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## Dual Antiplatelet Treatment up to 72 Hours after Ischemic Stroke

Y. Gao, W. Chen, Y. Pan, J. Jing, C. Wang, S.C. Johnston, P. Amarenco, P.M. Bath, L. Jiang, Y. Yang, T. Wang, S. Han, X. Meng, J. Lin, X. Zhao, L. Liu, J. Zhao, Y. Li, Y. Zang, S. Zhang, H. Yang, J. Yang, Yuanwei Wang, D. Li, Yanxia Wang, D. Liu, G. Kang, Yongjun Wang, and Yilong Wang, for the INSPIRES Investigators\*

### ABSTRACT

#### BACKGROUND

Dual antiplatelet treatment has been shown to lower the risk of recurrent stroke as compared with aspirin alone when treatment is initiated early ( $\leq 24$  hours) after an acute mild stroke. The effect of clopidogrel plus aspirin as compared with aspirin alone administered within 72 hours after the onset of acute cerebral ischemia from atherosclerosis has not been well studied.

#### METHODS

In 222 hospitals in China, we conducted a double-blind, randomized, placebo-controlled, two-by-two factorial trial involving patients with mild ischemic stroke or high-risk transient ischemic attack (TIA) of presumed atherosclerotic cause who had not undergone thrombolysis or thrombectomy. Patients were randomly assigned, in a 1:1 ratio, within 72 hours after symptom onset to receive clopidogrel (300 mg on day 1 and 75 mg daily on days 2 to 90) plus aspirin (100 to 300 mg on day 1 and 100 mg daily on days 2 to 21) or matching clopidogrel placebo plus aspirin (100 to 300 mg on day 1 and 100 mg daily on days 2 to 90). There was no interaction between this component of the factorial trial design and a second part that compared immediate with delayed statin treatment (not reported here). The primary efficacy outcome was new stroke, and the primary safety outcome was moderate-to-severe bleeding — both assessed within 90 days.

#### RESULTS

A total of 6100 patients were enrolled, with 3050 assigned to each trial group. TIA was the qualifying event for enrollment in 13.1% of the patients. A total of 12.8% of the patients were assigned to a treatment group no more than 24 hours after stroke onset, and 87.2% were assigned after 24 hours and no more than 72 hours after stroke onset. A new stroke occurred in 222 patients (7.3%) in the clopidogrel–aspirin group and in 279 (9.2%) in the aspirin group (hazard ratio, 0.79; 95% confidence interval [CI], 0.66 to 0.94;  $P=0.008$ ). Moderate-to-severe bleeding occurred in 27 patients (0.9%) in the clopidogrel–aspirin group and in 13 (0.4%) in the aspirin group (hazard ratio, 2.08; 95% CI, 1.07 to 4.04;  $P=0.03$ ).

#### CONCLUSIONS

Among patients with mild ischemic stroke or high-risk TIA of presumed atherosclerotic cause, combined clopidogrel–aspirin therapy initiated within 72 hours after stroke onset led to a lower risk of new stroke at 90 days than aspirin therapy alone but was associated with a low but higher risk of moderate-to-severe bleeding. (Funded by the National Natural Science Foundation of China and others; INSPIRES ClinicalTrials.gov number, NCT03635749.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Yilong Wang can be contacted at [yilong528@aliyun.com](mailto:yilong528@aliyun.com) or at Beijing Tiantian Hospital, No. 119 S. 4th Ring W. Rd., Fengtai District, Beijing 100070, China.

\*A full list of the INSPIRES investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

Drs. Gao and Chen contributed equally to this article.

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PATIENTS WITH ACUTE MILD ISCHEMIC stroke or transient ischemic attack (TIA) have a risk of recurrent stroke of approximately 5 to 10% within 90 days after the onset of the initial event.<sup>1</sup> Guidelines recommend dual antiplatelet therapy with clopidogrel combined with aspirin in patients who have a minor ischemic stroke (defined as a National Institutes of Health Stroke Scale [NIHSS] score of  $\leq 3$ , on a scale from 0 to 42, with higher scores indicating more severe stroke) and who can be treated within 24 hours.<sup>2</sup> The 24-hour time window and low NIHSS score threshold have limited the application of dual antiplatelet therapy in patients with ischemic stroke.

A time-course analysis of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial indicated that combined clopidogrel–aspirin therapy may be beneficial in preventing recurrent stroke when it is initiated as long as 3 days after stroke onset.<sup>3</sup> Meta-analyses have suggested the same for noncardioembolic ischemic stroke or TIA.<sup>4,5</sup> In an exploratory analysis of the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) trial, patients with mild ischemic stroke (defined as an NIHSS score of 4 or 5) who were treated with ticagrelor and aspirin within 24 hours had a lower risk of subsequent stroke than those treated with aspirin alone, without a higher risk of severe bleeding.<sup>6</sup>

In addition, the effectiveness of dual antiplatelet therapy potentially varies depending on the pathogenesis of ischemic stroke; in particular, patients with large-artery atherosclerotic stenosis or multiple acute infarctions may benefit from dual treatment.<sup>1,7-11</sup> In the Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial, we tested the hypothesis that dual antiplatelet therapy with clopidogrel and aspirin initiated within 72 hours after onset would be superior to aspirin alone with regard to the risk of new ischemic or hemorrhagic stroke among patients with mild ischemic stroke or high-risk TIA presumably caused by atherosclerosis (stenosis of extracranial or intracranial artery ipsilateral to the ischemic field) or multiple infarctions with nonstenotic atherosclerotic plaque ipsilateral to the ischemic field.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We conducted this multicenter, double-blind, randomized, placebo-controlled, two-by-two factorial trial at 222 sites in China. Results regarding the antiplatelet therapy are presented here; the results regarding immediate intensive atorvastatin therapy as compared with intensive statin treatment delayed for 3 days are not shown here. Details of the rationale, design, and methods of the trial have been described previously<sup>12</sup> and are provided in the protocol, which is available with the full text of this article at NEJM.org.

The trial was approved by the ethics committees of Beijing Tiantan Hospital and all other participating sites. Before enrollment, patients or their representatives provided written informed consent. The trial was conducted in accordance with the principles of the 18th World Medical Assembly International Council for Harmonisation guidelines for Good Clinical Practice that have been established for trials in China.<sup>13,14</sup>

The steering committee was responsible for the design and conduct of the trial and for the interpretation of the data, as well as for ensuring the integrity of the data, the analyses, and the presentation of the results. The members of the steering committee vouch for the fidelity of the trial to the protocol. The executive committee collected blinded data and provided guidance for the trial. An independent data and safety monitoring board monitored the progress of the trial on a regular basis to guarantee that the trial met ethical requirements and patient safety standards. An independent clinical-event adjudication committee reviewed all the clinical-outcome events (including stroke, myocardial infarction, death, and moderate-to-severe bleeding) and made final adjudications. Statisticians from the statistical and data management center of the China National Clinical Research Center for Neurological Diseases completed the statistical analysis, and the third author was responsible for the statistical plan and analysis. Lists of the committee members are provided in the Supplementary Appendix, available at NEJM.org.

Sanofi and Beijing Jialin Pharmaceutical provided the trial drugs (clopidogrel and atorvastatin) and the matching placebos. Neither company was involved in the design or implementation

of the trial or in the analysis and interpretation of the trial data. No confidentiality agreements were in place between the authors and any commercial entity. The first two authors prepared the initial draft of the manuscript, with input from all the authors. The authors vouch for the completeness and accuracy of the data.

#### PATIENTS

Patients were eligible if they were 35 to 80 years of age and had had an ischemic stroke with an NIHSS score of 5 or less or a high-risk TIA with a score of 4 or higher on the ABCD<sup>2</sup> scale (which estimates the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus; range, 0 to 7, with higher scores indicating higher stroke risk) within 24 to 72 hours after symptom onset or had had an ischemic stroke (NIHSS score, 4 or 5) within 24 hours after symptom onset. Patients had to meet at least one of the following imaging criteria: at least 50% stenosis of a major intracranial or extracranial artery, as confirmed by carotid duplex ultrasonography or vascular imaging, that was likely to have accounted for the clinical presentation and cerebral infarction; or acute new multiple infarctions documented by computed tomography or magnetic resonance imaging of the head (excluding previous infarcts) of presumed large-artery atherosclerosis origin, including those with nonstenotic unstable plaque ipsilateral to the infarction.

Patients with a qualifying minor ischemic stroke (NIHSS score,  $\leq 3$ ) or high-risk TIA (ABCD<sup>2</sup> score,  $\geq 4$ ) within the previous 24 hours were included in the trial before the time in 2019 that the American Heart Association (AHA) and the American Stroke Association (ASA) updated their recommendation that dual antiplatelet therapy be initiated within 24 hours after the onset of ischemic stroke (NIHSS score,  $\leq 3$ ) due to non-cardioembolic causes. The trial protocol was amended at the time of that change to exclude patients who had had a stroke with an NIHSS score of 3 or less or a TIA within the previous 24 hours.<sup>2</sup>

Patients were ineligible to participate if they had received thrombolysis or endovascular therapy; an additional anticoagulant, defibrinogenation, or antiplatelet therapy except for clopidogrel and aspirin after the index event; or dual

antiplatelet therapy with aspirin and clopidogrel or intensive statin therapy within 2 weeks before randomization. Other key exclusion criteria were a presumed cardioembolic TIA or ischemic stroke that was diagnosed by the investigators on the basis of medical history, electrocardiography, echocardiography, and other appropriate examinations; other determined cause of ischemic stroke or TIA (e.g., aortic dissection and vasculitis); or a preexisting disability with a score of 2 or higher on the modified Rankin scale (range, 0 to 6, with a score of 0 to 1 indicating no disability, a score of 2 to 5 indicating increasing disability, and a score of 6 indicating death). Persons with a history of intracranial hemorrhage or with a planned surgery or revascularization that would have necessitated the discontinuation of the trial medications within the subsequent 90 days after randomization were not eligible. Further details are provided in the protocol.

#### TRIAL PROCEDURES

Eligible patients were randomly assigned in a 1:1 ratio within 72 hours after symptom onset to receive combined clopidogrel plus aspirin (clopidogrel–aspirin group) or matching clopidogrel placebo plus aspirin (aspirin group). Random numbers that were generated centrally, corresponding to trial drug kits, were used for trial-group assignment, and block sizes of eight, stratified according to center, were used to balance the numbers of patients in the trial groups.

Patients who had been assigned to the clopidogrel–aspirin group received clopidogrel at a loading dose of 300 mg on the first day, followed by 75 mg daily on days 2 to 90, plus aspirin at a dose of 100 to 300 mg on the first day, then 100 mg daily for days 2 to 21 and then a matching aspirin placebo for days 22 to 90. Patients in the aspirin group received matching clopidogrel placebo for 90 days, plus aspirin at a dose of 100 to 300 mg on day 1, then 100 mg daily for days 2 to 90. In both groups, the decision regarding the aspirin dose on day 1 was made by the physician.

Patients received the initial doses as soon as feasible within 1 hour after being assigned to a trial group. Patients received standard care according to the latest AHA–ASA guidelines and Chinese guidelines and were followed for an ad-

ditional 9 months after the 90-day randomized portion of the trial in order for investigators to collect data on outcomes and adverse events.<sup>2,15,16</sup>

#### OUTCOMES

The primary efficacy outcome was any new stroke (ischemic or hemorrhagic) within 90 days. The secondary efficacy outcomes were a composite of cardiovascular events (stroke, myocardial infarction, or death from cardiovascular causes) within 90 days, ischemic stroke, TIA, myocardial infarction, death from cardiovascular causes, and poor functional outcome (modified Rankin scale score, 2 to 6). The type of cardiovascular events and the modified Rankin scale score at 90 days were used to classify the new stroke or TIA on a six-level scale: a score of 5 indicated fatal stroke (stroke with subsequent death), 4 severe stroke (stroke followed by a modified Rankin scale score of 4 or 5), 3 moderate stroke (stroke followed by a modified Rankin scale score of 2 or 3), 2 mild stroke (stroke followed by modified Rankin scale score of 0 or 1), 1 TIA, and 0 no stroke or TIA.<sup>17</sup> This scale has been used in other trials<sup>18,19</sup> but has not been independently validated in broad populations of patients with stroke. Definitions of the cardiovascular events are provided in the trial protocol and the Supplemental Appendix.

The primary safety outcome was moderate-to-severe bleeding as defined according to criteria from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial.<sup>20</sup> Other safety outcomes included hepatotoxic events (alanine aminotransferase or aspartate aminotransferase level of >3 times the upper limit of the normal range), muscle toxic effects (creatinine kinase level of >10 times the upper limit of the normal range or the presence of muscle pain, myopathy, or rhabdomyolysis pertaining to statin treatment in the other component of the trial), death from any cause, intracranial hemorrhage, any bleeding, and other adverse or serious adverse events within 90 days.

#### STATISTICAL ANALYSIS

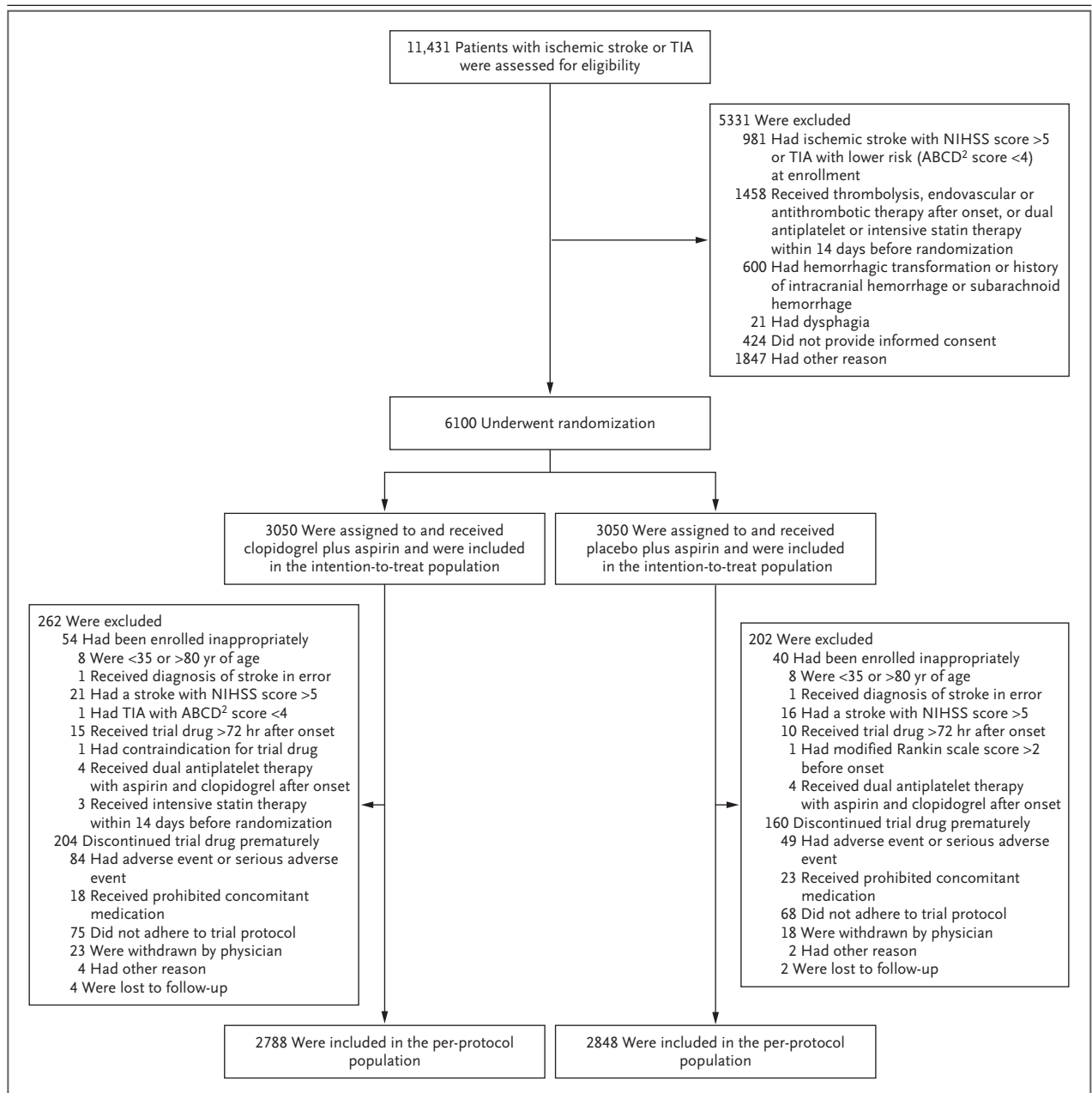
On the basis of previous trials, we assumed that the risk of new stroke over a period of 90 days would be 11.5% in the aspirin group and that dual antiplatelet therapy would lead to a 22% lower risk.<sup>7,8,21-23</sup> We estimated that a sample size of 6100 would provide the trial with 80% power

to detect a hazard ratio of 0.80 in favor of dual antiplatelet therapy, at a two-sided alpha level of 0.05, with an assumption that 5% of the patients would be lost to follow-up.

Efficacy and safety analyses were performed in accordance with the intention-to-treat principle (population that included all the patients who had undergone randomization). We estimated the cumulative risks of new stroke events and moderate-to-severe bleeding events within 90 days with the use of the Kaplan–Meier method. Differences between the clopidogrel–aspirin group and the aspirin group in the risk of stroke at 90 days were estimated by means of the marginal Cox proportional-hazards model with adjustment for pooled trial centers (those with ≥20 enrolled patients), and hazard ratios with 95% confidence intervals are presented. As a sensitivity analysis, Cox models with trial centers set as a random effect (trial centers with <20 enrolled patients were pooled for this purpose) were also evaluated for the primary outcome. The proportional-hazards assumption was affirmed by assessment of the interaction between trial group and a logarithmic function of survival time. Data for patients who did not have a 90-day assessment were censored on the date of a primary-outcome event or of the last visit if the patient withdrew from the trial or was lost to follow-up, whichever came first. The model used the time to the first event when there was more than one occurrence of the same type.

Similar approaches were applied to compare the secondary efficacy outcomes of composite cardiovascular events, ischemic stroke, hemorrhagic stroke, myocardial infarction, TIA, and death from cardiovascular causes, as well as the safety outcomes of bleeding and death from any cause. We conducted a shift analysis for the secondary outcome of our ordinal six-level scale of stroke and TIA combined with the modified Rankin scale outcome between the two groups by means of ordinal logistic regression with the proportionality assumption met, to determine a common odds ratio with a 95% confidence interval. Poor functional outcome, hepatotoxic effects, and muscle toxic effects were evaluated with the use of a generalized linear model, and relative risks are presented with 95% confidence intervals.

All the patients who completed the trial and had no major protocol deviations were included in the per-protocol population, and the same



**Figure 1. Enrollment and Randomization.**

Patients who had been enrolled inappropriately or who discontinued a trial drug were included in the intention-to-treat analysis, as were patients who were lost to follow-up. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42 points, with higher scores indicating greater neurologic deficits. The ABCD<sup>2</sup> score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of transient ischemic attack (TIA), and the presence or absence of diabetes mellitus; scores range from 0 to 7, with higher scores indicating greater risk. Scores on the modified Rankin scale range from 0 to 6 points, with higher scores indicating worse functional outcome.

statistical methods as for the primary outcome were used for efficacy and safety outcomes. In addition, for the primary outcome, we performed a sensitivity analysis in the population with exclusion of patients who had had a qualifying

minor stroke (NIHSS score,  $\leq 3$ ) or high-risk TIA (ABCD<sup>2</sup> score,  $\geq 4$ ) within the previous 24 hours and had been recruited before the above-described protocol revision. Because of the low mortality in each trial group, we did not conduct

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	Clopidogrel–Aspirin (N = 3050)	Aspirin (N = 3050)
Median age (interquartile range) — yr	65 (57–71)	65 (57–71)
Female sex — no. (%)	1063 (34.9)	1122 (36.8)
Medical history — no. (%)		
Hypertension	2047 (67.1)	2036 (66.8)
Diabetes mellitus	830 (27.2)	828 (27.1)
Dyslipidemia	103 (3.4)	123 (4.0)
Previous ischemic stroke	901 (29.5)	908 (29.8)
Current smoking — no. (%)	892 (29.2)	891 (29.2)
Use of agents before qualifying event — no. (%)		
Aspirin	390 (12.8)	403 (13.2)
Clopidogrel	21 (0.7)	22 (0.7)
Lipid-lowering agent	296 (9.7)	291 (9.5)
Qualifying event — no. (%)		
TIA	399 (13.1)	402 (13.2)
Acute single infarction	588 (19.3)	586 (19.2)
Acute multiple infarctions	2063 (67.6)	2062 (67.6)
≥50% symptomatic stenosis — no. (%)†		
Yes	2448/2985 (82.0)	2467/2983 (82.7)
No	537/2985 (18.0)	516/2983 (17.3)
Time to randomization after onset of symptoms — no. (%)		
≤24 hr	401 (13.1)	382 (12.5)
>24 to ≤48 hr	1255 (41.1)	1297 (42.5)
>48 to 72 hr	1394 (45.7)	1371 (45.0)
NIHSS score in qualifying ischemic stroke — no./total no. (%)‡		
≤3	2007/2651 (75.7)	2026/2648 (76.5)
4 or 5	644/2651 (24.3)	622/2648 (23.5)
ABCD <sup>2</sup> score in qualifying TIA — no./total no. (%)§		
4 or 5	326/399 (81.7)	315/402 (78.4)
>5	73/399 (18.3)	87/402 (21.6)

\* Percentages may not total 100 because of rounding. TIA denotes transient ischemic attack.

† Data were missing for 132 patients owing to the absence of both intracranial and extracranial arterial vascular assessments or because patients did not have more than 50% stenosis in intracranial (or extracranial) arteries but also did not have extracranial (or intracranial) vascular assessments.

‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42 for patients with ischemic stroke, with higher scores indicating more severe stroke.

§ The ABCD<sup>2</sup> score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus in patients with transient ischemic attack. Scores range from 0 to 7, with higher scores indicating greater risk.

a competing-risk analysis. Comparisons of other adverse events and serious adverse events were conducted by means of the chi-square test or Fisher's exact test. The primary outcome was analyzed in prespecified subgroups according to age; sex; systolic blood pressure; the presence or absence of hypertension, diabetes, dyslipidemia,

or symptomatic stenosis; number of acute infarctions; NIHSS score in the qualifying ischemic stroke; randomization time group; use of antiplatelet or statin therapy; and assignment to receive immediate or delayed intensive statin therapy. Details of the subgroup definitions have been published previously.<sup>12</sup>

The statistical analysis plan, which is available with the protocol, did not contain a plan for adjustment of the widths of confidence intervals for multiplicity when testing secondary or other outcomes, and no definite conclusions can be drawn from these results. The confidence intervals cannot be used to infer treatment effects for secondary outcomes. All the statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From September 17, 2018, through October 15, 2022, a total of 11,431 patients with ischemic stroke or TIA were screened at 222 hospitals; 6100 patients underwent randomization, with 3050 assigned to the clopidogrel–aspirin group and 3050 to the aspirin group (Fig. 1). Among the enrolled patients, 364 patients discontinued the trial drugs, and 21 patients in the clopidogrel–aspirin group and 18 in the aspirin group died from causes other than stroke; all these patients were included in the intention-to-treat analysis. At the 90-day follow-up, 4 patients in the clopidogrel–aspirin group and 2 in the aspirin group were lost to follow-up; the data for these patients were treated as censored. Seven patients had missing data regarding disability.

The characteristics of the patients at baseline were similar in the two groups (Table 1). The median age of the patients was 65 years, 35.8% of the patients were women, and 98.5% were Han Chinese. (The ethnic groups of the 1.5% of the patients who were not Han Chinese are shown in Table S1 in the Supplementary Appendix, and the representativeness of the trial population is shown in Table S9.) Overall, 87.2% of the patients were randomly assigned to a treatment group after 24 hours and no more than 72 hours after symptom onset, and 12.8% were assigned no more than 24 hours after onset. Most of the patients (67.6%) had multiple acute infarctions on imaging (on the same side or different sides of the cerebrum); 19.2% of the patients had an acute single infarction as an index event, and 13.1% had a TIA as an index event. Among patients with an acute ischemic stroke, 76.1% had an NIHSS score of 3 or less. Within 1 month before the index event, 13.0% of the patients had taken aspirin and 0.7% had taken clopidogrel. Vascular imaging data that were col-

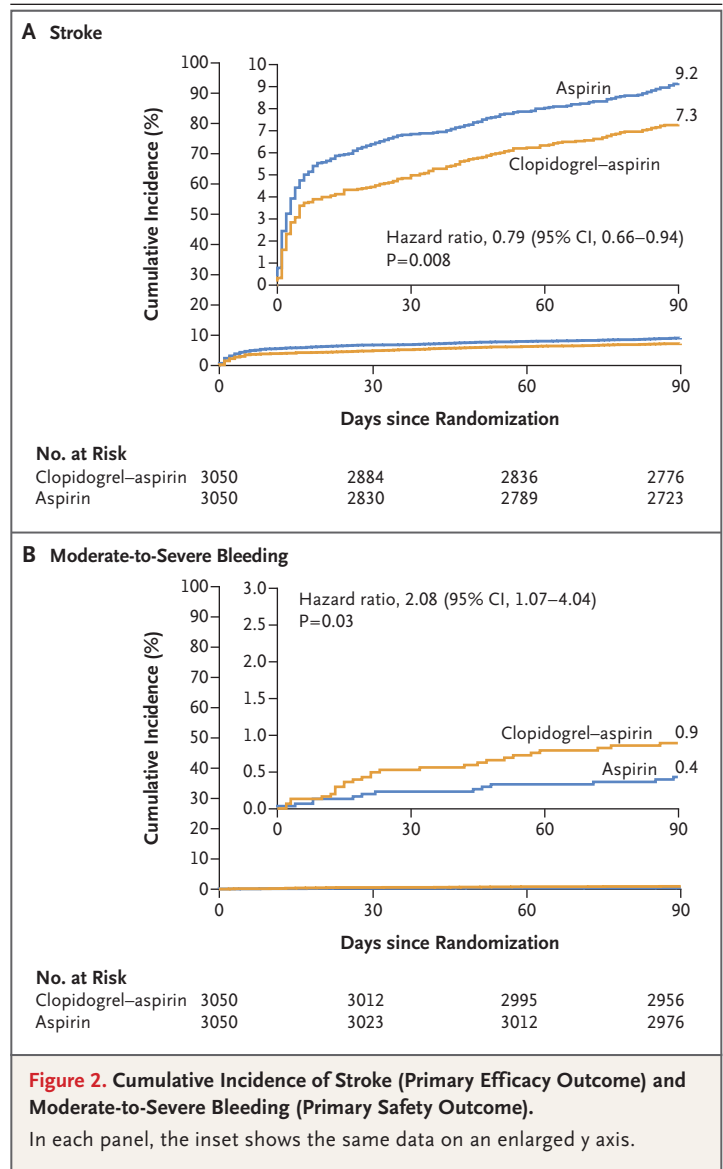


Figure 2. Cumulative Incidence of Stroke (Primary Efficacy Outcome) and Moderate-to-Severe Bleeding (Primary Safety Outcome).

In each panel, the inset shows the same data on an enlarged y axis.

lected for centralized interpretation were missing or incomplete in 65 patients in the clopidogrel–aspirin group and in 67 patients in the aspirin group.

EFFICACY OUTCOMES

A new stroke within 90 days (primary efficacy outcome) occurred in 222 patients (7.3%) in the clopidogrel–aspirin group and in 279 patients (9.2%) in the aspirin group (marginal estimated hazard ratio, 0.79; 95% confidence interval [CI], 0.66 to 0.94; P=0.008) (Fig. 2A and Table 2), with a hazard ratio estimated by the random-effect model of 0.79 (95% CI, 0.66 to 0.94). The trial-center effect was nonnegligible (Fig. S1 and Table S2).

**Table 2. Efficacy and Safety Outcomes.**

Outcome	Clopidogrel–Aspirin (N = 3050)		Aspirin (N = 3050)		Hazard Ratio or Relative Risk (95% CI)*	P Value
	Patients with Event	Incidence†	Patients with Event	Incidence†		
		%		%		
<b>Primary outcome</b>						
Stroke, including ischemic and hemorrhagic stroke — no.	222	7.3	279	9.2	0.79 (0.66–0.94)	0.008
<b>Secondary outcomes</b>						
Composite cardiovascular event (stroke, myocardial infarction, or death from cardiovascular causes) — no.	229	7.5	282	9.3	0.80 (0.67–0.96)	
Ischemic stroke — no.	208	6.8	274	9.0	0.75 (0.63–0.90)	
Recurrent stroke	159	5.3	205	6.8	0.77 (0.62–0.94)	
TIA with infarction	5	0.2	11	0.4	0.45 (0.16–1.29)	
Progressive stroke‡	44	1.5	58	1.9	0.75 (0.51–1.11)	
Hemorrhagic stroke — no.	15	0.5	5	0.2	3.01 (1.09–8.28)	
TIA — no.	21	0.7	39	1.3	0.54 (0.32–0.91)	
Myocardial infarction — no.	5	0.2	2	0.1	2.50 (0.49–12.90)	
Death from cardiovascular causes — no.	21	0.7	15	0.5	1.40 (0.72–2.72)	
Poor functional outcome — no./total no.§	301/3047	9.9	346/3046	11.4	0.87 (0.76–0.99)	
Six-level assessment of new stroke — no./total no.¶					0.76 (0.64–0.91)	
5: Fatal stroke	20/3049	0.7	13/3049	0.4		
4: Severe stroke	28/3049	0.9	27/3049	0.9		
3: Moderate stroke	69/3049	2.3	102/3049	3.3		
2: Mild stroke	104/3049	3.4	136/3049	4.5		
1: TIA	21/3049	0.7	35/3049	1.1		
0: No stroke or TIA	2807/3049	92.1	2736/3049	89.7		
<b>Primary safety outcome</b>						
Moderate-to-severe bleeding — no.	27	0.9	13	0.4	2.08 (1.07–4.04)	0.03
<b>Secondary safety outcomes</b>						
Hepatotoxic effects — no.**	39	1.3	32	1.0	1.22 (0.86–1.74)	
Muscle toxic effects — no.††	2	0.07	1	0.03	2.00 (0.18–22.04)	
Death from any cause — no.	37	1.2	30	1.0	1.24 (0.76–2.00)	
Any bleeding — no.	94	3.1	63	2.1	1.50 (1.09–2.06)	
Intracranial hemorrhage	17	0.6	8	0.3	2.13 (0.92–4.93)	
Mild bleeding	70	2.3	51	1.7	1.38 (0.96–1.97)	

\* Relative risks are shown for poor functional outcome, hepatotoxic effects, and muscle toxic effects. The common odds ratio is shown for ordinal stroke or TIA. Hazard ratios are shown for other outcomes. The widths of the confidence intervals for secondary outcomes were not adjusted for multiplicity and may not be used for hypothesis testing.

† The event rates of poor functional outcome, ordinal stroke or TIA, hepatotoxic effects, and muscle toxic effects are raw estimates, whereas the rates of other outcomes are Kaplan–Meier estimates of the percentage of patients with an event at 90 days.

‡ The definition of progressive stroke is provided on page 16 of the Supplementary Appendix.

§ A poor functional outcome was defined as a modified Rankin scale score of 2 to 6. Scores on the modified Rankin scale range from 0 to 6, with a score of 0 to 1 indicating no disability, a score of 2 to 5 indicating increasing disability, and a score of 6 indicating death). The modified Rankin scale score at 90 days was missing for three patients in the clopidogrel–aspirin group and for four in the aspirin group.

**Table 2. (Continued.)**

- ¶ The severity of new stroke and TIA was classified on a six-level ordered categorical scale that combined cardiovascular events with the score on the modified Rankin scale. A score of 5 on this scale indicates fatal stroke (stroke with subsequent death), 4 severe stroke (stroke followed by a modified Rankin scale score of 4 or 5), 3 moderate stroke (stroke followed by a modified Rankin scale score of 2 or 3), 2 mild stroke (stroke followed by a modified Rankin scale score of 0 or 1), 1 TIA, and 0 no stroke or TIA. Among patients with new stroke, the modified Rankin scale score at 90 days was missing for one patient in each trial group.
- || Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.<sup>20</sup>
- \*\* Hepatotoxic effects were defined as an alanine aminotransferase or aspartate aminotransferase level that was more than three times the upper limit of the normal range.
- †† Muscle toxic effects were defined as a creatine kinase level that was more than 10 times the upper limit of the normal range or as presence of muscle pain, myopathy, or rhabdomyolysis.

With regard to secondary outcomes, a composite cardiovascular event occurred in 229 patients (7.5%) in the clopidogrel–aspirin group and in 282 patients (9.3%) in the aspirin group (hazard ratio, 0.80; 95% CI, 0.67 to 0.96). The overall risk of ischemic stroke was 6.8% in the clopidogrel–aspirin group and 9.0% in the aspirin group (hazard ratio, 0.75; 95% CI, 0.63 to 0.90). The risk of TIA was 0.7% in the clopidogrel–aspirin group and 1.3% in the aspirin group (hazard ratio, 0.54; 95% CI, 0.32 to 0.91). A shift in the severity of stroke or TIA at 90 days combined with the modified Rankin scale outcome on the six-level scale toward a better outcome with dual antiplatelet therapy resulted in a common odds ratio of 0.76 (95% CI, 0.64 to 0.91). The widths of the confidence intervals for the between-group differences in secondary outcomes are not adjusted for multiplicity, and no definite conclusions can be drawn from these data. Other secondary outcomes are shown in Table 2.

In the subgroup of patients who had undergone randomization within 24 hours after symptom onset, the risk of new stroke was 11.5% in the clopidogrel–aspirin group and 13.4% in the aspirin group (hazard ratio, 0.84; 95% CI, 0.57 to 1.25). In the subgroup of patients who had undergone randomization after 24 hours and no more than 48 hours after onset, the risk was 7.6% in the clopidogrel–aspirin group and 8.9% in the aspirin group (hazard ratio, 0.84; 95% CI, 0.64 to 1.11); the corresponding risks among those who had undergone randomization after 48 hours and no more than 72 hours after onset were 5.8% and 8.2%, respectively (hazard ratio, 0.70; 95% CI, 0.53 to 0.93). Other subgroup analyses are shown in Figure 3 and Figure S2.

The results regarding efficacy outcomes in the per-protocol population were consistent with

those in the intention-to-treat population (Table S4). The sensitivity analysis after the exclusion of patients with a qualifying minor ischemic stroke (NIHSS score,  $\leq 3$ ) or high-risk TIA (ABCD<sup>2</sup> score,  $\geq 4$ ) within the previous 24 hours showed results similar to those of the primary outcome (Table S5). There was no significant interaction between antiplatelet treatment assignment and statin treatment in the two components of the factorial trial ( $P=0.16$  for interaction in the primary outcome).

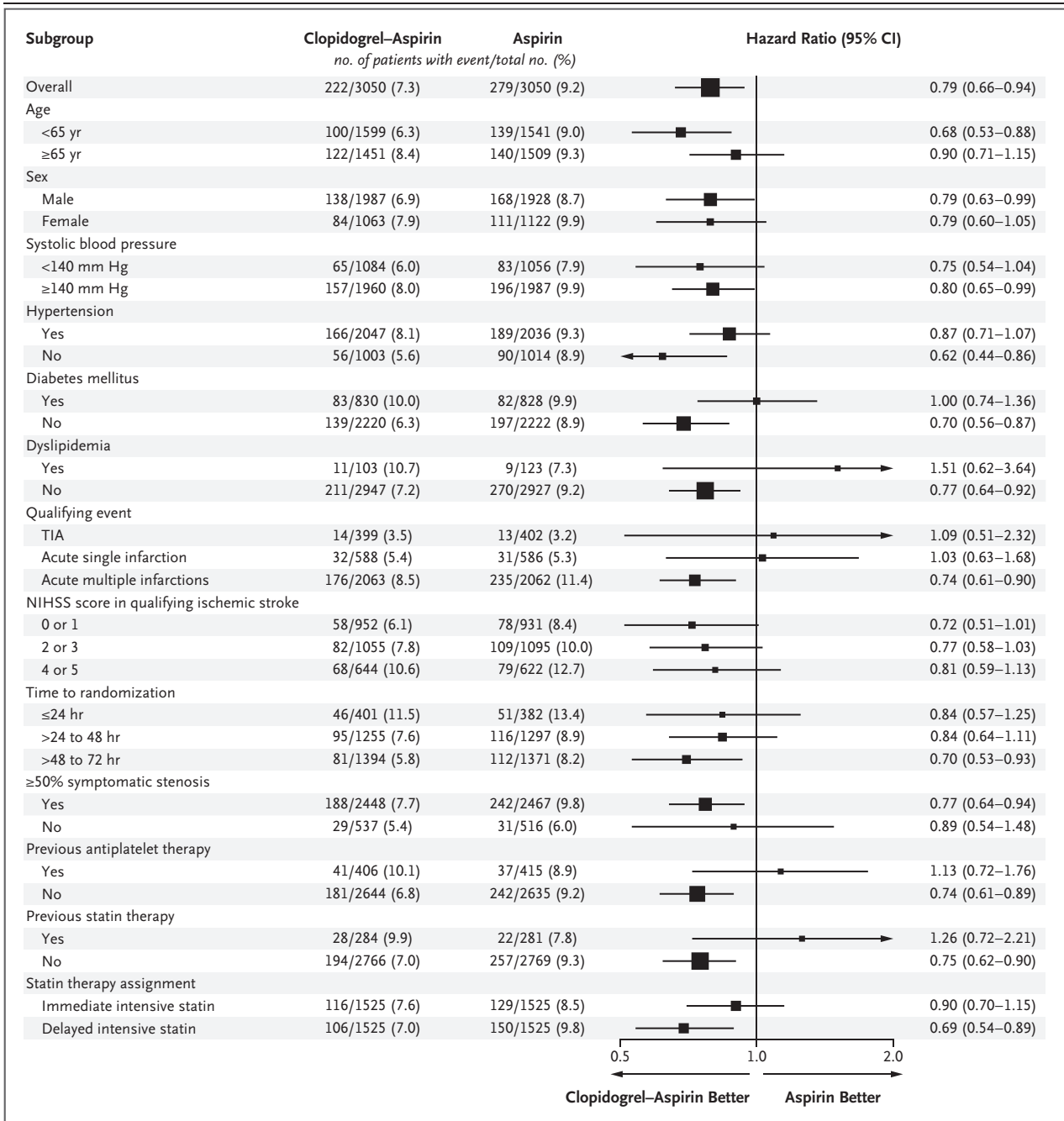
#### SAFETY OUTCOMES

Moderate-to-severe bleeding (primary safety outcome) occurred in 27 patients (0.9%) in the clopidogrel–aspirin group and in 13 patients (0.4%) in the aspirin group (hazard ratio, 2.08; 95% CI, 1.07 to 4.04;  $P=0.03$ ) (Fig. 2B and Table 2). The risk of any bleeding was higher in the clopidogrel–aspirin group (3.1%) than in the aspirin group (2.1%) (hazard ratio, 1.50; 95% CI, 1.09 to 2.06).

Adverse events occurred in 650 patients (21.3%) in the clopidogrel–aspirin group and in 648 patients (21.3%) in the aspirin group (Table S6), and serious adverse events occurred in 107 patients (3.5%) and 89 patients (2.9%), respectively (Table S7). Adverse events or serious adverse events leading to the discontinuation of a trial treatment are shown in Table S8. The results regarding safety outcomes in the per-protocol population were similar to those in the primary analysis.

#### DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled, two-by-two factorial trial conducted in China, patients with acute mild ischemic stroke or high-risk TIA of presumed



**Figure 3. Hazard Ratios for Stroke in Prespecified Subgroups.**

Percentages for the overall population are Kaplan–Meier estimates, and those for all the subgroups are raw estimates. The trial was not powered to allow definite conclusions on the basis of the results of the subgroup analyses. The size of the boxes is proportional to the number of patients in the subgroup. Arrows indicate that the confidence interval extends past the graphed area. Data on the systolic blood pressure were missing for 6 patients in the clopidogrel–aspirin group and for 7 in the aspirin group. Data regarding symptomatic stenosis of 50% or more were missing for 65 patients in the clopidogrel–aspirin group and for 67 in the aspirin group.

atherosclerotic origin who received combined that was approximately 2 percentage points  
 clopidogrel and aspirin within 72 hours after lower than the risk with aspirin alone. The risk  
 symptom onset had a risk of stroke at 90 days of moderate-to-severe bleeding was approxi-

mately twice as high in the clopidogrel–aspirin group as in the aspirin group, although this risk was low in both groups.

Both the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial and the POINT trial enrolled patients with minor ischemic stroke (NIHSS score,  $\leq 3$ ) or high-risk TIA, the results of which indicated that combination therapy with clopidogrel and aspirin that was begun within 24 hours after onset led to a lower risk of subsequent stroke, without a higher risk of bleeding during 90 days, than aspirin therapy alone.<sup>21,24,25</sup> The results of our trial potentially broaden the time window for the initiation of treatment, although there was more bleeding with the dual regimen than with the monotherapy.

In the CHANCE trial, dual antiplatelet therapy led to a risk of recurrent stroke that was 3.5 percentage points lower than the risk with aspirin, with treatment started within 24 hours, which was greater than the difference of approximately 2 percentage points that we observed in the current trial. This disparity may be attributed to the longer time interval between symptom onset and randomization in our trial than in the earlier trial, given that the risk of stroke recurrence is higher during the acute post-stroke phase and also given that, in our trial, only approximately 13% of the patients were treated within 24 hours. The incidence of moderate-to-severe bleeding in the clopidogrel–aspirin group in our trial was 0.9%; this represents a risk that is more than two times as high as the risk with aspirin alone (0.4%), and it is higher than the risk of 0 to 0.5% that has been reported in most previous studies.<sup>7,9,19,21,26,27</sup>

There are several limitations to this trial. Some important populations of patients with stroke or TIA were excluded, such as patients with stroke of presumed cardioembolic origin, those with moderate or severe stroke (NIHSS score,  $>5$ ), and those who had undergone thrombolysis or thrombectomy. Furthermore, 98.5% of the enrolled patients were Han Chinese; the higher proportion of intracranial artery stenosis in this population than in other populations may have contributed to the benefit from dual antiplatelet therapy. The results cannot necessarily be generalized to White and Black patients with stroke. Finally, clopidogrel is known to require hepatic cytochrome P450 enzymes to generate active metabolites for its antiplatelet effects; however, the genotype of drug metabolism was not included in the criteria for enrollment in this trial.<sup>28</sup>

In this trial conducted in China that involved patients with mild ischemic stroke or high-risk TIA from presumed intracranial or extracranial atherosclerosis, treatment with clopidogrel and aspirin initiated within 72 hours after symptom onset led to a lower risk of new stroke but a higher risk of moderate-to-severe bleeding than treatment with aspirin alone over a period of 90 days.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

#### APPENDIX

The authors' full names and academic degrees are as follows: Ying Gao, M.D., Weiqi Chen, M.D., Yuesong Pan, Ph.D., Jing Jing, M.D., Ph.D., Chunjuan Wang, M.D., Ph.D., S. Claiborne Johnston, M.D., Ph.D., Pierre Amarengo, M.D., Philip M. Bath, D.Sc., Lingling Jiang, Ph.D., Yingying Yang, M.D., Tingting Wang, M.D., Shangrong Han, M.D., Xia Meng, M.D., Ph.D., Jinxi Lin, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., Jinguo Zhao, M.D., Ying Li, M.D., Yingzhuo Zang, M.D., Shuo Zhang, M.D., Hongqin Yang, M.D., Jianbo Yang, M.D., Yuanwei Wang, M.D., Dali Li, M.D., Yanxia Wang, M.D., Dongqi Liu, M.D., Guangming Kang, M.D., Yongjun Wang, M.D., and Yilong Wang, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Neurology, Beijing Tiantan Hospital (Y.G., W.C., Y.P., J.J., C.W., Y.Y., T.W., S.H., X.M., X.Z., L.L., Yongjun Wang, Yilong Wang), the Advanced Innovation Center for Human Brain Protection (Yongjun Wang, Yilong Wang), Beijing Laboratory of Oral Health (Yilong Wang), and Beijing Municipal Key Laboratory of Clinical Epidemiology (Yilong Wang), Capital Medical University, the China National Clinical Research Center for Neurological Diseases (Y.P., J.J., C.W., L.J., X.M., J.L., X.Z., L.L., Yongjun Wang, Yilong Wang), the National Center for Neurological Disorders (Yongjun Wang, Yilong Wang), the Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences (Yongjun Wang), and the Chinese Institute for Brain Research (Yilong Wang), Beijing, the Department of Neurology, Weihai Wendeng District People's Hospital, Weihai (J.Z.), the Department of Neurology, Sui Chinese Medical Hospital, Shangqiu (Y.L.), the Department of Neurology, Qinghe People's Hospital, Xingtai (Y.Z.), the Department of Neurology, Biyang People's Hospital, Zhumadian (S.Z.), the Department of Neurology, Jiyuan Chinese Medical Hospital, Jiyuan (H.Y.), the Department of Neurology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an (J.Y.), the Department of Neurology, Affiliated Shuyang Hospital of Xuzhou Medical University, Suqian (Yuanwei Wang), the

Department of Neurology, Mengzhou People's Hospital (D. Li), and the Department of Neurology, Xiuwu People's Hospital (G.K.), Ji-aozuo, and the Department of Neurology, Hejian People's Hospital, Cangzhou (Yanxia Wang, D. Liu) — all in China; the Department of Neurology, University of California, San Francisco, San Francisco (S.C.J.); the Department of Neurology and Stroke Center, Assistance Publique-Hôpitaux de Paris, Bichat Hospital, INSERM Laboratory for Vascular Translational Science-Unité 1148, University of Paris, Paris (P.A.); the Population Health Research Institute, McMaster University, Hamilton, ON, Canada (P.A.); and the Stroke Trials Unit, Mental Health and Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom (P.M.B.).

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