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Research Article

Efficacy And Safety Alteplase for Acute Ischemic Stroke

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Abstract
Background: Worldwide, 16.5 million people experience a stroke each year, with 5.7 million losing their lives as a direct result. This accounts for 11.5% of all deaths globally, according to the World Health Organization. Master administration rules issued by the European Stroke Association and American Stroke Association/American Heart Affiliation prescribe that alteplase is managed inside 4.5 hours of stroke side effect onset and now not indicate an upper age restrain. There is currently no more compelling intravenous treatment for AIS than alteplase-based intravenous thrombolysis. To improve prognosis for patients with acute ischemic stroke (AIS), alteplase intravenous thrombolysis administered within 4.5 hours after onset is recommended. Thus, this study set out to assess alteplase's effectiveness, safety, and effectivity in treating acute ischemic stroke.
Methods: This meta-analysis was performed according to the PRISMA guidelines. PubMed, Cochrane Library, and Sciences Direct literature searches, using alteplase, acute ischaemic stroke, as a keywords was conducted in March 2024. Statistical analysis uses Review Manager version 5.4.
Results: Based on these findings, a statistically significant difference in the improvement of NIHSS between baseline and 24 hours OR 1.21 CI 95%; (1.04 – 1.40) and adverse events OR 1.24 CI 95%; (1.06 -1.46).
Conclusions: Although administration of alteplase may reduce the severity of stroke, there is a risk of increased incidence of adverse events such as intracranial haemorrhage.

Key words: Standard dose alteplase, Meta-analysis, acute ischemic stroke.

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Introductions

A clot in a blood vessel is the defining feature of the neurological disease known as a stroke. A blood clot shapes within the brain, blocking blood stream, clogging supply routes, and causing blood vessels to break and cause bleeding (Kuriakose & Xiao, 2020). Cerebral infarction is the primary symptom of an ischemic stroke. A temporary decrease in tissue function and, eventually, infarction (the death of neurons and other supporting structures) are the results of inadequate blood flow to the brain. Ischemia initiates a series of events that starts with the cessation of electrical function, leading to the entry of calcium into cells, calcium-induced excitotoxicity, impairment of membrane function due to the production of reactive oxygen species, and finally death of cell

membranes and cells (Feske, 2021; Kuriakose & Xiao, 2020).

Stroke is the second most prevalent cause of mortality globally (Kuriakose & Xiao, 2020). As per the World Health Organization, around 16.5 million individuals experience a stroke year, resulting in 5.7 million deaths due to stroke-related complications. This accounts for 11.5% of all global fatalities (Shen et al., 2023). Because of improvements in clinical interventions and falling mortality rates, the prevalence of ischemic strokes—which account for about 60% to 80% of all strokes—has increased dramatically between 1990 and 2016 (Chugh, 2019; Song et al., 2023).

Recombinant DNA technology may have resulted in the development of a thrombolytic agent known as alteplase. The FDA has affirmed it for utilize in acute ischemic stroke, aspiratory embolism, acute myocardial localized necrosis, and catheter occlusion (Reed et al., 2025). No maximum age limit is specified for the administration of alteplase, however according to master administration rules provided by the European Stroke Organization and the American Stroke Association/American Heart Association, it should be administered within 4.5 hours after the start of stroke side symptoms (Berge et al., 2021; Kuriakose & Xiao, 2020). Researchers at the National Institute of Neurological Disorders and Stroke (NINDS) developed recombinant tissue plasminogen activator, also known as alteplase, the most effective intravenous thrombolytic medication (Berge et al., 2021; Kuriakose & Xiao, 2020).

The majority of AIS treatment guidelines8 suggest alteplase (Qiu & Xu, 2020). Multiple trials have found no benefit and ongoing risk from administering alteplase 3–4.5 hours after stroke start (Alper et al., 2020; J. Huang et al., 2024). In terms of safety outcomes, such as symptomatic intracerebral hemorrhage, alteplase did not vary from comparable trials (J. Huang et al., 2024). Accordingly, alteplase's effectiveness and safety in AIS patients were the main goals of this investigation.

Methods

Literature search

As shown in Figure 1, this meta-analysis was conducted in March 2024 in accordance with PRISMA recommendations. A literature search in PubMed, Cochrane Library, and Sciences Direct used alteplase, acute stroke infark as keywords, and a search strategy adapted to each database. Finally, we included all randomized controlled trials from 1995 to 2018.

Inclusion and Exclusion Criteria

Participation inclusion criteria are as follows: (1) The participant must be over the age of 18. (2) Randomized controlled trials (RCTs). (3) Comparison of alteplase alone or in combination with placebo or other drugs. (4) at least one report of Improved NIHSS results from baseline to 24 hours, modified Rankin Scale (mRS) score 0–1 after 3 months, and an adverse event. Exclusion criteria were: (1) participants under 18 years of age; (2) No RCTs, no relevant results, only abstract articles. (3) Data that cannot be extracted or computed.

Outcome and study

The primary endpoint was to describe improvements in NIHSS and mRS scores. A secondary outcome was to investigate possible adverse events associated with alteplase. Jadad score was used on a scale of 0 to 5 to assess the quality of RCTs. In addition, scores were categorized into high, medium, and low depending on whether the score was 4 points or 3 points or less. Lastly, we used the criteria established by the Oxford Center for Evidence-Based Medicine to evaluate the strength of each study's evidence (Bluhmki et al., 2009).

Statistical Analysis

Review Manager version 5.4 statistical analysis was used to calculate each parameter, and data from multiple studies were aggregated using the Mantel-Hanzel method. ORs with 95% confidence intervals (CIs) were used to represent binary or categorical data types. Cochrane chi-square test plus inconsistency (I2) analysis also tested for study heterogeneity. P value is 50%. The effects model was random and fixed and was used when heterogeneity was greater or less than 50%.

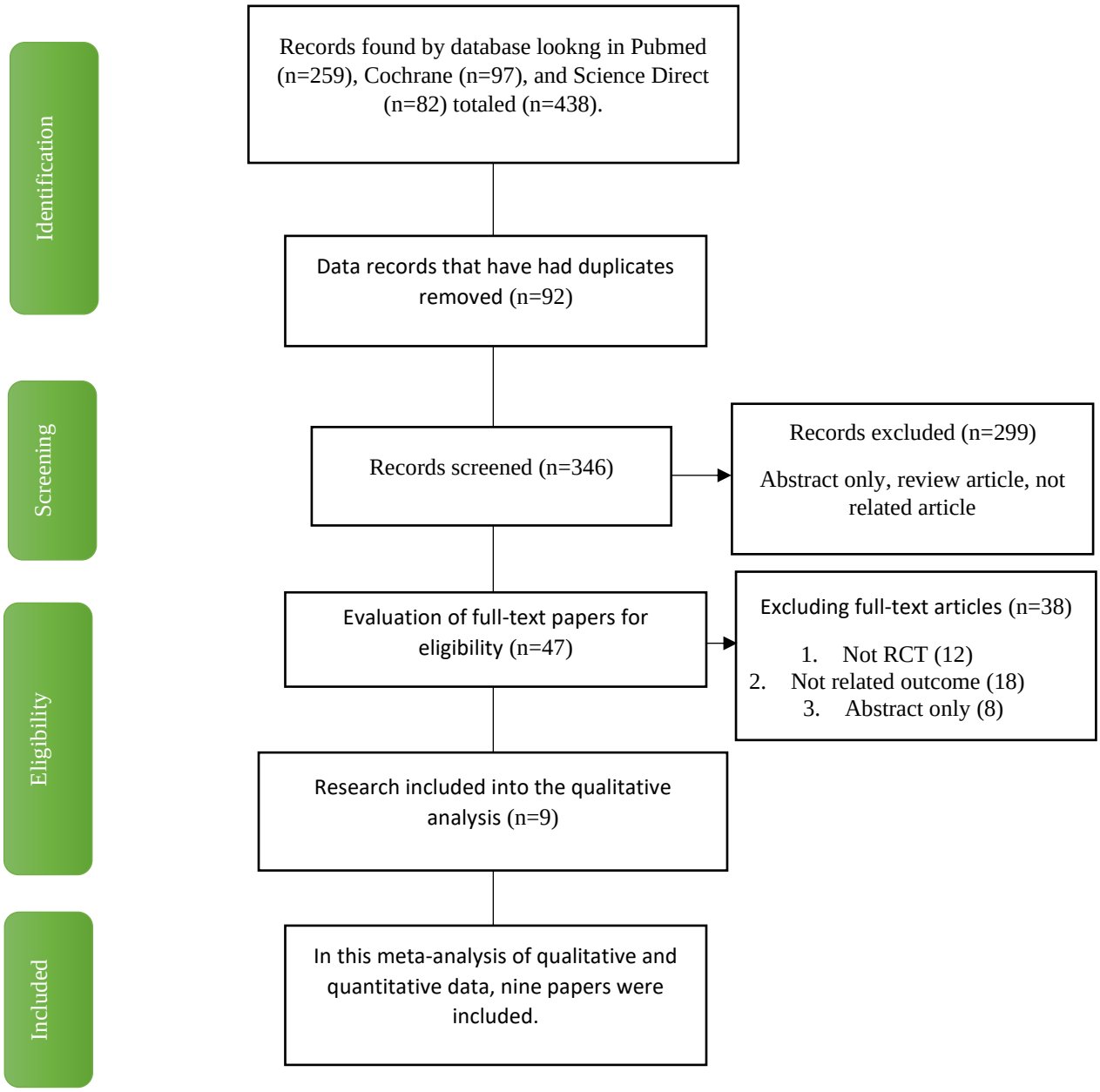

Figure 1. Complete the record screening process with a PRISMA flow diagram

Results

Initial Characteristic

A total 438 articles were recovered from the three databases. After screening the tittles, removed the duplicates, and avoided articles that improper with the consideration and prohibition criteria, the final results articles that included in qualitative and quantitative synthesis is 9 studies. The complete sample size was 4951, 3188 of alteplase sample, 3161 of placebo sample. Table 1 lists the characteristics of the included studies (Berkhemer et al., 2015; Bluhmki et al., 2009; G. Chen et al., 2018; Davis et al., 2008; Hacke et al., 2008; X. Huang et al., 2015; Logallo et al., 2017; Parsons et al., 2012; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, 1995). The trials were of a high caliber, with significance scores in the range of 2e5 and an evidence base determination level of 1b for 9 RCTs.

Enhancement of NIHSS from baseline to 24 hours

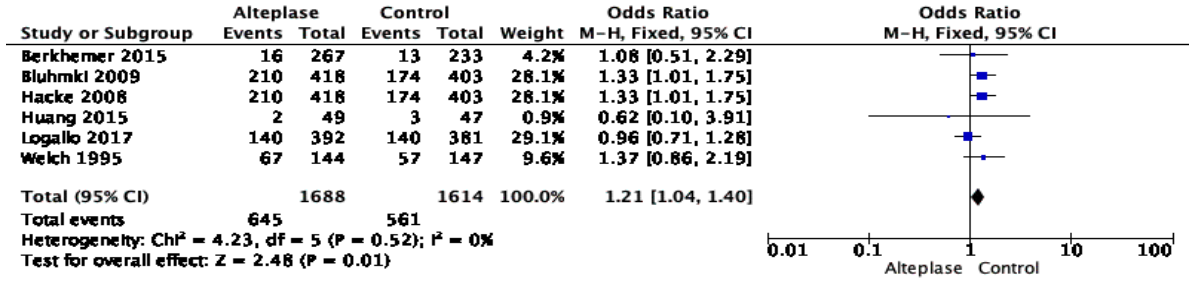

Figure 2. Forest plot Enhancement of NIHSS from baseline to 24 hours

A statistically significant difference in the amount of time that patients' NIHSS scores improved between baseline and 24 hours was seen in the six studies including 1688 alteplase patients and 1614 placebo patients OR 1.21 CI 95%; (1.04 to1.40) with p-value 0.01 and had no heterogeneity I^2= 0%.

Modified rankin scale (mRS) score 0-1 at 3 months

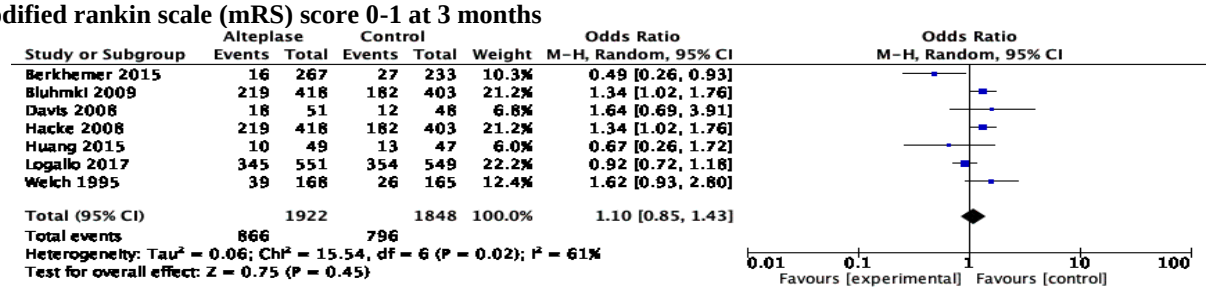

Figure 3. Forest plot modified rankin scale (mRS) score 0-1 at 3 months

According to seven studies including a total of 1922 alteplase patients and 1848 placebo patients, there was no statistically significant difference in the groups' 0–1 modified rankin scale (mRS) scores at 3 months (OR 1.10 CI 95%; (0.85 to 1.43) with heterogeneity I2= 61%.

Adverse events

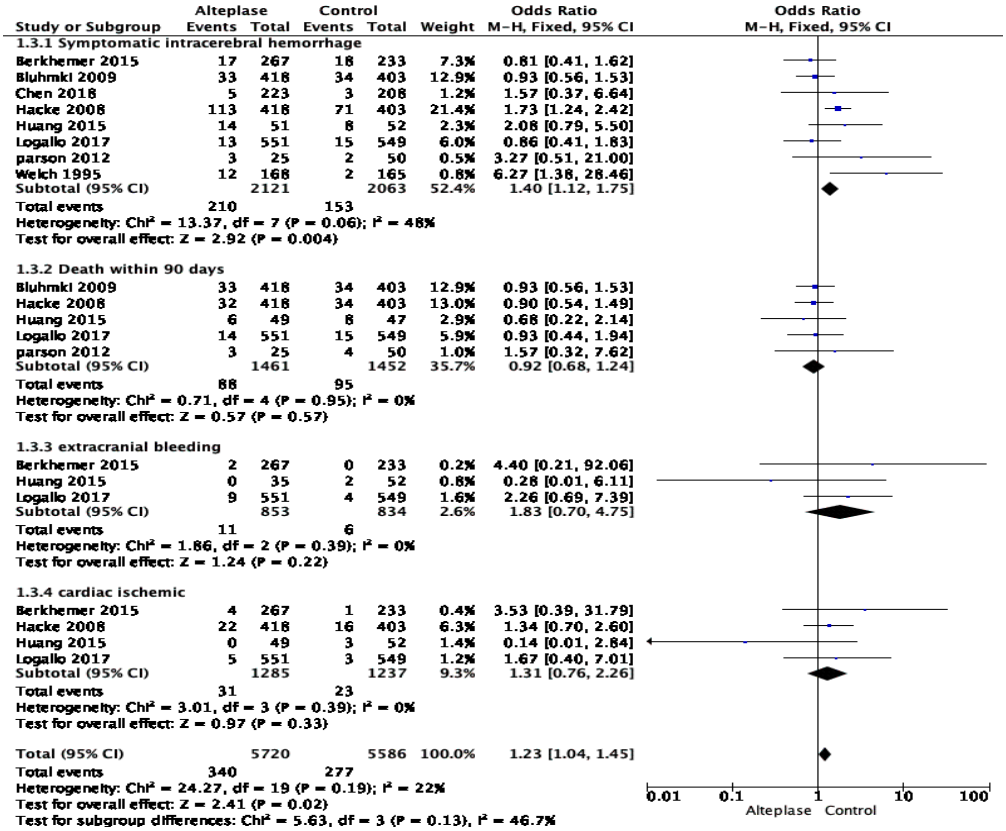

Figure 4. Forest plot adverse events

A total of eight studies involving 5,720 alteplase patients and 5,586 placebo patients found a statistically significant difference in adverse events between the two groups, with OR 1.24 (95% CI: 1.04 to1.45) and a low level of heterogeneity (I2= 22%).

Table 1. Study and article quality characteristics

Study author	Country	Study type	Age, years	No. of cases		Comparison	Intervention	Treatment
				Alteplase	Control			
Berkhemer, 2015 (Berkhemer et al., 2015)	Netherlands	RCT	>=18 years	267	233	Alteplase vs Alteplase and mechanical treatment	0.9 mg/kg alteplase	about six hours following the stroke's beginning
Bluhmki, 2009 (Bluhmki et al., 2009)	Germany	RCT	18-80 years	418	403	Alteplase vs Placebo	0.9 mg/kg alteplase	3.0-4.5 hours after the stroke first occurred
Chen, 2018 (Chen et al., 2018)	China	RCT	>=18 years	1096	1115	Alteplase standard dose vs low dose	0.9 mg/kg alteplase	4.5 hours after the stroke first occurred
Davis, 2008 (Davis et al., 2008)	Australia	RCT	>=18 years	52	49	Alteplase vs Placebo	0.9 mg/kg alteplase	3-6h afrer the stroke first occured
Hacke, 2008 (Hacke et al., 2008)	Germany	RCT	18-80 years	418	403	Alteplase vs Placebo	0.9 mg/kg alteplase	3.0-4.5 hours after the stroke first occurred
Huang, 2015 (Huang et al., 2015)	Scotland	RCT	>=18 years	49	47	Alteplase vs Tenecteplase	0.9 mg/kg alteplase	4.5 hours after the stroke first occurred
Logallo, 2017 (Logallo et al., 2017)	Norway	RCT	>=18 years	551	549	Alteplase vs Tenecteplase	0.9 mg/kg alteplase	4.5 hours after the stroke first occurred
Parson, 2012 (Parson et al., 2012)	Newcastle	RCT	>=18 years	25	50	Alteplase vs Tenecteplase	0.9 mg/kg alteplase	about six hours following the stroke's beginning
Welch, 1995 (Welch et al., 1995)	Bethesda	RCT	>=18 years	312	312	Alteplase vs Placebo	0.9 mg/kg alteplase	3.0 hours after the stroke first occurred

Table 2. Shows the Jadad Score Assessment

Article	Randomization	Blinding	Withdrawals or Dropout	Jadad Scale
Berkhemer, 2015 (Berkhemer et al., 2015)	2	1	1	4
Bluhmki, 2009 (Bluhmki et al., 2009)	2	2	1	5
Chen, 2018 (Chen et al., 2018)	2	1	1	4
Davis, 2008 (Davis et al., 2008)	2	2	1	5
Hacke, 2008 (Hacke et al., 2008)	2	2	1	5
Huang, 2015 (Huang et al., 2015)	2	1	1	4
Logallo, 2017 (Logallo et al., 2017)	2	1	1	4
Parson, 2012 (Parson et al., 2012)	2	1	1	4
Welch, 1995 (Welch et al., 1995)	2	2	1	5

*If the randomization method is appropriate, add an extra 1 points to the randomization score. (eg. Computer generated) *If the blinding technique is applicable, add an additional 1 point. *Withdrawals: If the quantity and justification were given, one point.

Discussion

From these results, alteplase had a significant impact on the difference in NIHSS scores from the baseline and 24 hours comparison with the placebo group. The findings align with the research carried out by Agarwal et al 2020, patients treated with alteplase showed significantly greater improvement within 24 hours (p=0.045). Early neurological improvement is considered successful reperfusion during acute stroke treatment (Agarwal et al., 2020). Other studies have stated that the NIHSS score is a notable indicator of his good outcome after 3 months and that alteplase may be decreased in the NIHSS score (p = 0.018) (Salem et al., 2021). A multivariate logistic regression study found that the NIHSS score at 24 hours post-admittance and the beginning of hospitalization were significant predictors for prognosis (p = 0.006) (Li et al., 2019). Using binary logistic regression analysis, the present study looked at what variables predicted good results at the 3-months, the data revealed that the only significant predictor of positive outcomes was an NIHSS score of 13 or lower. A 2.338 degree increase in favorable outcomes was related with each drop in NIHSS score (OR=0.097, p=0.018, 95% CI: 0.014 to 0.673) (Salem et al., 2021). The mRS score ranged from 2 to 6 points, with higher scores indicating a poorer prognosis, A total of 6 points were assigned to the mRS (Li et al., 2019). After comparing the control group to the Alteplase group for AIS, it seemed like there was no significant difference. Even though alteplase is safe, observational research from merlino 2023 suggests that it does not improve clinical outcomes in critically selected individuals with non-disabling AIS (Merlino et al., 2023). At three months, half of the patients in the Alteplase group and almost half of the patients in the TNK group experienced significant functional recovery within the quiet with expanding vascular stroke (P = 0.76) (Dhar et al., 2022). According to a multinominal computed relapse demonstration, there is no significant difference between mRS scores as efficacy outcomes after 90 days (p=0.440) (Alper et al., 2020).

In line with the mRS score research conducted 90 days after therapy, the control group consisted of 32 patients with favorable prognosis and 28 patients with unfavorable prognosis, whereas the alteplase group contained 44 patients with favorable prognosis and 16 patients with unfavorable prognosis. According to the chi-square analysis, the estimate in the control group was significantly lower than in the alteplase group ($p = 0.023$) (Li et al., 2019). Earlier research found that when treatment was initiated within three hours of the stroke beginning, 32.9% of alteplase patients and 23.1% of control group patients had a favorable 3-month result (defined as a modified rankin scale score of or 1), based on a meta-analysis of nine randomized controlled trials (Mohammed, 2022).

Alteplase is a fibrinolytic agent that is also known as tissue plasminogen activator (tPA). Alteplase transforms plasminogen to the proteolytic protein plasmin, which dissolves the thrombus (Jilani & Siddiqui, 2025; Potla & Ganti, 2022; Reed et al., 2025). Despite the fact that a dose of 0.9 mg/kg alteplase is widely administered in most regulations for AIS patients, the high likelihood of sICH following alteplase thrombolysis must be overlooked, especially in Asians (Xu et al., 2023). The use of alteplase for AIS significantly reduces adverse effects, particularly cerebral bleeding, as shown in our results. About 6.8% of patients in the alteplase group and 1.3% of patients in the control group experienced significant cerebral bleeding (Mohammed, 2022). After alteplase destruction, the risk of SICH must be taken seriously. Compared to low-dose alteplase (0.6 mg/kg), standard intravenous doses may be associated with a higher risk of sICH (Zhai et al., 2023). Higher sICH was linked to standard dosing regimens ($p = 0.01$) (C.-H. Chen et al., 2022). On the other hand, the incidence of sICH was considerably reduced among patients whose dosages were kept low ($p = 0.01$) (Alper et al., 2020; C.-H. Chen et al., 2022; Zhai et al., 2023). When it came to bleeding, the incidence of fatal cerebral hemorrhage was significantly reduced in individuals who took low-dose alteplase ($p = 0.020$) (Sadeghi-Hokmabadi et al., 2018).

Conclusions

From this meta-analysis, administration of alteplase can reduce the severity of stroke but alteplase has the risk of increasing the incidence of adverse events such as intracranial bleeding.

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Conflict of interest

The authors declare that there is no conflict of interest.

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