ACUTE ISCHAEMIC STROKE PUBLICATION ALERT NEWSLETTER (03/2022)

Please be aware that the purpose of this Newsletter is to make you familiar with the most recent scientific publications, and you must keep in mind that all aspects may not be covered by the label. Please always refer to the current prescribing information as in force in your country.

Treatment with endovascular thrombectomy results in successful reperfusion in 71% of patients with acute ischaemic stroke (AIS) caused by large-vessel occlusion (LVO). Despite this, most patients who undergo such treatment either die or continue to experience some degree of disability. It is commonly believed that such poor outcomes are the result of irreversible damage to the brain tissue that occurs before reperfusion is established. However, an alternative theory states that persistent micro-occlusions in the capillary bed of the ischaemic tissue contribute to continued functional impairment. In this issue of the Acute Ischaemic Stroke Publication Alert Newsletter, we focus on the results of the randomized, controlled Chemical Optimization of Cerebral Embolectomy (CHOICE) trial, which evaluated whether treatment with adjunct intra-arterial alteplase after successful thrombectomy improves outcomes in patients with AIS due to LVO. Adjunct intra-arterial alteplase was associated with a higher likelihood of excellent neurological outcome at 90 days compared with placebo. At the same time, differences in angiographic scores were minor, pointing to improved microcirculatory reperfusion as the cause.

Another topic covered in this issue of the Newsletter is the use of mobile stroke units (MSU). A systematic review and meta-analysis of 13 studies conducted by Turc *et al*. assessed whether the use of MSUs leads to better functional outcomes in patients with AIS compared with conventional care. MSU use resulted in an increase of approximately 65% in the odds of excellent outcome and a 30-minute reduction in the onset-to-intravenous thrombolysis (IVT) time, with no safety concerns. Guidelines from the European Stroke Organisation (ESO) recommend the use of MSUs for patients with suspected stroke. The Newsletter concludes with a discussion of a pooled analysis of the Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trials in elderly patients.

The list of presented publications is as follows:

1. Renú A *et al*. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. *JAMA* 2022.
2. Khatri P. Intra-arterial thrombolysis to target occlusions in distal arteries and the microcirculation. *JAMA* 2022.
3. Turc G *et al*. Comparison of mobile stroke unit with usual care for acute ischemic stroke management: a systematic review and meta-analysis. *JAMA Neurol* 2022.
4. Walter S *et al.* European Stroke Organisation (ESO) guidelines on mobile stroke units for prehospital stroke management. *Eur Stroke J* 2022.
5. Yogendrakumar V *et al*. Safety and efficacy of tenecteplase in older patients with large vessel occlusion: a pooled analysis of the EXTEND-IA TNK trials. *Neurology* 2022.

1. DOES THE USE OF ADJUNCT INTRA-ARTERIAL THROMBOLYSIS FOLLOWING AN ANGIOGRAPHICALLY SUCCESSFUL THROMBECTOMY IMPROVE FUNCTIONAL OUTCOMES IN PATIENTS WITH AIS DUE TO LVO?[1,2]

CHOICE; Spanish study; Renú et al. Accompanying editorial by Khatri

SUMMARY

- In patients with AIS due to LVO and successful reperfusion following thrombectomy, the use of adjunct intra-arterial alteplase was associated with a higher likelihood of excellent neurological outcome at 90 days compared with placebo
- Differences in angiographic scores were minor, suggesting that this outcome may be because of improved microcirculatory reperfusion
- Due to the relatively small sample size and the early termination of the study, these findings should be considered preliminary

Endovascular thrombectomy is considered to be the optimal treatment for patients with AIS due to LVO. In previous randomized trials, 71% of patients achieved successful reperfusion. However, only 27% of patients were disability-free at 90 days. As capillaries account for ≥90% of the total intracerebral vascular volume, it is possible that incomplete

microcirculatory reperfusion could be contributing to this outcome. The randomized, double-blind, placebo-controlled Phase 2b CHOICE trial was conducted to investigate whether treatment with adjunct intra-arterial alteplase after thrombectomy improves outcomes following reperfusion.[1]

In the accompanying editorial, Dr Khatri noted that, while the treatment effect observed in CHOICE is remarkable, wide confidence intervals and small sample size suggest that caution should be exercised when drawing conclusions. In addition, as premature termination of the 60-minute intravenous alteplase infusion was permitted, it could have led to some patients being underdosed, possibly in an imbalanced manner between treatment groups. The author pointed out that, to confirm that the improved outcomes associated with the use of adjunct intra-arterial alteplase were due to improved microcirculatory reperfusion, a larger cohort of patients with complete angiographic reperfusion would be required, as CHOICE included only 26 (23%) such patients. Finally, Dr Khatri suggested that a mechanistic biomarker for persistent micro-occlusions of ischaemic tissue capillary beds should be established, such as relative cerebral blood volume or flow with greater than 15% asymmetry compared with the contralateral region.[2]

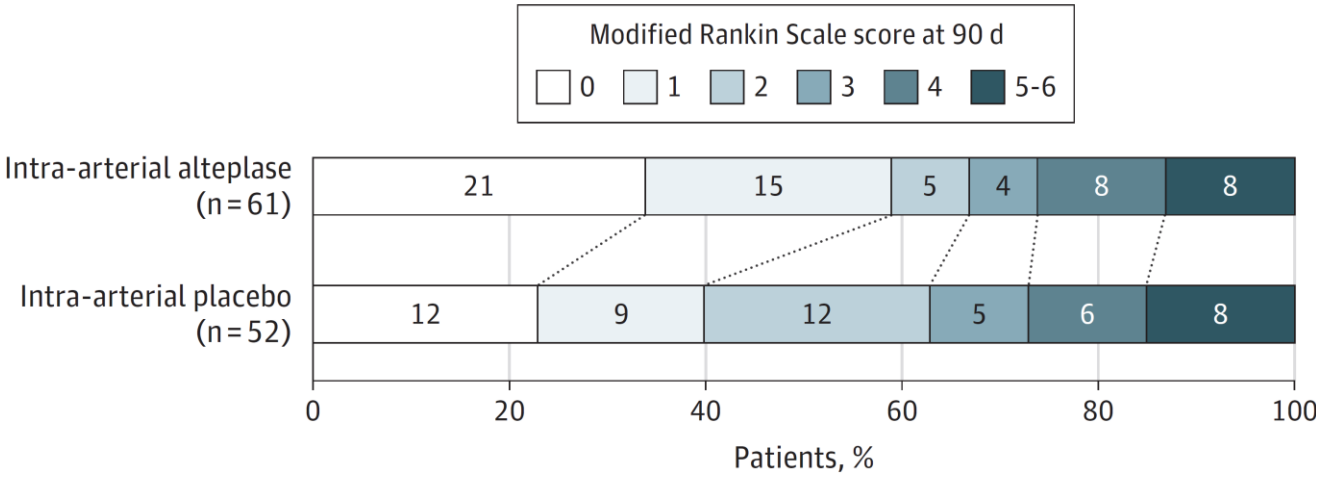
Study details

- This trial was conducted at seven stroke centres in Catalonia, Spain, from December 2018 through May 2021, in 121 patients
- The main inclusion criteria were:
    - Age ≥18 years
    - AIS due to LVO in the anterior, middle, or posterior cerebral artery
    - Treatment with thrombectomy within 24 h after the last time they were seen well
    - Post-thrombectomy expanded treatment in cerebral ischaemia (eTICI) of ≥2b50
- Participants were randomly assigned to receive intra-arterial alteplase (0.225 mg/kg; maximum dose: 22.5mg) infused over 15–30 min (n=61) or placebo (n=52)
- The primary efficacy outcome was the difference in the proportion of patients with excellent outcome, defined as a modified Rankin Scale (mRS) score of 0 or 1, at 90 days
- Safety outcomes included rate of symptomatic intracranial haemorrhage (sICH), defined as neurological deterioration (≥4-point increase in the National Institutes of Health Stroke Scale [NIHSS] score) within 24 h after treatment and evidence of intracranial haemorrhage (ICH) on imaging studies, and death at 90 days

Study results

- The study was terminated early due to the inability to maintain placebo availability and the slow enrolment rate because of the COVID-19 pandemic
- Eight patients did not receive study treatment because of early re-occlusion of the treated vessel (n=4), periprocedural complications (n=2), and COVID-19 infection diagnosed immediately after randomization (n=2)
- The treated-as-randomized analysis included 61 patients in the intra-arterial alteplase group and 52 in the placebo group
- Baseline characteristics were similar in the two groups
    - The median NIHSS score was 14 (interquartile range [IQR]: 9–20), the median Alberta Stroke Program Early CT Score (ASPECTS) was 9 (IQR: 8–10), intravenous alteplase was administered to 69 patients (57%)
    - The median time from stroke onset to randomization was 306 (IQR: 228–609) min, from symptom onset to randomization 318 (IQR: 229–641) min and from symptom onset to start of the study treatment 328 (IQR: 240–676) min
- The proportion of patients with excellent outcomes at 90 days was 59.0% (36/61) with alteplase and 40.4% (21/52) with placebo (adjusted risk difference: 18.4%; 95% confidence interval [CI]: 0.3–36.4; ***p*=0.047**) (**Figure 1**)
- The proportion of participants with angiographic improvement in the eTICI score was 8.5% with alteplase and 7.7% with placebo (risk difference: 0.6%; 95% CI: −9.5 to 10.7; *p*=0.91)
    - After exclusion of patients with a pretreatment eTICI score of 3, the proportion of patients with angiographic improvement was 11.4% with alteplase and 9.3% with placebo (risk difference: 1.8%; 95% CI: −11.0 to 14.5; *p*=0.78)
- sICH within 24 h occurred in none of the patients in the alteplase group and in 3.8% (n=2) of patients in the placebo (risk difference: −3.8%; 95% CI: −13.2 to 2.5)
- At 90 days, mortality was 8.2% (n=5) in the alteplase group and 15.4% (n=8) in the placebo group (risk difference: −7.3%; 95% CI: −19.3 to 4.6)

Figure 1. Distribution of mRS scores at 90 days



Study limitations

- The study was terminated early for logistical reasons due to the COVID-19 pandemic
- The confidence interval for the primary efficacy outcome was relatively wide, with the lower limit of 0.3% for the adjusted risk difference
- The results of the study may not be generalizable, as only 7% of patients who were treated with thrombectomy in Catalonia during the study period were evaluated
- The size of the patient population was insufficient to accurately assess the effects of intra-arterial thrombolysis

Study conclusions

- Among patients with AIS due to LVO and successful reperfusion following thrombectomy, the use of adjunct intra-arterial alteplase resulted in a greater likelihood of excellent neurological outcome at 90 days compared with placebo
- At the same time, differences in angiographic scores were minor, suggesting that this outcome may be due to improved microcirculatory reperfusion
- However, the findings should be considered preliminary until replicated

"Adjunct administration of intra-arterial alteplase at the end of the endovascular procedure resulted in improved clinical outcome despite only minor differences between the treatment groups in angiographic scores or in other surrogate imaging. This suggests that the improved functional outcome may be explained by an amelioration in the microcirculatory reperfusion."[1]

"This approach runs counter to the recent movement to consider bypass of intravenous alteplase altogether in thrombectomy-eligible patients, and suggests that additional or perhaps more targeted thrombolysis will be the most beneficial approach."[2]

2. IN PATIENTS WITH AIS, DOES MSU (MOBILE STROKE UNIT) USE LEAD TO BETTER FUNCTIONAL OUTCOMES THAN USUAL CARE?[3]

Systematic review and meta-analysis by Turc et al.

SUMMARY

- MSU use was associated with an approximately 65% increase in the odds of excellent outcome and a 30-minute reduction in onset-to-IVT times compared with conventional care
- No safety concerns were noted

The effectiveness of IVT and mechanical thrombectomy (MT) in patients with AIS is highly time dependent. MSUs are specialized ambulances equipped with computed tomography (CT) scanner, point-of-care laboratory, telemedicine connection, and neurological expertise. MSUs are designed to address the prehospital phase of stroke management. This

systematic review and meta-analysis was conducted to determine the magnitude of the benefit from using MSUs and whether MSU implementation should be included in guidelines.[3]

Study details

- MEDLINE, Cochrane Library, and Embase were searched for controlled studies comparing MSU and usual care for prehospital management of adult patients with suspected AIS of <6-h duration, and published from 1960 to 2021
- Data were extracted independently by two authors; in the case of studies with overlapping populations, unpublished disentangled results were obtained
- The risk of bias in each study was determined using the Cochrane's Risk of Bias 2 (RoB2) for randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for non-randomized studies
- Data were pooled in random-effects meta-analyses
- The primary endpoint was excellent outcome, defined as an mRS score of 0–1, at 90 days
- Secondary efficacy endpoints were:
    - Good outcome (mRS score of 0–2)
    - Reduced disability (improvement in the mRS score of ≥1 point)
    - The proportion of patients treated with IVT
    - The proportion of golden-hour thrombolysis (IVT started within 60 min of symptom onset) among IVT-treated patients
- Safety endpoints were:
    - All-cause mortality at 7 and 90 days
    - sICH among IVT-treated patients
    - The proportion of IVT-treated patients ultimately diagnosed as stroke mimics

Study results

- In total, 14 articles met the inclusion criteria, of which 4 articles reported on 3 randomized controlled trials, 2 reported on large prospective non-randomized interventional studies with blinded assessment, and 8 articles reported on observational studies
- MSU use was associated with higher likelihood of excellent outcome in adjusted and crude analyses (**Table 1**)
- In addition, MSU use was associated with a higher likelihood of reduced disability in adjusted and crude analyses, and with a higher likelihood of good outcome, with a higher proportion of patients who received IVT, with increased probability of IVT administration within the golden hour, and with shorter onset-to-IVT and alarm-to-IVT times
    - There were no significant differences in onset-to-MT and alarm-to-MT times, in all-cause mortality at 7 or 90 days, or in the likelihood of sICH after IVT or of stroke mimics among IVT-treated patients

Table 1. Summary of findings

Outcome	Pooled effect size (95% CI)	*p* value	I^2, %	Studies (patients), No
Excellent outcome, mRS score of 0–1 at 90 d	Adjusted OR: 1.64 (1.27–2.13)	<0.001	48	5 (3228)
	Crude OR: 1.37 (1.19–1.58)	<0.001	0	5 (3228)
Reduced disability, lower mRS score at 90 d	Adjusted common OR: 1.39 (1.14–1.70)	0.001	0	3 (1563)
	Crude common OR: 1.30 (1.12–1.50)	0.001	21	5 (3228)
Good outcome, mRS score of 0–2 at 90 d	Crude OR: 1.25 (1.09–1.44)	0.001	0	6 (3266)
Proportion of IVT among patients with AIS	Crude OR: 1.83 (1.58–2.12)	<0.001	13	7 (4790)
IVT within the golden hour	Crude OR: 7.71 (4.17–14.25)	<0.001	75	8 (3351)
Onset-to-IVT time, min	Difference of medians: 31 (23–39)	<0.001	47	13 (3322)
Alarm-to-IVT time, min	Difference of medians: 29 (25–33)	<0.001	78	13 (3319)
Onset-to-MT time, min	Difference of medians: 27 (–17 to 71)	0.23	86	5 (666)
Alarm-to-MT time, min	Difference of medians: 14 (–15 to 43)	0.35	89	5 (671)
Death				
7 d	Crude OR: 0.74 (0.51–1.09)	0.13	33	9 (8599)
90 d	Crude OR: 0.82 (0.58–1.17)	0.28	56	7 (3924)
sICH after IVT	Crude OR: 0.80 (0.52–1.24)	0.32	0	5 (1977)
Stroke mimic among IVT-treated patients	Crude OR: 1.22 (0.70–2.14)	0.48	0	3 (666)

OR, odds ratio

Study limitations

- MSU use is a novel area of research and relatively little literature is available on this topic
- The assessment of functional outcomes relied primarily on the results of two large, non-randomized, prospective, controlled studies which used alternating weeks and availability of MSUs for patient allocation
- The definitions of some endpoints (e.g. sICH) varied between studies
- This meta-analysis did not evaluate outcomes in patients with non-ischaemic stroke or stroke mimics
- Most of the data used were obtained from studies conducted in metropolitan areas and may not be generalizable to non-urban settings
- This meta-analysis did not evaluate the health economics of MSUs, which require a sizable investment and maintenance costs

Study conclusions

- Compared with usual care, MSU use was associated with an approximately 65% increase in the odds of excellent outcome and a 30-minute reduction in onset-to-IVT times, without safety concerns
- These results should help guideline writing committees and policy makers

"[…] treating patients in an MSU currently seems to be the only realistic way to treat a substantial proportion of patients within 60 minutes after stroke onset."[3]

3. WHAT ARE THE EUROPEAN STROKE ORGANISATION'S RECOMMENDATIONS TO DECISION-MAKERS REGARDING MSUs?[4]

European Stroke Organisation (ESO) Guidelines; Walter et al.

SUMMARY

- ESO Guidelines recommend MSU use for patients with suspected stroke, as it improved functional outcome at 90 days in those with AIS and was not associated with any safety signals
- The following reasons and evidence-based recommendations were cited:
    - In patients with AIS, prehospital management with an MSU improves functional outcomes, increases the rates of treatment with IVT, including the rates of thrombolysis within the golden hour, and shortens onset to treatment time without any safety concerns. Quality of evidence: *moderate*
    - In patients with ICH, prehospital management with an MSU increases the proportion of patients primarily transported to tertiary care stroke centres, without concerns on short-term mortality. Quality of evidence: *low*
    - In other patients (e.g. stroke mimics), no signal of safety concerns was identified. Quality of evidence: *very low*
    - Overall strength of recommendation: *weak*

Only 0.8–1.3% of patients with AIS receive IVT within the first 60 minutes after symptom onset (the so-called 'golden hour'), when chances of full recovery are highest. Similarly, for patients with intracerebral haemorrhage, shorter time to treatment is associated with better clinical outcomes. MSUs are emergency ambulances equipped with a CT scanner for multimodal brain imaging, point-of-care blood analysis, and telemedicine connection to stroke centres, and are staffed with specialist teams. These Guidelines were created to provide recommendations about whether MSU ambulances are of advantage for prehospital stroke management.[4]

The authors concluded, based on 12 studies, that there was moderate-quality evidence that, for patients with confirmed AIS, MSU use is associated with improved functional outcome at 90 days, increased the proportion of patients who were treated with IVT and the likelihood of receiving IVT within 60 minutes from onset, and shortened onset-to-treatment time, compared with conventional care. There was low-quality evidence derived from three studies that, compared with conventional care, MSU use was associated with an increased proportion of patients with ICH being transported primarily to tertiary care stroke centres.

No safety concerns, such as increased all-cause mortality, proportion of stroke mimics treated with IVT, symptomatic intracranial bleeding, or major extracranial bleeding, could be identified when patients were managed with an MSU compared with conventional care.

Based on these findings, the authors suggested using MSUs to improve prehospital management of patients with suspected stroke. This recommendation applied to all patients with suspected stroke, as currently it is not possible to dispatch MSUs to a selected subgroup of patients only (such as only to those with AIS).

Further research is needed regarding the benefits of MSUs for patients with ICH, non-acute stroke, and stroke mimics. In addition, studies demonstrating the benefits of MSUs were all conducted in settings characterized by highly efficient stroke care. It is unclear if such findings would translate to different care settings, or to rural or suburban geographical areas. The efficiency of MSUs and their costs also depend on dispatch accuracy. At the moment, stroke mimics account for a significant proportion of dispatches and additional real-world data are needed to improve dispatch accuracy. Data on the cost-effectiveness of MSUs are also limited.

Conclusions

Optimization of prehospital care for AIS is essential for improving outcomes in this patient population. ESO Guidelines recommend MSU use for patients with suspected stroke as it improves functional outcome at 90 days in those with AIS and is not associated with any safety signals.

"Future research into MSUs will have to focus not only on the implementation of novel therapeutic strategies but also on the best setting for this prehospital acute stroke care approach including optimal dispatch organisation and cost-benefit analysis."[4]

4. HOW DOES THE SAFETY AND EFFICACY OF TENECTEPLASE COMPARE WITH ALTEPLASE IN PATIENTS WITH AIS OVER 80 YEARS OLD?[5]

Pooled analysis of the EXTEND-IA TNK trials; Australian and New Zealand trials; Yogendrakumar et al.

SUMMARY

- Alteplase is effective in patients with AIS who are >80 years old; data on the use of tenecteplase (TNK) in this patient population are limited
- In patients aged >80 years, TNK 0.25 mg/kg was associated with improved mRS score at 90 days compared with TNK 0.40 mg/kg or alteplase
- TNK 0.25 mg/kg was also associated with lower mortality rate than TNK 0.40 mg/kg, but not alteplase

Patients over 80 years old are under-represented in thrombolytic and endovascular trials, despite accounting for 25–40% of stroke events. Alteplase has been shown to be effective as thrombolytic therapy in patients with AIS who are >80 years old.[6] TNK has shown promise in this indication; however, the data are limited and there is some evidence that TNK is associated with increased risk of ICH when used in higher doses in patients aged ≥75 years with ST-segment elevation myocardial infarction.[5]

This is a pooled analysis of the Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial and the Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischemic Stroke trial (EXTEND-IA TNK Part 2). These randomized, controlled, open-label trials included patients with LVO who were recruited within 4.5 hours of symptom onset. In EXTEND-IA TNK, patients received TNK 0.25 mg/kg or 0.90 mg/kg; in EXTEND-IA TNK Part 2, patients received TNK 0.25 mg/kg or 0.40 mg/kg.

A total of 502 patients were included in this analysis, of whom 251 (50%) patients received TNK 0.25 mg/kg, 150 (30%) received TNK 0.40 mg/kg, and 101 (20%) received alteplase 0.90 mg/kg. There were no significant differences in baseline characteristics between treatment groups.

At the time of treatment, 137 (27%) patients were aged >80 years. Compared with patients aged ≤80 years, the group of patients aged >80 years contained a higher proportion of females and had higher baseline glucose and higher rates of hypertension, previous stroke/transient ischaemic attack, anticoagulant use, and cardio-embolic aetiology. In addition, median time to thrombolysis (139 vs 128 minutes; p=0.03) and median time to arterial puncture (190 vs 175 minutes; p=0.02) were longer, and the median baseline ischaemic core volume was lower (5 vs 13 mL; p<0.01) in patients aged >80 years vs those aged ≤80 years.

In patients aged >80 years, TNK 0.25 mg/kg was associated with a median mRS score of 3 at 90 days compared with 4 for TNK 0.40 mg/kg (adjusted common OR: 2.70; 95% CI: 1.23–5.94) and 4 for alteplase (adjusted common OR: 2.28; 95% CI: 1.03–5.05). TNK 0.25 mg/kg was also associated with lower mortality rate (23%) compared with TNK 0.40 mg/kg (34%; adjusted common OR: 0.34; 95% CI: 0.13–0.91). There were no differences in the mRS score at 90 days or in mortality between alteplase and TNK 0.40 mg/kg.

sICH occurred in four patients (12%) treated with TNK 0.40 mg/kg, one patient treated with alteplase (3%), and none of the patients treated with TNK 0.25 mg/kg in the group of patients aged >80 years.

Limitations of this analysis include the fact that its generalizability is limited to patients with LVO, the potential for selection bias among patients aged >80 years, and the fact that the studies used in the analysis were not powered to assess the difference between treatments in age subgroups.

Conclusions

In patients aged >80 years with LVO stroke, TNK 0.25 mg/kg was associated with improved mRS score at 90 days compared with TNK 0.40 mg/kg or alteplase. TNK 0.25 mg/kg was also associated with lower mortality than TNK 0.40 mg/kg, but not alteplase. The increased mortality seen in patients who received TNK 0.40 mg/kg may be attributed to higher rates of sICH.

"From an efficacy standpoint, TNK 0.25 mg/kg was associated with improved clinical performance when compared to TNK 0.4 mg/kg or alteplase."

"Symptomatic intracranial hemorrhage was observed in 4 older patients treated with TNK 0.40 mg/kg, 1 patient treated with alteplase, and zero patients treated with TNK 0.25 mg/kg."[5]

AIS, acute ischaemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; CHOICE, Chemical Optimization of Cerebral Embolectomy; CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; ESO, European Stroke Organisation; eTICI, expanded treatment in cerebral ischaemia; EXTEND-IA TNK, Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke; ICH, intracranial haemorrhage; EXTEND-IA TNK Part 2, Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischemic Stroke; IQR, interquartile range; IVT, intravenous thrombolysis; LVO, large-vessel occlusion; mRS, modified Rankin Scale; MSU, mobile stroke unit; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RoB2, Risk of Bias 2; ROBINS-1, Risk of Bias in Non-Randomized Studies of Interventions; sICH, symptomatic intracranial haemorrhage; TNK, tenecteplase

References

1. Renú A *et al*. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. *JAMA* 2022;e221645.
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