studies to evaluate the efficacy or safety between intravenous and intra-arterial thrombolysis, subgroup analysis was not conducted in this meta-analysis. Therefore, the heterogeneity of this combined therapy may have introduced potential bias.

In summary, our meta-analysis evaluated the efficacy and safety of rt-PA for UTOS patients, and the results demonstrated that patients treated with rt-PA for UTOS had significantly more favorable outcomes and more intracranial hemorrhage at 90 days than patients who were not treated with thrombolytic treatment or KOS patients who were treated with standard thrombolysis. The possibility of thrombolytic treatment should be actively considered for UTOS patients as early as possible. Finally, due to the potential heterogeneity among the included studies, the results of this analysis should be confirmed with new and larger studies in the future.

Declarations

Disclosures

The authors declare no conflicts of interest. Ruo-lin Zhu and Kai Wang contributed to the design of the study. Ruo-lin Zhu searched the databases and wrote the paper. Ruo-lin Zhu and Jing Xu selected the eligible studies. Cheng-juan Xie and Ying Hu participated in helpful discussion. Jing Xu conducted the statistical analyses. All authors revised and approved the final version of the article.

Sources of Funding

The study was funded by the National Basic Research Program of China (973 Program, Grant No. 2015CB856405), the National Natural Science Foundation of China (Grant No. 91432301) and the National Natural Science Foundation of China (Grant No. 31571149).

References

1. Roger VL, Go AS, Lloydjones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update. *Circulation*. 2011;125:e18-e209
2. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. Mri-guided thrombolysis for stroke with unknown time of onset. *N. Engl. J. Med.* 2018
3. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N. Engl. J. Med.* 2008;359:1317-1329
4. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes. *A Pooled Analysis of 9 Trials*. 2016;47:2373-2379
5. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N. Engl. J. Med.* 2008;359:1317-1329
6. Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at get with the guidelines–stroke hospitals. *Circ. Cardiovasc. Qual. Outcomes*. 2013;6:543-549

7. Chaturvedi S, Adams HP, Woolson RF. Circadian variation in ischemic stroke subtypes. *Stroke*. 1999;30:1792-1795
8. Mackey J, Kleindorfer D, Sucharew H, Moomaw CJ, Kissela BM, Alwell K, et al. Population-based study of wake-up strokes. *Neurology*. 2011;76:1662-1667
9. Barreto AD, Martinschild S, Hallevi H, Morales MM, Abraham AT, Gonzales NR, et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke*. 2009;40:827-832
10. Fink JN, Kumar S, Horkan C, Linfante I, Selim MH, Caplan LR, et al. The stroke patient who woke up: Clinical and radiological features, including diffusion and perfusion mri. *Stroke*. 2002;33:988-993
11. Todo K, Moriwaki H, Saito K, Tanaka M, Oe H, Naritomi H. Early ct findings in unknown-onset and wake-up strokes. *Cerebrovasc. Dis.* 2006;21:367-371
12. Breuer L, Schellinger PD, Huttner HB, Halwachs R, Engelhorn T, Doerfler A, et al. Feasibility and safety of magnetic resonance imaging-based thrombolysis in patients with stroke on awakening: Initial single-centre experience. *Int. J. Stroke*. 2010;5:68-73
13. Barreto AD, Martin-Schild S, Hallevi H, Morales MM, Abraham AT, Gonzales NR, et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke*. 2009;40:827-832
14. Kim JT, Park MS, Nam TS, Choi SM, Kim BC, Kim MK, et al. Thrombolysis as a factor associated with favorable outcomes in patients with unclear-onset stroke. *Eur. J. Neurol.* 2011;18:988-994
15. Anaissie JE, Monlezun DJ, Siegler JE, Waring ED, Dowell LN, Samai AA, et al. Intravenous tissue plasminogen activator for wake-up stroke: A propensity score-matched analysis. *J. Stroke Cerebrovasc. Dis.* 2016;25:2603-2609
16. Manawadu D, Bodla S, Jarosz J, Keep J, Kalra L. A case-controlled comparison of thrombolysis outcomes between wake-up and known time of onset ischemic stroke patients. *Stroke*. 2013;44:2226-2231
17. Roveri L, La Gioia S, Ghidinelli C, Anzalone N, De Filippis C, Comi G. Wake-up stroke within 3 hours of symptom awareness: Imaging and clinical features compared to standard recombinant tissue plasminogen activator treated stroke. *J. Stroke Cerebrovasc. Dis.* 2013;22:703-708
18. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: The prisma-ipd statement. *JAMA*. 2015;313:1657-1665
19. Aoki J, Kimura K, Shibazaki K, Sakamoto Y. Negative fluid-attenuated inversion recovery-based intravenous thrombolysis using recombinant tissue plasminogen activator in acute stroke patients with unknown onset time. *Cerebrovasc Dis Extra*. 2013;3:35-45
20. Bai Q, Zhao Z, Fu P, Sui H, Xie X, Chen J, et al. Clinical outcomes of fast mri-based trombolysis in wake-up strokes compared to superacute ischemic strokes within 12 hours. *Neurol. Res.* 2013;35:492-497
21. Cho A-H, Sohn S-I, Han M-K, Lee DH, Kim JS, Choi CG, et al. Safety and efficacy of mri-based thrombolysis in unclear-onset stroke. *Cerebrovasc. Dis.* 2008;25:572-579

22. Ebinger M, Scheitz JF, Kufner A, Endres M, Fiebach JB, Nolte CH. Mri-based intravenous thrombolysis in stroke patients with unknown time of symptom onset. *Eur. J. Neurol.* 2012;19:348-350
23. Morelli N, Rota E, Immovilli P, Cosottini M, Giorgi-Pierfranceschi M, Magnacavallo A, et al. Computed tomography perfusion-based thrombolysis in wake-up stroke. *Intern. Emerg. Med.* 2015;10:977-984
24. A Hayden J, Côté P, Bombardier C. *Evaluation of the quality of prognosis studies in systematic reviews*. 2006.
25. Disorders NIoN, Group Sr-PSS. Tissue plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* 1999;341:1581-1587
26. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *J. Vasc. Surg.* 2008;48:1634-1635

Tables

Table. The clinical and imaging criteria for thrombolysis in UTOS patients.

Study	Clinical criteria	Time window	Imaging criteria
Anaissie, 2016	Neurologically normal before going to sleep and deficits upon awakening for >3 h; had been treated with IV tPA; no contraindications to IV tPA.	UTOS: LSN >3 h; KOS: 0-4.5 h.	NCCT: Hypodensity <1/3 MCA territory.
Aoki, 2013	Stroke with unknown onset time when the 'last known normal time' was not consistent with AT.	UTOS: FAT 3-12 h. KOS: <3 h.	MRI: Negative FLAIR.
Bai, 2013	Age between 18-80 years; acute ischemic stroke; neurological symptoms and/or physical examination findings >1 hour; NIHSS 4-24.	UTOS: not reported; KOS: <12 h.	NCCT: Absence of, or early stage cerebral ischemic changes; MRI: DWI lesion <33% MCA territory.
Barreto, 2009	Neurologically normal before going to sleep and witnessed with deficits on awakening.	UTOS: LSN <3 h; KOS: <3 h.	NCCT: Hypodensity <1/3 MCA territory.
Breuer, 2010	Stroke occurred during sleep; became aware of the neurological symptoms upon waking.	UTOS: FAT <6 h.	NCCT: Hypodensity <1/3 MCA territory; MRI: DWI lesion <33% MCA territory and PWI-DWI mismatch.
Cho, 2008	Wake-up strokes or unwitnessed strokes.	UTOS: LSN >3 h and FAT <6 h; KOS: 0-3 h.	NCCT: Hypodensity <1/3 MCA territory; MRI: PWI-DWI mismatch larger than 20%.
Ebinger, 2012	Suspected stroke or TIA within 24 hours from symptom onset.	UTOS: LSN >4.5 h; KOS: <3 h.	MRI: PWI-DWI mismatch larger than 20%.
Kim, 2011	Acute ischaemic stroke; baseline NIHSS >4; unclear-onset stroke.	UTOS: FAT <3 h.	NCCT: early infarct signs <1/3 MCA territory; MRA/MRI: a large MTT delay in PWI; DWI lesions <33% MCA territory; and catheter-accessible MCA on MRA.
Manawadu, 2013	No neurological deficits when last seen awake; NIHSS ≥5; no absolute contraindications to rt-PA.	UTOS: LSN >4.5 h or <12 h KOS: 0-4.5 h.	NCCT: early ischemic changes <1/3 MCA territory;
Morelli,	ECASS-3 inclusion/exclusion criteria.	UTOS:	NCCT: early ischemia signs <1/3

2015		FAT <3 h; KOS: 0-4.5 h.	MCA territory; CTP: ischemic core <70 ml MCA; ischemic penumbra >20%.
Roveri, 2013	ECASS-3 inclusion/exclusion criteria.	UTOS: FAT <4.5 h; KOS: 0-4.5 h.	NCCT: ASPECTS scoring.
Thomalla, 2018	Clinical signs of acute stroke; 18-80 years of age; able to carry out usual activities before the stroke.	UTOS: LSN >4.5 h.	MRI: DWI-FLAIR mismatch.

LSN, last seen normal time; FAT, the first found abnormality time; NCCT, noncontrast-enhanced computed tomography; CTP, computed tomography perfusion imaging; MRI, magnetic resonance imaging; PWI, perfusion-weighted imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MTT, mean transit time; MAC, middle cerebral artery; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ECASS-3, European Cooperative Acute Stroke Study III.

Figures

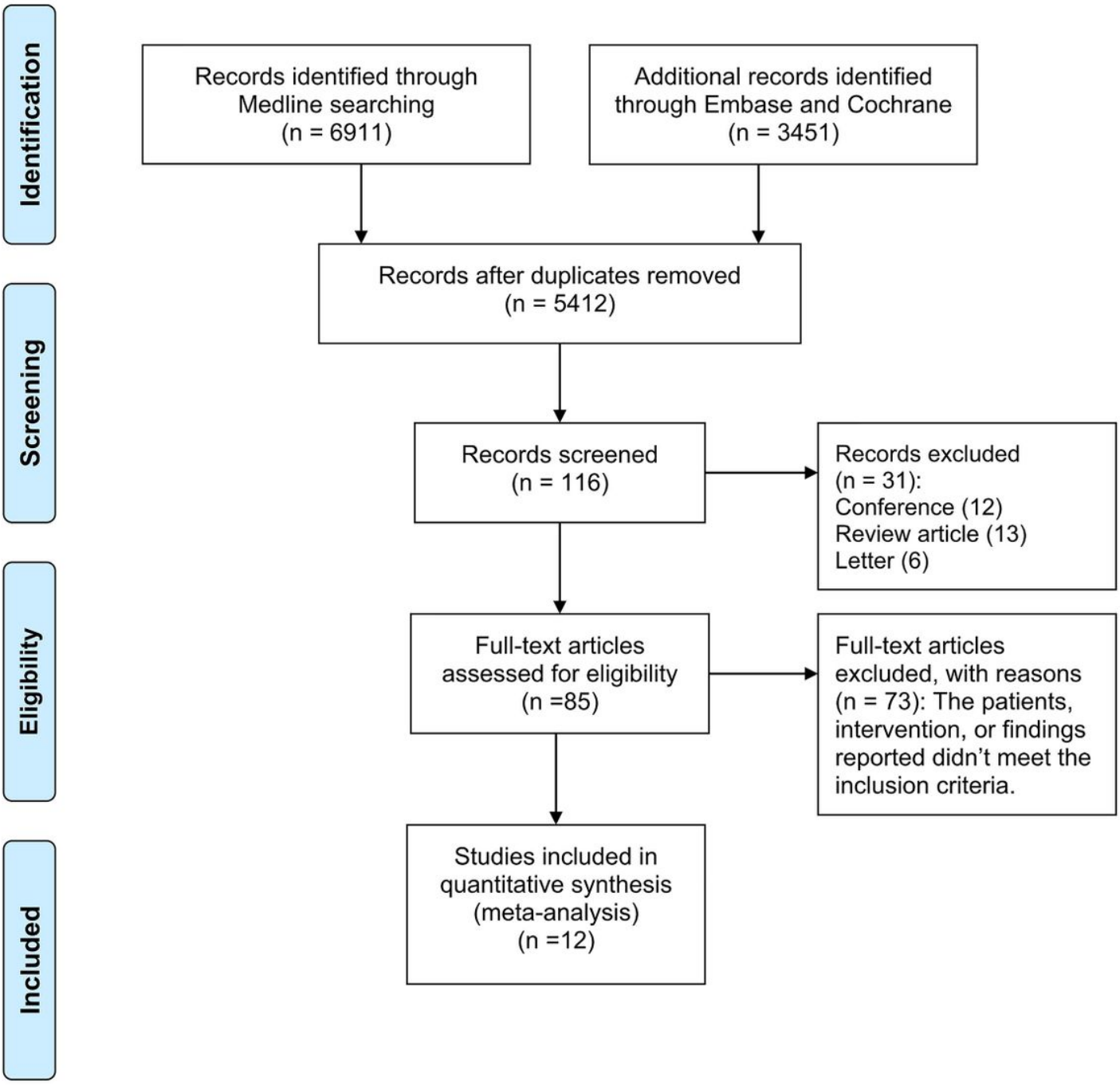

Figure 1

Flowchart of the study selection.

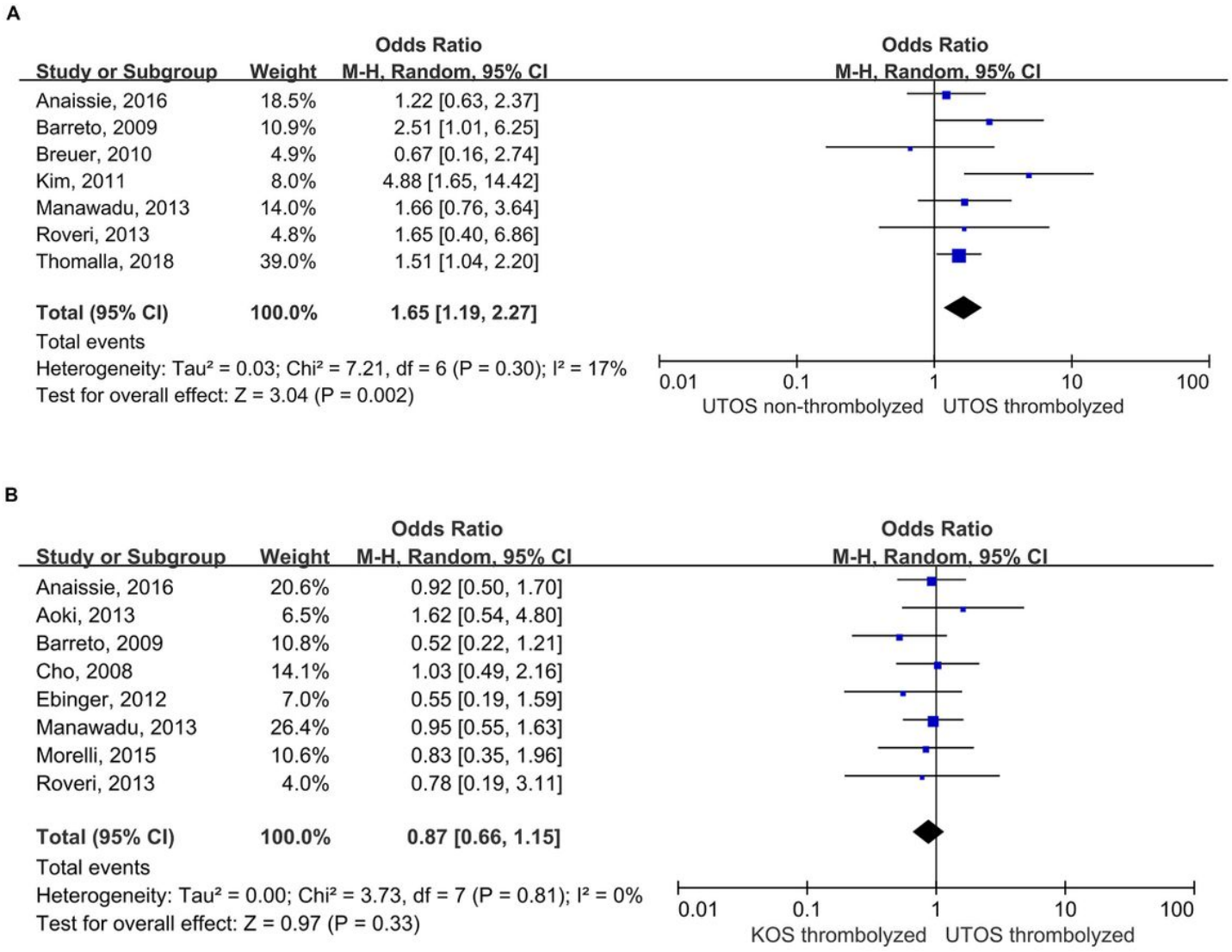

Figure 2

Forest plots of functional outcomes in thrombolyzed UTOS patients compared with non-thrombolyzed UTOS patients or thrombolyzed KOS patients. A, Comparison of mRS scores of 0-2 between thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients. B, Comparison of mRS scores of 0-2 between thrombolyzed UTOS patients vs. thrombolyzed KOS patients.

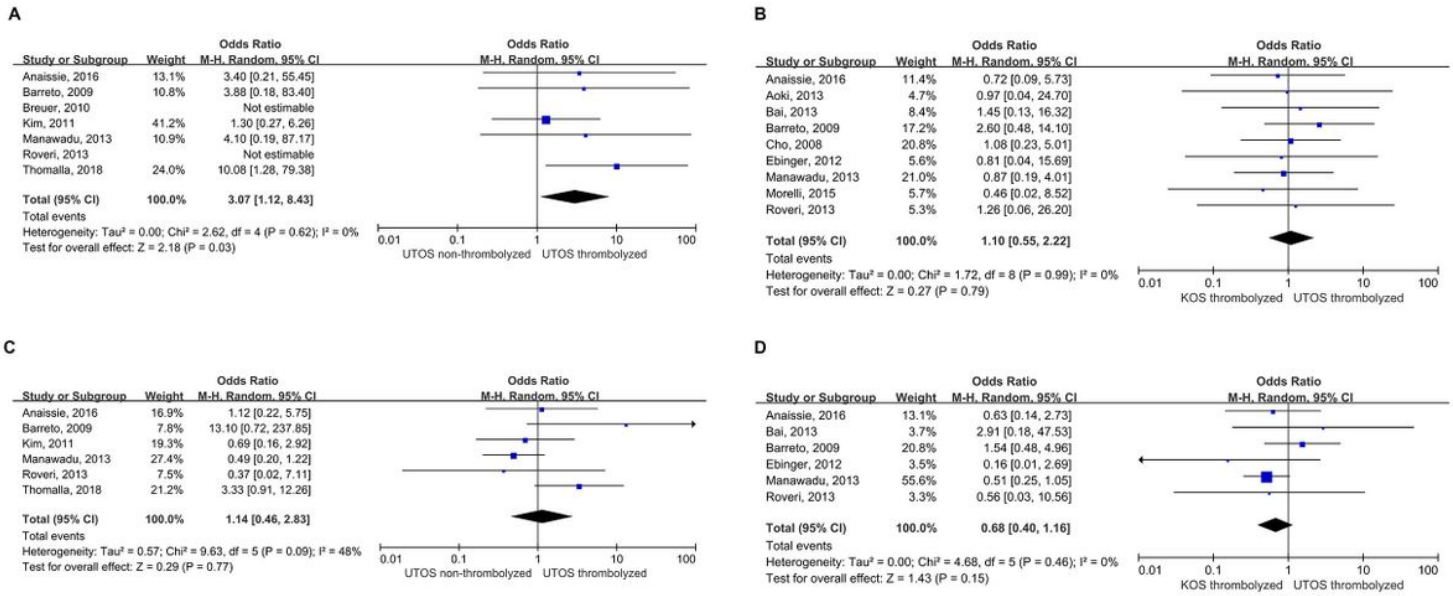

Figure 3

Forest plots of the safety of thrombolysis in thrombolyzed UTOS patients. A and B, Comparison of the incidence of SICH between thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients (A) and thrombolyzed UTOS patients vs. thrombolyzed KOS patients (B). C and D, Comparison of mortality between thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients (C) and thrombolyzed UTOS patients vs. thrombolyzed KOS patients (D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.docx