

JAMA | Original Investigation

Effect of Argatroban Plus Alteplase on Excellent Functional Outcome in Patients With Acute Ischemic Stroke: The ARAIS Randomized Clinical Trial

Hui-Sheng Chen, MD; Yu Cui, PhD; Zhong-He Zhou, MD; Ying-Jie Dai, MD; Gao-Hua Li, MM; Zhao-Long Peng, BSM; Yi Zhang, BSM; Xiao-Dong Liu, MM; Zhi-Mei Yuan, MM; Chang-Hao Jiang, BSM; Qing-Cheng Yang, BSM; Ying-Jie Duan, MM; Guang-Bin Ma, BSM; Li-Wei Zhao, BSM; Rui-Xian Wang, MM; Yuan-Lin Sun, MD; Lei Shen, MM; Er-Qiang Wang, MM; Li-Hua Wang, MD; Ye-Fang Feng, BSM; Feng-Yun Wang, BSM; Ren-Lin Zou, BSM; He-Ping Yang, MD; Kai Wang, MD; Duo-Lao Wang, PhD; Yi-Long Wang, MD; for the ARAIS Investigators

IMPORTANCE Previous studies suggested a benefit of argatroban plus alteplase (recombinant tissue-type plasminogen activator) in patients with acute ischemic stroke (AIS). However, robust evidence in trials with large sample sizes is lacking.

OBJECTIVE To assess the efficacy of argatroban plus alteplase for AIS.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, open-label, blinded end point randomized clinical trial including 808 patients with AIS was conducted at 50 hospitals in China with enrollment from January 18, 2019, through October 30, 2021, and final follow-up on January 24, 2022.

INTERVENTIONS Eligible patients were randomly assigned within 4.5 hours of symptom onset to the argatroban plus alteplase group (n = 402), which received intravenous argatroban (100 µg/kg bolus over 3-5 minutes followed by an infusion of 1.0 µg/kg per minute for 48 hours) within 1 hour after alteplase (0.9 mg/kg; maximum dose, 90 mg; 10% administered as 1-minute bolus, remaining infused over 1 hour), or alteplase alone group (n = 415), which received intravenous alteplase alone. Both groups received guideline-based treatments.

MAIN OUTCOMES AND MEASURES The primary end point was excellent functional outcome, defined as a modified Rankin Scale score (range, 0 [no symptoms] to 6 [death]) of 0 to 1 at 90 days. All end points had blinded assessment and were analyzed on a full analysis set.

RESULTS Among 817 eligible patients with AIS who were randomized (median [IQR] age, 65 [57-71] years; 238 [29.1%] women; median [IQR] National Institutes of Health Stroke Scale score, 9 [7-12]), 760 (93.0%) completed the trial. At 90 days, 210 of 329 participants (63.8%) in the argatroban plus alteplase group vs 238 of 367 (64.9%) in the alteplase alone group had an excellent functional outcome (risk difference, -1.0% [95% CI, -8.1% to 6.1%]; risk ratio, 0.98 [95% CI, 0.88-1.10]; P = .78). The percentages of participants with symptomatic intracranial hemorrhage, parenchymal hematoma type 2, and major systemic bleeding were 2.1% (8/383), 2.3% (9/383), and 0.3% (1/383), respectively, in the argatroban plus alteplase group and 1.8% (7/397), 2.5% (10/397), and 0.5% (2/397), respectively, in the alteplase alone group.

CONCLUSIONS AND RELEVANCE Among patients with acute ischemic stroke, treatment with argatroban plus intravenous alteplase compared with alteplase alone did not result in a significantly greater likelihood of excellent functional outcome at 90 days.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT03740958](https://clinicaltrials.gov/ct2/show/study/NCT03740958)

JAMA. doi:10.1001/jama.2023.0550
Published online February 9, 2023.

[View Abstract](#)

[See Article in PDF](#)

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Hui-Sheng Chen, MD, Department of Neurology, General Hospital of Northern Theatre Command, 83# WenHua Rd, ShenHe District, ShenYang, China 110840 (chszh@aliyun.com); Yi-Long Wang, MD, Department of Neurology, Beijing Tiantan Hospital, Beijing 100070, China (yilong528@aliyun.com).

Current guidelines recommend reperfusion therapies, such as intravenous thrombolysis and endovascular thrombectomy, as the most effective strategies for management of acute ischemic stroke (AIS). Vessel recanalization was strongly associated with lower mortality and improved functional outcome of reperfusion therapies in patients with AIS. However, only 23% of patients achieved complete recanalization through intravenous thrombolysis, while approximately 30% of patients with large artery occlusion did not achieve successful reperfusion after endovascular thrombectomy. Although endovascular therapy has been shown to be effective in AIS with large artery occlusion, its use in clinical practice was limited due to a reliance on device availability and experienced clinicians. In addition, 36% to 47% of the population with initial recanalization underwent reocclusion after alteplase (recombinant tissue-type plasminogen activator) thrombolysis and had clinical deterioration and poor outcomes. Thus, an effective and simple method is needed to improve vessel recanalization, prevent reocclusion, and reduce AIS disability.

Argatroban, a selective thrombin inhibitor, directly inhibits free and clot-associated thrombin as well as thrombin-induced events and has been widely used to treat AIS, particularly in Asian countries such as China and Japan. Growing evidence from preclinical studies demonstrated the effect of argatroban plus alteplase in ischemic stroke by enhancing and sustaining arterial recanalization. Translating into clinical practice, early-phase trials have explored the safety and possible efficacy of argatroban plus alteplase in patients receiving intravenous thrombolysis and endovascular treatments. There is a lack of robust evidence for the effect of argatroban plus alteplase in AIS patients because of small sample sizes. In addition, argatroban was found to have neuroprotective potential. In this context, a multicenter, open-label, blinded end point randomized trial was designed to explore the efficacy of argatroban plus alteplase for AIS within 4.5 hours from onset.

Methods

Study Design

The Argatroban Plus Recombinant Tissue-Type Plasminogen Activator for AIS (ARAIS) study was a multicenter, open-label, blinded end point randomized trial to assess the efficacy of argatroban plus alteplase in patients with AIS within 4.5 hours from symptom onset. The study protocol is available in [Supplement 1](#) and the statistical analysis plan is available in [Supplement 2](#). The trial was conducted at 10 medical sites (eAppendix 1 in [Supplement 1](#)) in China. Details of the study design and rationale have been published elsewhere. The trial protocol was approved by the appropriate regulatory and ethical authorities of the ethics committee of the General Hospital of Northern Theatre Command and other participating hospitals. An independent data monitoring committee (eAppendix 2 in [Supplement 1](#)) monitored the progress of the trial every 6 months. An independent clinical research organization (Nanjing

Key Points

Question Does argatroban improve neurologic function in patients with acute ischemic stroke who received intravenous recombinant tissue-type plasminogen activator (alteplase)?

Findings In this randomized clinical trial that included 808 patients with acute ischemic stroke, excellent neurologic function at 90 days (modified Rankin Scale score of 0 to 1) in those randomized to receive argatroban plus intravenous alteplase compared with intravenous alteplase alone occurred in 63.8% vs 64.9% of participants, a difference that was not statistically significant.

Meaning Among patients with acute ischemic stroke who received intravenous alteplase, argatroban was not significantly associated with better neurologic function.

Service Pharmaceutical Technology Co) monitored the trial for quality control. Signed informed consent was obtained from patients or their legally authorized representatives.

Participants

Eligible patients were adults aged 18 to 80 years with AIS at the time of randomization (baseline National Institutes of Health Stroke Scale [NIHSS] score of more than 3; range, 3 to 25, with higher scores indicating greater stroke severity) and were enrolled up to 4.5 hours after the onset of stroke symptoms (the time the patient was last seen well). Whole-head computed tomography or magnetic resonance imaging was performed on admission to identify patients with ischemic stroke. Key exclusion criteria were as follows: presence of disability in the community (modified Rankin Scale [mRS] score 3; range, 1 [no symptoms] to 6 [death]) before the stroke, history of intracerebral hemorrhage, gastrointestinal or urinary tract bleeding in the last 7 days, and need for concomitant use of anticoagulants other than argatroban. A full list of inclusion and exclusion criteria is available in the study protocol ([Supplement 1](#)).

Randomization and Masking

In the trial, eligible patients were randomly assigned to either the argatroban plus alteplase group or the alteplase alone group using a block randomization method with a block size of 4, through a computer-generated random sequence that was centrally administered via a password-protected web-based program (Beijing Zhinan Medical Technology Co). The study team members were blinded to the treatment randomization.

Procedures

In both treatment groups, intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg; 10% administered as a 10-minute bolus, the remaining infused over 1 hour; Boehringer Ingelheim Co) was administered within 4.5 hours after symptom onset. Patients in the argatroban plus alteplase group received a 0.45 g/kg intravenous argatroban (Tianjin Institute of Pharmaceutical Research Co) bolus over 20 minutes within 1 hour of the alteplase bolus, followed by an argatroban infusion of 0.225 g/kg per minute for 4 hours. Standard treatments

based on current guidelines were also received by the patients in both groups.

Argatroban infusion rates were adjusted to achieve a target activated partial thromboplastin time (APTT) of ≥ 1.5 –baseline ($\geq 50\%$). A dosing algorithm was developed so that standardized increments or decrements of argatroban infusion rate took place in response to the APTT. APTT was monitored at baseline and at 1, 2, 4, 6, and 8 hours after initiation of argatroban; within 1 to 2 hours of any argatroban infusion adjustment; and in the event of major systemic bleeding. Argatroban infusion was terminated immediately if major systemic bleeding or symptomatic intracranial hemorrhage was suspected.

The NIHSS was used to assess neurologic status at baseline, 1 hour, 2 hours, 4 days, and 8 days after randomization. A detailed flowchart of the assessment schedule is provided in the study protocol (Supplement). Data on demographic and clinical characteristics were obtained at randomization. Follow-up data were collected at 1 day, 2 days (or at hospital discharge if earlier), and 8 days after randomization. Remote and on-site quality control monitoring and data verification were conducted throughout the study.

Q u e s t i o n s

The primary end point was excellent functional outcome at 8 days, defined as a score of 1 to 5 on the mRS for the evaluation of neurologic disability, assessed in person or, if an in-person visit was not possible, through a structured interview for telephone assessment by personnel certified in the scoring of the mRS 8 days after randomization (eMethods in Supplement).

The secondary end points were favorable functional outcome (mRS score of ≤ 4) at 8 days; the occurrence of early neurologic improvement compared with baseline at 1 hour, defined as a decrease in NIHSS score of greater than or equal to 2; the occurrence of early neurologic deterioration compared with baseline at 1 hour, defined as an increase in NIHSS score of greater than or equal to 2; change in NIHSS score compared with baseline at 8 days; and the occurrence of stroke or other vascular events (transient ischemic attack, myocardial infarction, and vascular death) within 8 days.

Any adverse events that occurred during the study were recorded. The prespecified adverse event outcomes were symptomatic intracranial hemorrhage, parenchymal hematoma type 2, and major systemic bleeding that occurred during the study. Symptomatic intracranial hemorrhage was defined as any evidence of bleeding on the head computed tomography scan associated with clinically significant neurologic deterioration (≥ 2 -point increase in NIHSS score) in the opinion of the clinical investigator or independent safety monitor. Parenchymal hematoma type 2 was defined as confluent bleeding occupying more than 10% of the infarct volume and causing significant mass effect. Major systemic bleeding was defined as a drop in the hemoglobin level by at least 2 g/dL or a transfusion of at least 2 U of blood. Follow-up head computed tomography was performed at 1 hour (alteplase alone group) or 2 hours (argatroban plus alteplase group) after randomization or at any time when neurologic

deterioration occurred (eFigure in Supplement). A central core laboratory for imaging was set to judge intracranial bleeding events and severity.

The baseline and follow-up NIHSS scores were evaluated by the same certified neurologist, who was not blinded to the treatment randomization due to the difficulty of blinding to the open label of argatroban. Final follow-up was performed at 8 days in person or, if an in-person visit was not possible, a structured interview for telephone assessment was performed by a trained and certified staff member in each center who was unaware of the randomized treatment assignment. A training course was held for all the investigators at each center to ensure the validity and reproducibility of the evaluation, and only certified investigators were eligible to evaluate NIHSS or mRS scores. Central adjudication of clinical outcomes and adverse events was also performed by assessors unaware of treatment randomization or clinical details. If there was disagreement between local and central assessors, a consensus was reached by discussion. The local assessor retained control of the final mRS score following any discussion. In addition, there was no disagreement between the central adjudicator and the local assessor.


S a m p l e S i z e C a l c u l a t i o n

Power calculations were based on the estimated treatment effects based on a binary assessment of excellent functional outcome at 8 days. In the Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke (ARTSS-) study, argatroban plus alteplase resulted in a 10% improvement in the primary end point compared with alteplase alone. Therefore, 10% was chosen as the difference used to power this study. Based on the assumption that the percentage of participants with excellent functional outcome was 10% in the argatroban plus alteplase group and 0% in the alteplase alone group (equivalent to a risk ratio [RR] of 1.1), a sample size of 1,000 (500 per group) was estimated to provide more than 80% power (using a 1-sided $\alpha = 0.05$) to detect the 10% greater excellent functional outcome in the argatroban plus alteplase group. Assuming a 10% loss to follow-up, the total sample size was 1,111 (556 participants per group).

S a m p l e S i z e A d j u s t m e n t

Statistical analyses were performed on the full analysis set, which included all randomized participants with at least 1 post-baseline efficacy evaluation. Generalized linear models (GLMs) were performed for the analyses of the primary and secondary outcomes of favorable functional outcome at 8 days, the occurrence of early neurologic improvement, and early neurologic deterioration. The treatment effects for the above outcomes are presented as RRs and risk differences (RDs) with their 95% CIs. In sensitivity analyses, missing values in the primary outcome were imputed using the last observation carried forward approach, the worst-case scenario approach, the best-case scenario approach, and post hoc multiple imputation. No interim analyses were performed in this study.

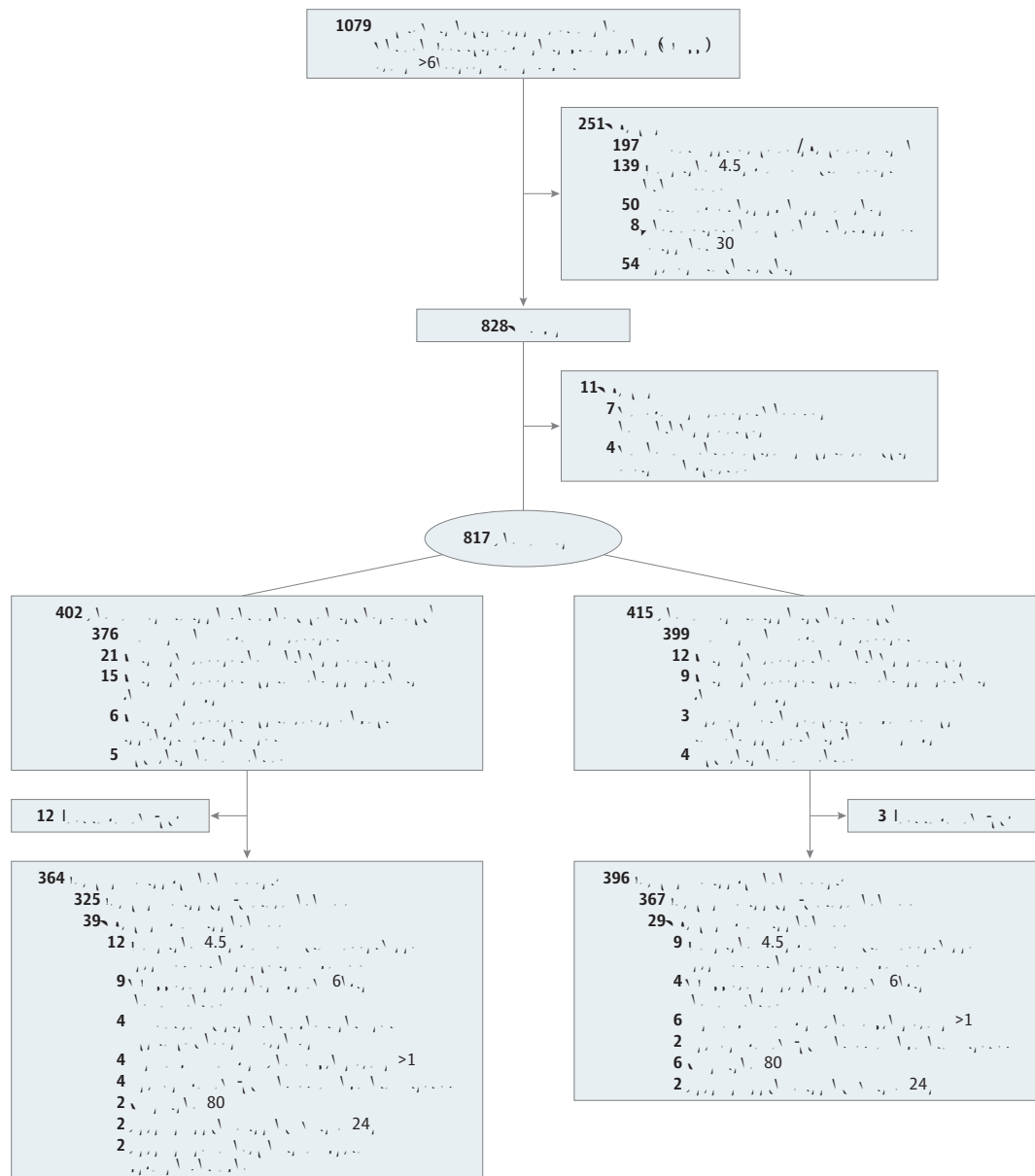
A GLM was also used to compare changes in NIHSS score between admission and 8 days, and the geometric mean ratio and 95% CI were calculated between the argatroban plus



alteplase and alteplase alone groups. The time-to-event outcomes of stroke or other vascular events were compared using Cox regression models, and the corresponding treatment effects were presented as hazard ratios with 95% CIs. The hazard proportionality assumption was tested by introducing an interaction between time and treatment in the Cox model.

The primary analyses of the primary and secondary outcomes were unadjusted. Covariate-adjusted GLM analyses were also performed for all outcomes, adjusting for pre-specified prognostic factors: age, sex, NIHSS score at randomization, time from symptom onset to thrombolysis, pre-morbid function (mRS score of 1 or 2), and history of stroke or transient ischemic attack. Endovascular therapy and large artery occlusion were planned in the covariate-adjusted analyses but were excluded due to skewed distribution or

Flowchart of the Study Population



^a A total of 383 patients in the argatroban plus alteplase group and 397 patients in the alteplase group were included in the safety population.

^c Baseline characteristics in patients missing primary outcome data are shown in eTable 4 in Supplement 3.

^b Patients lost to follow-up due to missing any follow-up assessments after treatment.

per-protocol analyses (eTable 1 in Supplement 3). A post hoc ordinal logistic regression analysis showed no significant differences in the mRS score improvement at 90 days, in which the proportional odds assumption was met ($P = .12$; Table 1 and eTable 1 in Supplement 3).

A prespecified subgroup analysis showed no evidence of effect modification in the risks of having a primary outcome between the argatroban plus alteplase and alteplase alone groups by age, sex, NIHSS score at randomization, endovascular therapy, large artery occlusion, time from the onset of

symptoms to treatment, mRS score at admission, and history of stroke or transient ischemic attack (eFigure 1 in Supplement 3). The results of the per-protocol analysis were similar to those of the full analysis set population for the primary outcome (eFigure 1 in Supplement 3).

Adverse Events

The occurrence of adverse events was similar across the groups, including symptomatic intracranial hemorrhage, other intracranial bleeding events, major bleeding events, other

Table 1. Baseline Characteristics of Patients in the Full Analysis Set and the Randomization Set

Characteristic	Full analysis set		Randomization set	
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Argatroban plus alteplase (n = 402)	Alteplase alone (n = 415)
Age (mean), y	66 (58-72)	64 (56-71)	66 (58-72)	64 (56-71)
Sex				
Male	249 (68.4)	289 (73.0)	271/397 (68.3)	299/411 (72.7)
Female	115 (31.6)	107 (27.0)	126/397 (31.7)	112/411 (27.3)
Race				
White	131 (36.0)	141 (35.6)	141/396 (35.6)	143/411 (34.8)
Black	69/354 (19.5)	69/389 (17.7)	73/386 (18.9)	69/404 (17.1)
Hispanic				
White	203 (55.8)	223 (56.3)	216/397 (54.4)	232/411 (56.4)
Black	91 (25.0)	81 (20.5)	100/397 (25.2)	87/410 (21.2)
Hispanic	74 (20.3)	68 (17.2)	82/397 (20.7)	74/411 (18.0)
Other				
White	18/346 (5.2)	21/378 (5.6)	19/365 (5.2)	22/388 (5.7)
Black	3 (0.8)	3 (0.8)	3/397 (0.8)	4/411 (1.0)
Hispanic	3 (0.8)	4 (1.0)	3/397 (0.8)	5/411 (1.2)
Unknown				
Other				
Unknown	22.9 (21.0-24.0)	23.7 (21.0-24.0)	22.7 (20.1-24.0)	23.5 (21.0-24.0)
Stroke severity				
NIHSS score (mean), range				
≤140	154 (139-170)	150 (136-166)	152 (138-170)	150 (136-165)
>140	242 (66.5)	250 (63.1)	257/397 (64.7)	250/411 (60.8)
NIHSS score (mean), range				
≤90	90 (80-98)	88 (80-97)	90 (80-98)	88 (80-97)
>90	142 (39.0)	142 (35.9)	151/397 (38.0)	145/411 (35.3)
NIHSS score (mean), range				
≤126	118.8 (102.8-164.0)	121.0 (102.6-160.7)	120.8 (102.6-162.2)	120.6 (102.6-163.8)
>126	128/293 (43.7)	143/324 (44.1)	144/321 (44.9)	150/335 (44.8)
NIHSS score (mean), range				
9 (7-12)	9 (7-12)	8 (6-12)	9 (7-12)	9 (6-12)
75 (71-79)	75 (71-79)	74 (70-78)	75 (71-79)	74 (70-78)
9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)
NIHSS score (mean), range				
≤20	295 (81.0)	314 (79.3)	318/397 (80.1)	326/411 (79.3)
21-30	65 (17.9)	76 (19.2)	75/397 (18.9)	79/411 (19.2)
31-40	4 (1.1)	6 (1.5)	4/397 (1.0)	6/411 (1.5)
NIHSS score (mean), range				
233/356 (65.4)	233/356 (65.4)	270/389 (69.4)	242/370 (65.4)	276/401 (68.8)
18.8	67/356 (18.8)	74/389 (19.0)	71/370 (19.2)	76/401 (19.0)
9.3	33/356 (9.3)	29/389 (7.5)	34/370 (9.2)	33/401 (8.2)
5.6	20/356 (5.6)	15/389 (3.9)	20/370 (5.4)	15/401 (3.7)
0.8	3/356 (0.8)	1/389 (0.3)	3/370 (0.8)	1/401 (0.2)
NIHSS score (mean), range				
157/195 (80.5)	157/195 (80.5)	153/200 (76.5)	167/205 (81.5)	162/209 (77.5)
16.9	33/195 (16.9)	43/200 (21.5)	33/205 (16.1)	43/209 (20.6)
2.6	5/195 (2.6)	4/200 (2.0)	5/205 (2.4)	4/209 (1.9)

(continued)

Table 1. Baseline Characteristics of the Study Population and Effect of Functional Outcome at 90 Days After Acute Ischemic Stroke (Continued)

Characteristic	No. (%)			
	Final analysis set		Randomization set	
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Argatroban plus alteplase (n = 402)	Alteplase alone (n = 415)
Female sex	18/75 (24.0)	16/85 (18.8)	20/82 (24.4)	16/88 (18.2)
Age, mean (SD), y	44/75 (58.7)	49/85 (57.6)	47/82 (57.3)	52/88 (59.1)
Time from symptom onset to treatment, mean (SD), h	2/75 (2.7)	5/85 (5.9)	2/82 (2.4)	5/88 (5.7)
Time from symptom onset to randomization, mean (SD), h	4/75 (5.3)	5/85 (5.9)	4/82 (4.9)	5/88 (5.7)
Time from randomization to treatment, mean (SD), h	5/75 (6.7)	6/85 (7.1)	5/82 (6.1)	6/88 (6.8)
Time from randomization to discharge, mean (SD), h	4/75 (5.3)	4/85 (4.7)	4/82 (4.9)	4/88 (4.5)
Time from randomization to death, mean (SD), h	160 (120-208)	155 (114-201)	160 (120-208)	156 (115-201)
Time from randomization to discharge, mean (SD), h	10 (7-13)	9 (7-13)	10 (7-12)	10 (6-13)
Time from randomization to death, mean (SD), h	10 (2.7)	13 (3.3)	15/397 (3.7)	17/411 (4.1)

^a Defined as consuming alcohol at least once a week within 1 year prior to the onset of the disease.

^b Comorbidities based on family or patient report.

^c Prior ischemic stroke referred only to the patients with pre-morbid modified Rankin Scale (mRS) scores ≤1.

^d Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit; a mean NIHSS score of 8 to 9 indicates moderate neurologic deficit.

^e The GRASPS score uses 6 clinical variables to estimate risk of symptomatic intracranial hemorrhage after intravenous alteplase and ranges from 0 to 101, with higher scores indicating greater risk.

^f The Alberta Stroke Program Early CT Score (ASPECTS) determines the extent

of ischemic tissue based on computed tomography imaging. Scores range from 0 to 10, with higher scores indicating less infarct volume.

^g Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death).

^h The presumed stroke cause was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) using clinical findings, brain imaging, and laboratory test results. Other causes included nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorder.

ⁱ Definite conclusions based on vessel examination. The diagnosis was based on the clinician's interpretation of the clinical features and examination results at the time of hospital discharge.

bleeding events, and other most common adverse events between the groups (Table 3).

Discussion

This trial showed that treatment with argatroban plus intravenous alteplase compared with alteplase alone did not result in a significantly greater likelihood of excellent functional outcome at 90 days or identify a signal of harm among patients with acute ischemic stroke. Furthermore, there was no evidence of effect modification of prespecified subgroups on the treatment effect on the primary end point.

This study differed from previous studies in major ways. First, previous trials had relatively small sample sizes, ranging from 100 to 1000 participants. To date, the present study, including 760 participants, is the largest randomized trial that provides robust statistical evidence on the effect of argatroban plus alteplase on AIS. Second, the included patients with median NIHSS scores of 7 to 10 had less severe neurologic deficit than those in previous studies with a median NIHSS score of 10 to 15. Third, the target population in previous studies was patients with large artery occlusion, whereas this was not mandatory in the current study. Although previous studies suggested that argatroban plus alteplase increased the percentage of patients with excellent functional outcomes, unexpectedly, argatroban plus alteplase did not show a significant

improvement in neurologic function in the present study. The negative results may be attributed to the fewer enrolled patients with large artery occlusion in the current study (12.5%), because the promising results of argatroban plus alteplase were found in patients with a high percentage of large artery occlusion (15.0% to 20.0%),¹⁷ while argatroban plus alteplase may increase recanalization and decrease the reocclusion rates of large artery occlusion, resulting in better neurologic improvement. Namely, there may be a “floor” effect where smaller clots are lysed as much as possible by alteplase so there is less room for benefit, as opposed to larger clots that do not respond as well to alteplase. Because it is impractical to perform vessel imaging before intravenous thrombolysis in most stroke centers in China, large artery occlusion was not mandatory in this trial design. In addition, the rapid development of endovascular treatment after clinical trials resulted in more patients with large artery occlusion receiving endovascular treatment. Collectively, these reasons resulted in a lower proportion of patients with large artery occlusion enrolled in the trial. Having a similar profile of enrolled patients and study aim to this trial, the Multi-arm Optimization of Stroke Thrombolysis (MOST; NCT02700000) study is ongoing and the results will bring further evidence about the efficacy and safety of argatroban plus alteplase therapy.

In the current study, there was no effect of argatroban plus alteplase on early functional outcome, such as early neurologic improvement at 24 hours, early neurologic deterioration

Table 2. Primary and Secondary Outcomes of the Argatroban Plus Alteplase Study

Outcome	No. (%)		Unadjusted		P value	Adjusted ^a		P value
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Risk difference (95% CI)	Risk ratio (95% CI)		Risk difference (95% CI)	Risk ratio (95% CI)	
Primary								
NIHSS score at 90 days	210/329 (63.8)	238/367 (64.9)	1.0 (0.81, 1.16)	0.98 (0.88, 1.10)	.78	1.0 (0.76, 1.31)	1.03 (0.86, 1.23)	.78
Secondary								
NIHSS score at 90 days	250/329 (76.0)	280/367 (76.3)	0.3 (0.66, 0.60)	1.00 (0.92, 1.08)	.93	0.9% (0.52, 1.69)	0.99 (0.77, 1.26)	.92
NIHSS score at 48 hours	251 (69.0)	269 (67.9)	1.0 (0.56, 1.76)	1.03 (0.84, 1.27)	.76	1.0 (0.57, 1.77)	1.03 (0.84, 1.28)	.77
NIHSS score at 14 days	13 (3.6)	20 (5.1)	1.5 (0.44, 2.54)	0.71 (0.36, 1.40)	.31	1.7 (0.45, 6.82)	0.69 (0.35, 1.37)	.26
NIHSS score at 90 days	0.85 (0.16, 1.61, 0.25)	0.81 (0.19, 1.95, 0.29)	0.03 (0.16, 0.11)		.69	0.01 (0.15, 0.12)		.85
NIHSS score at 90 days	1/329 (0.3)	1/367 (0.3)	1.12 (0.07, 17.94)		.94	0.78 (0.04, 15.16)		.87
NIHSS score at 90 days			1.06 (0.81, 1.39)		.66	1.01 (0.58, 1.76)		.98

Abbreviations: GMR, geometric mean ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

^a Adjusted for prespecified prognostic variables (age, sex, NIHSS score at randomization, time from the onset of symptoms to thrombolysis, premorbid function [mRS score of 0 or 1], and history of stroke or transient ischemic attack).

^b mRS scores range from 0 to 6; a score of 0 indicates no symptoms; 1, symptoms without clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death.

^c Calculated using a generalized linear model.

^d Early neurologic improvement was defined as a decrease of ≥ 2 on the NIHSS score between baseline and 48 hours.

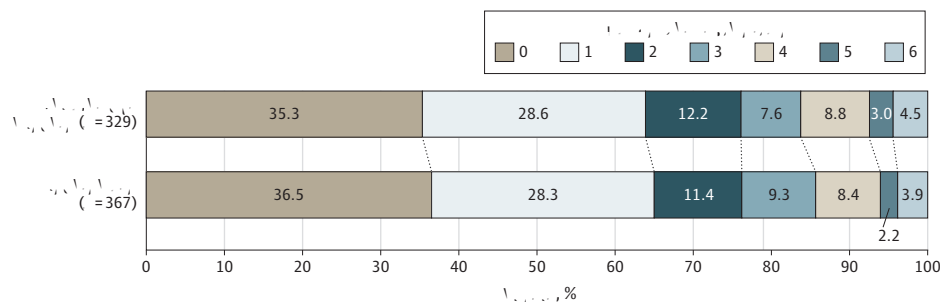
^e Early neurologic deterioration was defined as an increase of ≥ 4 on the NIHSS score between baseline and 48 hours, but not the result of cerebral hemorrhage.

^f NIHSS scores range from 0 to 42, with higher scores indicating greater stroke severity. The log (NIHSS score + 1) was analyzed using a generalized linear model.

^g Calculated using Cox regression model.

^h As a post hoc analysis, this outcome was used to describe a shift in measures of functioning according to the full range of scores on the mRS at 90 days.

Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days



A total of 760 patients were included in the full analysis set; however, 696 patients (329 in the argatroban plus alteplase group and 367 in the alteplase alone group) with 90-day follow-up data were included in the analysis of the primary outcome. The raw distribution of scores is shown. Scores ranged from 0 to 6, with 0 indicating no symptoms; 1, symptoms without clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately

severe disability; 5, severe disability; and 6, death. Treatment with argatroban plus alteplase was associated with an adjusted risk difference of -1.0% (95% CI, -7.6% to 5.7% ; $P = .78$) for the outcome of a score of 0 or 1 on the modified Rankin Scale at 90 days. The overall distribution of scores was not statistically significant in the ordinal logistic analysis (odds ratio, 1.06 [95% CI, 0.81-1.39]; $P = .66$; adjusted odds ratio, 1.01 [95% CI, 0.58-1.76]; $P = .98$).

at 90 hours, or change in NIHSS score compared with randomization at 90 days. The lack of a significant effect on early outcomes correlated well with the negative primary outcome because the changes in these early outcomes, such as an increase in early neurologic improvement and a decrease in early neurologic deterioration, will result in the high risk of excellent functional outcome at 90 days. Furthermore, no significant dif-

ference in risk of having other secondary outcomes, such as stroke or other vascular events within 90 days, was found between the groups.

For the adverse events, similar rates of bleeding events were observed between the argatroban plus alteplase group and the alteplase alone group, which was consistent with previous studies. In this trial, the symptomatic intracranial

Table 3. Adverse Events in the Safety Population^a

Adverse event	No. (%)	
	Argatroban plus alteplase (n = 383)	Alteplase alone (n = 397)
Death	8 (2.1)	7 (1.8)
Stroke	8 (2.1)	7 (1.8)
Myocardial infarction	13 (3.4)	14 (3.5)
Systemic embolism	9 (2.3)	8 (2.0)
Ischemic stroke		
Type 1	9 (2.3)	10 (2.5)
Type 2	7 (1.8)	8 (2.0)
Type 3		
Type 4		
Type 5		
Type 6		
Type 7		
Type 8		
Type 9		
Type 10		
Type 11		
Type 12		
Type 13		
Type 14		
Type 15		
Type 16		
Type 17		
Type 18		
Type 19		
Type 20		
Type 21		
Type 22		
Type 23		
Type 24		
Type 25		
Type 26		
Type 27		
Type 28		
Type 29		
Type 30		
Type 31		
Type 32		
Type 33		
Type 34		
Type 35		
Type 36		
Type 37		
Type 38		
Type 39		
Type 40		
Type 41		
Type 42		
Type 43		
Type 44		
Type 45		
Type 46		
Type 47		
Type 48		
Type 49		
Type 50		
Type 51		
Type 52		
Type 53		
Type 54		
Type 55		
Type 56		
Type 57		
Type 58		
Type 59		
Type 60		
Type 61		
Type 62		
Type 63		
Type 64		
Type 65		
Type 66		
Type 67		
Type 68		
Type 69		
Type 70		
Type 71		
Type 72		
Type 73		
Type 74		
Type 75		
Type 76		
Type 77		
Type 78		
Type 79		
Type 80		
Type 81		
Type 82		
Type 83		
Type 84		
Type 85		
Type 86		
Type 87		
Type 88		
Type 89		
Type 90		
Type 91		
Type 92		
Type 93		
Type 94		
Type 95		
Type 96		
Type 97		
Type 98		
Type 99		
Type 100		
Type 101		
Type 102		
Type 103		
Type 104		
Type 105		
Type 106		
Type 107		
Type 108		
Type 109		
Type 110		
Type 111		
Type 112		
Type 113		
Type 114		
Type 115		
Type 116		
Type 117		
Type 118		
Type 119		
Type 120		
Type 121		
Type 122		
Type 123		
Type 124		
Type 125		
Type 126		
Type 127		
Type 128		
Type 129		
Type 130		
Type 131		
Type 132		
Type 133		
Type 134		
Type 135		
Type 136		
Type 137		
Type 138		
Type 139		
Type 140		
Type 141		
Type 142		
Type 143		
Type 144		
Type 145		
Type 146		
Type 147		
Type 148		
Type 149		
Type 150		
Type 151		
Type 152		
Type 153		
Type 154		
Type 155		
Type 156		
Type 157		
Type 158		
Type 159		
Type 160		
Type 161		
Type 162		
Type 163		
Type 164		
Type 165		
Type 166		
Type 167		
Type 168		
Type 169		
Type 170		
Type 171		
Type 172		
Type 173		
Type 174		
Type 175		
Type 176		
Type 177		
Type 178		
Type 179		
Type 180		
Type 181		
Type 182		
Type 183		
Type 184		
Type 185		
Type 186		
Type 187		
Type 188		
Type 189		
Type 190		
Type 191		
Type 192		
Type 193		
Type 194		
Type 195		
Type 196		
Type 197		
Type 198		
Type 199		
Type 200		
Type 201		
Type 202		
Type 203		
Type 204		
Type 205		
Type 206		
Type 207		
Type 208		
Type 209		
Type 210		
Type 211		
Type 212		
Type 213		
Type 214		
Type 215		
Type 216		
Type 217		
Type 218		
Type 219		
Type 220		
Type 221		
Type 222		
Type 223		
Type 224		
Type 225		
Type 226		
Type 227		
Type 228		
Type 229		
Type 230		
Type 231		
Type 232		
Type 233		
Type 234		
Type 235		
Type 236		
Type 237		
Type 238		
Type 239		
Type 240		
Type 241		
Type 242		
Type 243		
Type 244		
Type 245		
Type 246		
Type 247		
Type 248		
Type 249		
Type 250		
Type 251		
Type 252		
Type 253		
Type 254		
Type 255		
Type 256		
Type 257		
Type 258		
Type 259		
Type 260		
Type 261		
Type 262		
Type 263		
Type 264		
Type 265		
Type 266		
Type 267		
Type 268		
Type 269		
Type 270		
Type 271		
Type 272		
Type 273		
Type 274		
Type 275		
Type 276		
Type 277		
Type 278		
Type 279		
Type 280		
Type 281		
Type 282		
Type 283		
Type 284		
Type 285		
Type 286		
Type 287		
Type 288		
Type 289		
Type 290		
Type 291		
Type 292		
Type 293		
Type 294		
Type 295		
Type 296		
Type 297		
Type 298		
Type 299		
Type 300		
Type 301		
Type 302		
Type 303		
Type 304		
Type 305		
Type 306		
Type 307		
Type 308		
Type 309		
Type 310		
Type 311		
Type 312		
Type 313		
Type 314		
Type 315		
Type 316		
Type 317		
Type 318		
Type 319		
Type 320		
Type 321		
Type 322		
Type 323		
Type 324		
Type 325		
Type 326		
Type 327		
Type 328		
Type 329		
Type 330		
Type 331		
Type 332		
Type 333		
Type 334		
Type 335		
Type 336		
Type 337		
Type 338		
Type 339		
Type 340		
Type 341		
Type 342		
Type 343		
Type 344		
Type 345		
Type 346		
Type 347		
Type 348		
Type 349		
Type 350		
Type 351		
Type 352		
Type 353		
Type 354		
Type 355		
Type 356		
Type 357		
Type 358		
Type 359		
Type 360		
Type 361		
Type 362		
Type 363		
Type 364		
Type 365		
Type 366		
Type 367		
Type 368		
Type 369		
Type 370		
Type 371		
Type 372		
Type 373		
Type 374		
Type 375		
Type 376		
Type 377		
Type 378		
Type 379		
Type 380		
Type 381		
Type 382		
Type 383		
Type 384		
Type 385		
Type 386		
Type 387		
Type 388		
Type 389		
Type 390		
Type 391		
Type 392		
Type 393		
Type 394		
Type 395		
Type 396		
Type 397		
Type 398		
Type 399		
Type 400		

^a The safety population consisted of all randomized participants who received at least 1 dose of the study drug.

^b The European Cooperative Acute Stroke Study (ECASS) defines symptomatic intracranial hemorrhage as any evidence of bleeding on the head computed tomography imaging associated with clinically

and try to ensure that the primary end point was measured objectively. Third, a lower proportion of patients with large artery occlusion was enrolled in the trial than in previous studies,¹⁷ which may be the main cause of the negative results of this trial. Thus, the effect of alteplase plus argatroban in patients with large artery occlusion warrants investigation in future trials. In addition, endovascular thrombectomy was used infrequently because most participating sites did not have endovascular thrombectomy capability. This limits generalizability to sites with readily available endovascular thrombectomy. Fourth, argatroban (0.5 g/kg bolus followed by 0.5 g/kg per minute) was used in our trial based on previous studies,¹⁷ while high-dose argatroban (0.5 g/kg bolus followed by 1 g/kg per minute) was used in previous studies.^{18,19} In addition, only 10.5% patients met target APTT at 2 hours, and it took approximately 4 hours to reach target APTT (eTable 1 and eFigure 1 in Supplement 1). The low dose of argatroban and low target APTT

rate may partially contribute to the neutral results, because high doses of argatroban and good target APTT theoretically may produce a better improvement of clinical outcome if symptomatic intracranial hemorrhage did not increase. Fifth, the dropout rate in this trial may have introduced attrition bias or possible confounding. Sixth, further confirmation of these conclusions in non-Chinese populations would be welcome, given the differences in body mass index, comorbidities, and etiology of patients with AIS.

Conclusions

Among patients with AIS, treatment with argatroban plus intravenous alteplase compared with alteplase alone did not result in a significantly greater likelihood of excellent functional outcome at 90 days.

ARTICLE INFORMATION

Accepted for Publication: January 16, 2023.

Published Online: February 9, 2023.

doi:10.1001/jama.2023.0550

Author Affiliations: Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China (Chen, Cui, Zhou, Dai); Department of Neurology, Liaoning Health Industry Group Fukuang General Hospital, Fushun, China (Li); Department of Neurology, The Affiliated Nanshi Hospital of Henan University, Nanyang, China (Peng); Department of Neurology, Tieling County Central Hospital, Tieling, China (Zhang); Department of Neurology, Tonghua Vascular Disease Hospital, Tonghua, China (Liu, Yuan); Department of Neurology, Lvshunkou Traditional Chinese Medicine Hospital, Dalian, China (Jiang); Department of Neurology, Anyang People's Hospital, Anyang, China (Q.-C. Yang); Department of Neurology, Liaoning Health Industry Group Fuxinkuang General Hospital, Fuxin, China (Duan); Department of Neurology, Haicheng Traditional Chinese Medicine Hospital, Haicheng, China (Ma); Department of Neurology, Anshan Changda Hospital, Anshan, China (Zhao); Department of Neurology, Tianjin Beichen Traditional Chinese Hospital, Tianjin, China (R.-X. Wang); Department of Neurology, Panjin Central Hospital, Panjin, China (Sun); Department of Neurology, Nanyang Central Hospital, Nanyang, China (Shen); Department of Neurology, Fuqing Hospital, Fuqing, China (E.-Q. Wang); Department of Neurology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China (L.-H. Wang); Department of Neurology, Huludao Second People's Hospital, Huludao, China (Feng); Department of Neurology, Liaocheng Brain Hospital, Liaocheng, China (F.-Y. Wang); Department of Neurology, Wafangdian Third Hospital, Dalian, China (Zou); Department of Neurology, Guangxi Zhuang Autonomous Region People's Hospital, Nanning, China (H.-P. Yang); Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, China (K. Wang); Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom (D.-L. Wang); Department of Neurology, Beijing Tiantan Hospital, Beijing, China (Y.-L. Wang).

Author Contributions: Dr Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chen, D. Wang, Y. Wang.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chen, Cui, Zhou, Dai, Li, Peng, Zhang, Liu, Yuan, Jiang, Q. Yang, Duan, Ma, Zhao, R. Wang, Sun, Shen, E. Wang, L. Wang, Feng, F. Wang, Zou, K. Wang, D. Wang, Y. Wang.

Critical revision of the manuscript for important intellectual content: Chen, H. Yang, D. Wang.

Statistical analysis: Cui, D. Wang.

Obtained funding: Chen, Y. Wang.

Administrative, technical, or material support: H. Yang.

Supervision: Chen, D. Wang.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study was funded by grants from the National Natural Science Foundation of China (81825007, 8207147), Beijing Outstanding Young Scientist Program (BJJWZYJH01201910025030), the National Key R&D Program of China (2017YFC1308200), and the Science and Technology Project Plan of Liao Ning Province (2019JH2/10300027).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The ARAIS investigators from each participating center are listed in eAppendix 3 in Supplement 3 and the principal investigators are listed in Supplement 4.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank the investigators and research staff at the participating sites, members of the executive committee, clinical research organization, and trial steering and data monitoring committees (eAppendix 2 in Supplement 3). We also thank the participants, their families, and their friends.

REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients

with acute ischemic stroke: 2019 update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211

2. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38(3):967-973. doi:10.1161/01.STR.0000258112.14918.24

3. Alexandrov AV, Grotta JC. Arterial recanalization in stroke patients treated with intravenous tissue plasminogen activator. *Neurology*. 2002;59(6):862-867. doi:10.1212/WNL.59.6.862

4. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X

5. Saqqur M, Molina CA, Salam A, et al; CLOTBUST Investigators. Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: a multicenter transcranial Doppler study. *Stroke*. 2007;38(1):69-74. doi:10.1161/01.STR.0000251800.01964.f6

6. Chen L, Cao S, Yang J. Argatroban plus aspirin versus aspirin in acute ischemic stroke. *Neurol Res*. 2018;40(10):862-867. doi:10.1080/01616412.2018.1495882

7. Hosomi N, Naya T, Kohno M, Kobayashi S, Koziol JA; Japan Standard Stroke Registry Study Group. Efficacy of anti-coagulant treatment with argatroban on cardioembolic stroke. *J Neurol*. 2007;254(5):605-612. doi:10.1007/s00415-006-0365-y

8. Jang IK, Gold HK, Leinbach RC, Fallon JT, Collen D. In vivo thrombin inhibition enhances and sustains arterial recanalization with recombinant tissue-type plasminogen activator. *Circ Res*. 1990;67(6):1552-1561. doi:10.1161/01.RES.67.6.1552

9. Morris DC, Zhang L, Zhang ZG, et al. Extension of the therapeutic window for recombinant tissue plasminogen activator with argatroban in a rat model of embolic stroke. *Stroke*. 2001;32(11):2635-2640. doi:10.1161/hs1101.097390

10. Barreto AD, Alexandrov AV, Lyden P, et al. The argatroban and tissue-type plasminogen activator stroke study: final results of a pilot safety study. *Stroke*. 2012;43(3):770-775. doi:10.1161/STROKEAHA.111.625574
11. Barreto AD, Ford GA, Shen L, et al; ARTSS-2 Investigators. Randomized, multicenter trial of ARTSS-2 (argatroban with recombinant tissue plasminogen activator for acute stroke). *Stroke*. 2017;48(6):1608-1616. doi:10.1161/STROKEAHA.117.016720
12. Berekashvili K, Soomro J, Shen L, et al. Safety and feasibility of argatroban, recombinant tissue plasminogen activator, and intra-arterial therapy in stroke (ARTSS-IA study). *J Stroke Cerebrovasc Dis*. 2018;27(12):3647-3651. doi:10.1016/j.jstrokecerebrovasdis.2018.08.036
13. Lyden P, Pereira B, Chen B, et al. Direct thrombin inhibitor argatroban reduces stroke damage in 2 different models. *Stroke*. 2014;45(3):896-899. doi:10.1161/STROKEAHA.113.004488
14. Yang Y, Zhou Z, Pan Y, Chen H, Wang Y; ARAIS Protocol Steering Group. Randomized trial of argatroban plus recombinant tissue-type plasminogen activator for acute ischemic stroke (ARAIS): rationale and design. *Am Heart J*. 2020; 225:38-43. doi:10.1016/j.ahj.2020.04.003
15. Sugg RM, Pary JK, Uchino K, et al. Argatroban tPA stroke study: study design and results in the first treated cohort. *Arch Neurol*. 2006;63(8):1057-1062. doi:10.1001/archneur.63.8.1057
16. Molina CA, Alvarez-Sabín J, Montaner J, et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. *Stroke*. 2002;33(6):1551-1556. doi:10.1161/01.STR.0000016323.13456.E5
17. Arenillas JF, Rovira A, Molina CA, Grivé E, Montaner J, Alvarez-Sabín J. Prediction of early neurological deterioration using diffusion- and perfusion-weighted imaging in hyperacute middle cerebral artery ischemic stroke. *Stroke*. 2002;33(9):2197-2203. doi:10.1161/01.STR.0000027861.75884.DF
18. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064-2089. doi:10.1161/STR.0b013e318296aeca
19. Rao NM, Levine SR, Gornbein JA, Saver JL. Defining clinically relevant cerebral hemorrhage after thrombolytic therapy for stroke: analysis of the National Institute of Neurological Disorders and Stroke tissue-type plasminogen activator trials. *Stroke*. 2014;45(9):2728-2733. doi:10.1161/STROKEAHA.114.005135
20. Fiorelli M, Bastianello S, von Kummer R, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke*. 1999;30(11):2280-2284. doi:10.1161/01.STR.30.11.2280
21. Deeds SI, Barreto A, Elm J, et al. The multiarm optimization of stroke thrombolysis phase 3 acute stroke randomized clinical trial: rationale and methods. *Int J Stroke*. 2021;16(7):873-880. doi:10.1177/17474932020978345
22. Zheng H, Yang Y, Chen H, et al. Thrombolysis with alteplase 3-4.5 hours after acute ischaemic stroke: the first multicentre, phase III trial in China. *Stroke Vasc Neurol*. 2020;5(3):285-290. doi:10.1136/svn-2020-000337
23. Li S, Pan Y, Wang Z, et al. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study. *Stroke Vasc Neurol*. 2022; 7(1):47-53. doi:10.1136/svn-2021-000978