JAMA | Original Investigation

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

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).

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

Key Points

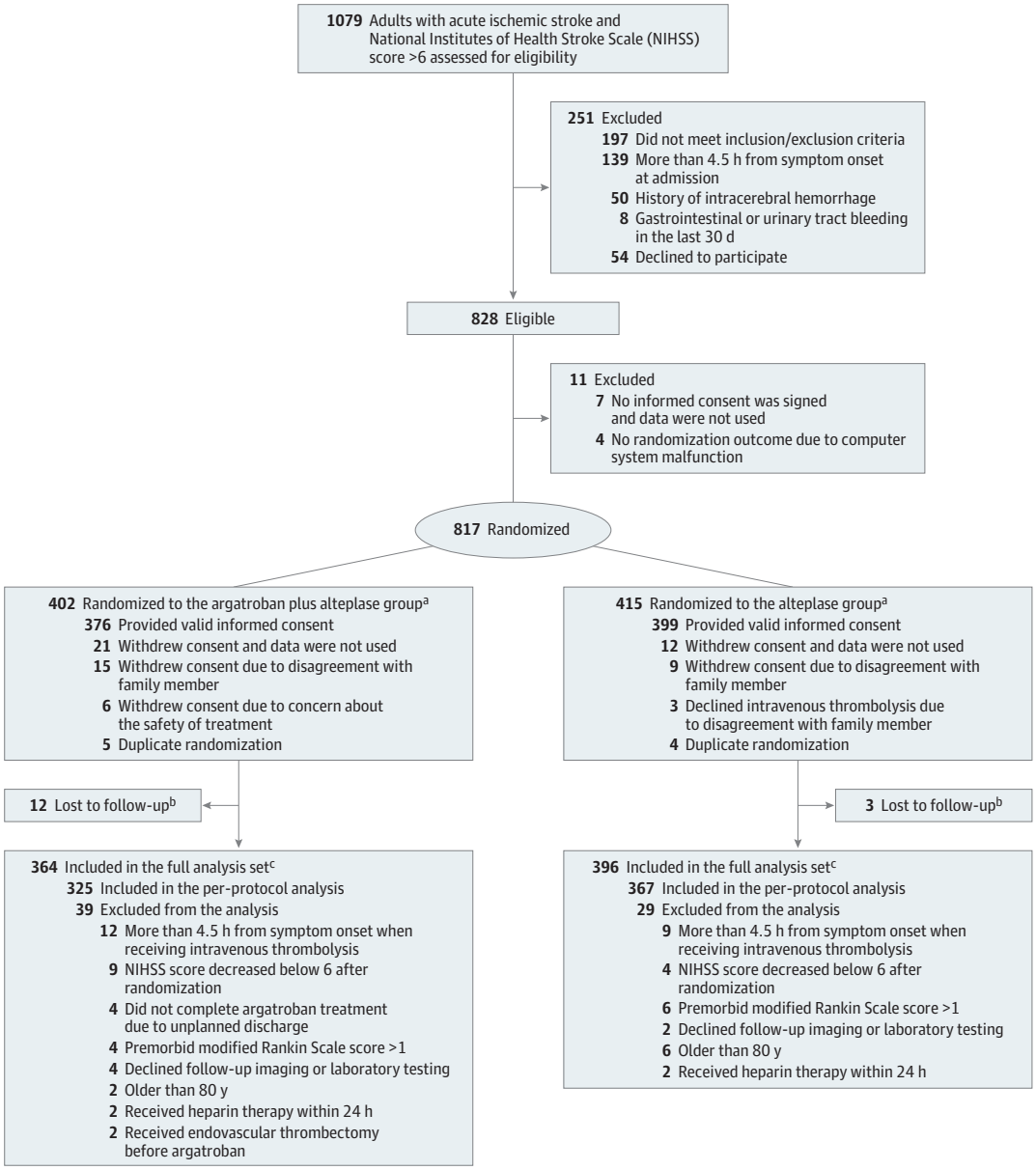
Question Does argatroban improve neurologic function in patients with acute ischemic stroke who received intravenous recombinant tissue-type plasminogen activator (alteplase)?

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.

Methods

Results



[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.

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

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

1.

Characteristic	No. (%)			
	Full analysis set		Randomization set	
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Argatroban plus alteplase (n = 402)	Alteplase alone (n = 415)
Age, median (IQR), y	66 (58-72)	64 (56-71)	66 (58-72)	64 (56-71)
Sex				
Men	249 (68.4)	289 (73.0)	271/397 (68.3)	299/411 (72.7)
Women	115 (31.6)	107 (27.0)	126/397 (31.7)	112/411 (27.3)
Currently smokes tobacco	131 (36.0)	141 (35.6)	141/396 (35.6)	143/411 (34.8)
Currently drinks alcohol[a]	69/354 (19.5)	69/389 (17.7)	73/386 (18.9)	69/404 (17.1)
Comorbidities[b]				
Hypertension	203 (55.8)	223 (56.3)	216/397 (54.4)	232/411 (56.4)
Diabetes	91 (25.0)	81 (20.5)	100/397 (25.2)	87/410 (21.2)
Prior ischemic or hemorrhagic stroke[c]	74 (20.3)	68 (17.2)	82/397 (20.7)	74/411 (18.0)
Atrial fibrillation	18/346 (5.2)	21/378 (5.6)	19/365 (5.2)	22/388 (5.7)
Hyperlipidemia	3 (0.8)	3 (0.8)	3/397 (0.8)	4/411 (1.0)
Prior transient ischemic attack	3 (0.8)	4 (1.0)	3/397 (0.8)	5/411 (1.2)
Body mass index, median (IQR)	22.9 (21.0-24.0)	23.7 (21.0-24.0)	22.7 (20.1-24.0)	23.5 (21.0-24.0)
Blood pressure at randomization				
Systolic				
Median (IQR), mm Hg	154 (139-170)	150 (136-166)	152 (138-170)	150 (136-165)
>140 mm Hg	242 (66.5)	250 (63.1)	257/397 (64.7)	250/411 (60.8)
Diastolic				
Median (IQR), mm Hg	90 (80-98)	88 (80-97)	90 (80-98)	88 (80-97)
>90 mm Hg	142 (39.0)	142 (35.9)	151/397 (38.0)	145/411 (35.3)
Blood glucose				
Median (IQR), mg/dL	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 mg/dL	128/293 (43.7)	143/324 (44.1)	144/321 (44.9)	150/335 (44.8)
NIHSS score at randomization, median (IQR)[d]	9 (7-12)	8 (6-12)	9 (7-12)	9 (6-12)
GRASPS score at randomization, median (IQR)[e]	75 (71-79)	74 (70-78)	75 (71-79)	74 (70-78)
ASPECTS score at randomization, median (IQR)[f]	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)
Estimated premorbid function (mRS score)[g]				
No symptoms (score of 0)	295 (81.0)	314 (79.3)	318/397 (80.1)	326/411 (79.3)
Symptoms without any disability (score of 1)	65 (17.9)	76 (19.2)	75/397 (18.9)	79/411 (19.2)
Mild disability (score of 2)	4 (1.1)	6 (1.5)	4/397 (1.0)	6/411 (1.5)
Presumed stroke cause[h]				
Undetermined	233/356 (65.4)	270/389 (69.4)	242/370 (65.4)	276/401 (68.8)
Large artery atherosclerosis	67/356 (18.8)	74/389 (19.0)	71/370 (19.2)	76/401 (19.0)
Small artery occlusion	33/356 (9.3)	29/389 (7.5)	34/370 (9.2)	33/401 (8.2)
Cardioembolic	20/356 (5.6)	15/389 (3.9)	20/370 (5.4)	15/401 (3.7)
Other	3/356 (0.8)	1/389 (0.3)	3/370 (0.8)	1/401 (0.2)
Location of responsible vessel[i]				
Anterior stroke	157/195 (80.5)	153/200 (76.5)	167/205 (81.5)	162/209 (77.5)
Posterior stroke	33/195 (16.9)	43/200 (21.5)	33/205 (16.1)	43/209 (20.6)
Anterior and posterior stroke	5/195 (2.6)	4/200 (2.0)	5/205 (2.4)	4/209 (1.9)

(continued)

1. ( )

Characteristic	No. (%)			
	Full analysis set		Randomization set	
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Argatroban plus alteplase (n = 402)	Alteplase alone (n = 415)
Location of responsible artery (≥50% stenosis)[i]				
Internal carotid	18/75 (24.0)	16/85 (18.8)	20/82 (24.4)	16/88 (18.2)
Middle cerebral	44/75 (58.7)	49/85 (57.6)	47/82 (57.3)	52/88 (59.1)
Anterior cerebral	2/75 (2.7)	5/85 (5.9)	2/82 (2.4)	5/88 (5.7)
Posterior cerebral	4/75 (5.3)	5/85 (5.9)	4/82 (4.9)	5/88 (5.7)
Basilar	5/75 (6.7)	6/85 (7.1)	5/82 (6.1)	6/88 (6.8)
Vertebral	4/75 (5.3)	4/85 (4.7)	4/82 (4.9)	4/88 (4.5)
Time from symptom onset to alteplase, median (IQR), min	160 (120-208)	155 (114-201)	160 (120-208)	156 (115-201)
Time from symptom onset to discharge, median (IQR), d	10 (7-13)	9 (7-13)	10 (7-12)	10 (6-13)
Endovascular treatment	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 premorbid 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.

(Table 3).

Discussion

Outcome	No. (%)		Unadjusted			Adjusted[a]		
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Risk difference (95% CI)	Risk ratio (95% CI)	*P* value	Risk difference (95% CI)	Risk ratio (95% CI)	*P* value
Primary								
mRS score of 0 to 1 at 90 d[b,c]	210/329 (63.8)	238/367 (64.9)	−1.0 (−8.1 to 6.1)	0.98 (0.88 to 1.10)	.78	−1.0 (−7.6 to 5.7)	1.03 (0.86 to 1.23)	.78
Secondary								
mRS score of 0 to 2 within 90 d[c]	250/329 (76.0)	280/367 (76.3)	−0.3 (−6.6 to 6.0)	1.00 (0.92 to 1.08)	.93	0.9% (−5.2 to 6.9)	0.99 (0.77 to 1.26)	.92
Early neurologic improvement within 48 h[c,d]	251 (69.0)	269 (67.9)	1.0 (−5.6 to 7.6)	1.03 (0.84 to 1.27)	.76	1.0 (−5.7 to 7.7)	1.03 (0.84 to 1.28)	.77
Early neurologic deterioration within 48 h[c,e]	13 (3.6)	20 (5.1)	−1.5 (−4.4 to 1.4)	0.71 (0.36 to 1.40)	.31	−1.7 (−4.5 to 1.2)	0.69 (0.35 to 1.37)	.26
Change in NIHSS score at day 14 from baseline, median (IQR)[f]	−0.85 (−1.61 to −0.25)	−0.81 (−1.95 to −0.29)	GMR, −0.03 (−0.16 to 0.11)		.69	GMR, −0.01 (−0.15 to 0.12)		.85
Stroke or other vascular events within 90 d[g]	1/329 (0.3)	1/367 (0.3)	Hazard ratio, 1.12 (0.07 to 17.94)		.94	Hazard ratio, 0.78 (0.04 to 15.16)		.87
mRS score distribution at 90 d[c,h]			Odds ratio, 1.06 (0.81 to 1.39)		.66	Odds ratio, 1.01 (0.58 to 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.

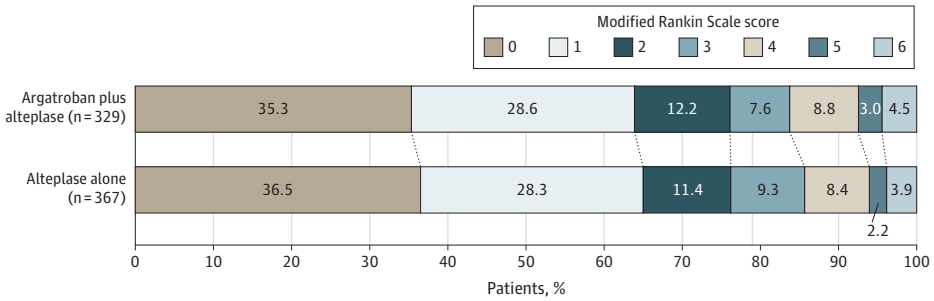
[d] Early neurologic improvement was defined as a decrease of ≥2 on the NIHSS score between baseline and 48 hours.

[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.



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).

Adverse event	No. (%)	
	Argatroban plus alteplase (n = 383)	Alteplase alone (n = 397)
Symptomatic intracranial hemorrhage definition		
ECASS-II[b]	8 (2.1)	7 (1.8)
SITS-MOST[c]	8 (2.1)	7 (1.8)
NINDS[d]	13 (3.4)	14 (3.5)
HBC[e]	9 (2.3)	8 (2.0)
Radiologic hemorrhage type		
Parenchymal hematoma		
Type 2[f]	9 (2.3)	10 (2.5)
Type 1[g]	7 (1.8)	8 (2.0)
Hemorrhagic infarction		
Type 2[h]	8 (2.1)	6 (1.5)
Type 1[i]	9 (2.3)	8 (2.0)
Remote parenchymal hemorrhage[j]	1 (0.3)	3 (0.8)
Major systemic bleeding[k]	1 (0.3)	2 (0.5)
Other bleeding events[l]	14 (3.7)	10 (2.5)
Other most common adverse events[m]	46 (12.0)	43 (10.8)

[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 significant neurologic deterioration (increase in National Institutes of Health Stroke Scale [NIHSS] score ≥4 points) in the opinion of the clinical investigator or independent safety monitor.

[c] The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) defined symptomatic intracranial hemorrhage as local or remote parenchymal hemorrhage type 2 on the imaging scan 22 to 36 hours after treatment combined with a neurologic deterioration of 4 points or more on the NIHSS score from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

[d] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study (NINDS) defined symptomatic intracranial hemorrhage as any hemorrhage plus any neurologic deterioration (NIHSS score ≥1) or that leads to death within 7 days.

[e] The Heidelberg Bleeding Classification (HBC) defined symptomatic intracranial hemorrhage as new intracranial hemorrhage detected by brain imaging associated with any of the following: (1) increase of ≥4 points in total NIHSS score at the time of diagnosis compared with immediately before worsening (note that a 4-point change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurologic status), (2) increase of ≥2 points in 1 NIHSS category, (3) leading to intubation/hemicraniectomy/endovascular thrombectomy placement or other major medical/surgical intervention, or (4) absence of alternative explanation for deterioration.

[f] Parenchymal hematoma type 2 was defined as confluent bleeding occupying more than 30% of the infarct volume and causing significant mass effect.

[g] Parenchymal hematoma type 1 was defined as confluent bleeding occupying less than 30% of the infarct volume with some slight mass effect.

[h] Hemorrhagic infarction type 2 was defined as confluent petechiae within the infarcted area but no space-occupying effect.

[i] Hemorrhagic infarction type 1 was defined as small petechiae along the margins of the infarct.

[j] Remote parenchymal hemorrhage was defined as intracranial hemorrhage outside the infarcted brain tissue.

[k] Major systemic bleeding was defined as a decrease in the hemoglobin level by ≥2 g/dL or a transfusion of ≥2 U of blood.

[l] Other bleeding events included skin, mucous membrane, gastrointestinal, urine, and gum bleeding.

[m] Other most common adverse events included constipation, insomnia, pneumonia, dyspnea, headache, and vomiting.

Conclusions

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.

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