Stroke

ORIGINAL CONTRIBUTION

Effect of Argatroban Plus Dual Antiplatelet in Branch Atherosclerosis Disease: A Randomized Clinical Trial

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BACKGROUND: Branch atherosclerosis disease (BAD) is prone to early neurological deterioration (END). The purpose of this study was to assess the efficacy and safety of argatroban plus dual antiplatelet therapy (DAPT) for preventing END in high-risk branch atherosclerosis disease patients.

METHODS: This multicenter, open-label, blinded end point, randomized controlled trial including branch atherosclerosis disease patients with mild stroke (National Institutes of Health Stroke Scale score ≤5) was conducted at 4 centers in China from May 18, 2021 to February 8, 2023. Within 48 hours after symptom onset, patients were randomly assigned to receive argatroban plus DAPT or DAPT alone in a 1:1 ratio. The primary end points were the incidence of END (National Institutes of Health Stroke Scale score increase ≥2) within 7 days and excellent functional outcome (modified Rankin Scale score of 0 to 1) at 90 days.

RESULTS: A total of 111 patients were randomized, with 11 excluded for specific reasons, resulting in 100 patients included in the modified intention-to-treat population. Among the 100 patients, 49 received argatroban plus DAPT and 51 received DAPT alone, 63 (63.0%) were men, and the median age was 64 (range, 55–74) years. END occurred in 20.4% (10/49) of the argatroban plus DAPT group and 47.1% (24/51) of the DAPT group (risk difference, 26.7% [95% CI, 14.1–39.2]; risk ratio, 2.31 [95% CI, 1.49–3.58]; *P*=0.006). At the 90-day follow-up, 87.8% (43/49) in the argatroban plus DAPT group and 68.6% (35/51) in the DAPT group achieved an excellent functional outcome (risk difference, −19.1% [95% CI, −30.3 to −8.0]; risk ratio, 0.78 [95% CI, 0.67–0.91]; *P*=0.025). There was 1 minor hemorrhage in each group.

CONCLUSIONS: Argatroban plus DAPT is a safe and effective strategy to reduce END occurrence and improve 90-day functional outcome in high-risk branch atherosclerosis disease patients.

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Key Words: argatroban ■ atherosclerosis ■ intention to treat analysis ■ ischemic stroke ■ platelet aggregation inhibitors

Branch atherosclerosis disease (BAD), initially proposed by Caplan in 1989, describes a pathology marked by the occlusion or narrowing of penetrating artery origins, causing infarctions in the internal capsule or pons.[1] BAD accounts for ≈10% to 15% of all acute ischemic strokes (AIS), yet its etiological classification

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
BAD	branch atherosclerosis disease
DAPT	dual antiplatelet therapy
END	early neurological deterioration
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
LSA	lenticulostriate arteries
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
RD	risk difference
RR	risk ratio

remains undetermined.[2,3] The condition predominantly involves the lenticulostriate arteries (LSA), paramedian pontine arteries, and anterior choroidal arteries.[4] A notable feature of BAD is its association with a high risk of early neurological deterioration (END), which frequently occurs within 48 to 72 hours after onset, with an incidence rate of 17% to 75%.[5–7] An observational study revealed that despite receiving dual antiplatelet therapy (DAPT), 34.5% of patients with BAD with a National Institutes of Health Stroke Scale (NIHSS) score of ≤5 within 48 hours of onset still experienced END during the first 48 hours after hospital admission, and 38.2% of patients presented poor functional outcome (modified Rankin Scale [mRS] score ≥2) at 3 months.[8] It indicated that the risk of END in patients with BAD remained high even when treated with DAPT, highlighting the necessity of exploring new antithrombotic strategies to prevent END in patients with BAD and reduce disability.

Argatroban is a direct thrombin inhibitor that effectively inhibits both free and clot-bound thrombin and is widely used to treat AIS, especially in Asian countries such as China and Japan.[9–11] Observational studies have suggested that short-term application of argatroban plus DAPT is safe and effective for treating AIS, including BAD, and this combination may also reduce the incidence of END.[12,13] Currently, there is a lack of compelling evidence demonstrating the efficacy of argatroban plus DAPT in patients with BAD. One study conducted in Japan has shown that treatment with argatroban plus DAPT can reduce the incidence of END in patients with BAD without increasing the risk of intracranial hemorrhage.[14] Our recent observational study, which included 80 patients with BAD who did not undergo intravenous thrombolysis, demonstrated that patients treated with argatroban plus DAPT exhibited a lower incidence of END and fewer poor functional outcome compared with those receiving DAPT alone, with no increase in the risk of intracranial hemorrhage.[8] These results indicated that argatroban combined with DAPT might be an effective strategy for reducing the incidence of END in patients with BAD.

Hence, we designed a multicenter, open-label, blinded end point randomized trial to investigate the efficacy and safety of combining argatroban with DAPT for treating BAD.

METHODS

Trial Design

The raw data supporting the conclusions of this article can be obtained from the corresponding author upon reasonable request.

This prospective, multicenter, open-label, randomized clinical trial with a blinded end point assessment aimed to assess the efficacy and safety of argatroban plus DAPT in comparison to DAPT alone for patients with BAD at high risk of END. The trial was conducted from May 18, 2021 to February 8, 2023, at 4 advanced stroke centers in the southwestern region of China (Second People's Hospital of Chengdu, Third Affiliated Hospital of Chongqing Medical University, Second Hospital of Chengdu University of Traditional Chinese Medicine, and Affiliated Hospital of Chengdu University). Ahead of the trial's initiation, each center underwent on-site training to ensure consistent implementation of the protocol and standards across all participating centers. We used both remote and on-site monitoring to ensure quality control throughout the study. This trial was approved by the ethics committee of Chengdu Second People's Hospital and all participating centers, and written informed consent was obtained from all patients or their family members. All procedures were performed in accordance with the Consolidated Standards of Reporting Trials reporting guidelines.[15]

Patients

The study participants were adults aged 18 to 80 years who presented with BAD within 48 hours of symptom onset or time last known to be well, with a NIHSS score of ≤5 points. Head computed tomography scans were performed to rule out intracranial hemorrhage after admission. In addition, neck and head computed tomography angiography or magnetic resonance angiography was conducted to assess for large vessel stenosis, and diffusion-weighted imaging with a slice thickness of 5 mm per layer was immediately performed upon admission. Patients with BAD at high risk of END were required to meet at least one of the following conditions (1) infarction in the internal capsule with a lesion diameter of ≥10 mm and involving ≥3 layers; (2) infarctions in the lower segment of the pons, where the lesion extended to the ventral side of the pons; (3) LSA posterior type infarction were located in the posterior corona radiata. On diffusion-weighted imaging, if more than half of the infarct lay behind the midpoint between 2 lines drawn along the lateral ventricle horns, it was classified as posterior type[16]; and (4) multiple infarctions located in the area of perforating branches.

If patients met the criteria for intravenous thrombolysis or mechanical thrombectomy, they received the standard treatment and were excluded from the trial. Other exclusion criteria were as follows: (1) preexisting disability before stroke

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occurrence (mRS score >1); (2) patients with atrial fibrillation or those on anticoagulant medications, including but not limited to dabigatran and rivaroxaban; and (3) a history of nontraumatic intracranial hemorrhage or imaging indicative of a high risk of intracranial hemorrhage, such as severe white matter lesions. The complete exclusion criteria are provided in the Supplemental Methods.

Randomization and Masking

Patients who met the criteria were randomly assigned at a 1:1 ratio to receive argatroban plus DAPT or DAPT alone (Figure 1). A simple randomization method was used, utilizing a computer-generated random sequence to allocate a sequence number based on the patient's time of enrollment. The baseline and follow-up NIHSS or mRS scores were assessed by the same professional assessor, who remained blinded to the study protocol, treatment allocation, and group assignments throughout the trial. To maintain blinding, the assessor received only essential clinical data required for evaluations, which underwent standardized preprocessing to remove any treatment-related information. Furthermore, all assessors completed standardized training and certification to ensure the objectivity of evaluations. mRS scores at admission and discharge were assessed face-to-face. For the 90-day follow-up, face-to-face visits were prioritized; if unavailable, structured assessments were conducted via telephone by certified personnel who were also blinded to treatment allocation. Central adjudication of outcomes and safety events was performed by a committee that was similarly blinded to treatment assignments.

Interventions

All patients received the drug treatment according to their assigned group immediately after randomization. Patients in the DAPT group received treatment as follows: 100 mg aspirin and 300 mg clopidogrel were administered orally on the first day, followed by 100 mg aspirin and 75 mg clopidogrel administered orally on the second day and continued daily for 3 weeks. After 3 weeks, maintenance treatment consisted of only 1 antiplatelet drug. In addition to the above treatment, patients in the DAPT plus argatroban group also received argatroban, which was continuously infused at a dose of 60 mg/d for 2 days, followed by 20 mg/d from days 3 to 7.[17] All other treatments administered for AIS followed the most recent guidelines of the American Heart Association.[18,19]

An independent committee for data and safety monitoring supervised the trial, with particular attention to any occurrences of hemorrhagic events. During argatroban infusion, if a hemorrhagic event occurs and intracranial or other systemic moderate or severe bleeding is suspected, the argatroban infusion should be immediately discontinued. If a patient experiences END during hospitalization, a follow-up brain noncontrast computed tomography or magnetic resonance imaging should be promptly performed.

Outcomes

The primary end points were the incidence of END within 7 days, defined as an increase of ≥2 points in NIHSS score[20,21] and excellent functional outcome at 90 days (mRS score of 0–1).[22] The secondary end points included the occurrence of early neurological improvement within 7 days, defined as a decrease of ≥2 points in NIHSS score from baseline; favorable functional outcome at 90 days, with an mRS score of 0 to 2; changes in NIHSS score within 7 days; and the occurrence of new vascular events within 90 days, including ischemic stroke, hemorrhagic stroke, transient ischemic attack, and myocardial infarction.

The safety outcomes included bleeding events, as defined by the criteria of the GUSTO trial (Global Utilization of

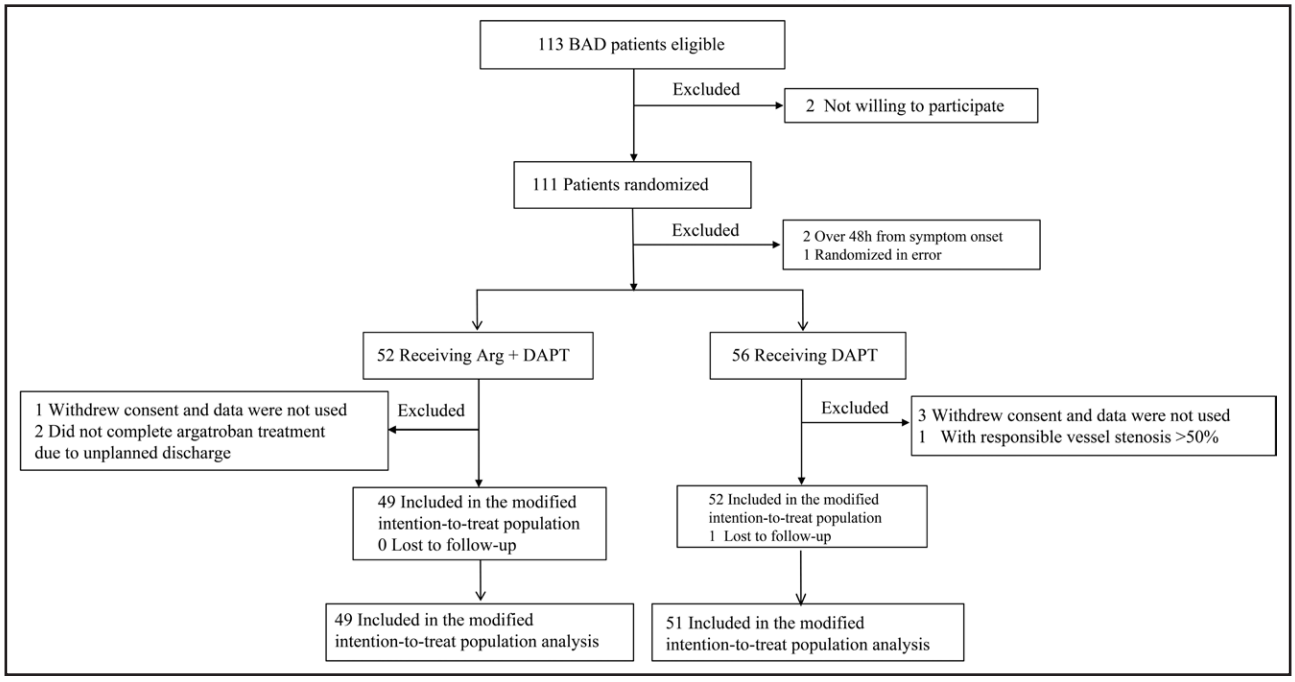

Figure 1. Study flow chart.
Arg indicates argatroban; BAD, branch atherosclerosis disease; and DAPT, dual antiplatelet therapy.

Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries),[23] covering severe, moderate, and minor bleeding, as well as death from any cause.

Clinical assessments were conducted using the NIHSS score and mRS score. The NIHSS score was utilized to evaluate the severity of neurological deficits, with scores ranging from 0 to 42; higher scores indicate more severe neurological impairment. NIHSS scores were assessed at baseline, 24 hours, 48 hours, 7 days after admission and at discharge, and when END occurred. The mRS score, which ranges from 0 (no symptoms) to 6 (death), is used to assess the functional status of patients, with assessments conducted at admission, discharge, and at the 90-day follow-up.

Sample Size Calculation

Considering the characteristics of the specific BAD population in this study and making conservative adjustments based on the results of previous studies,[8] we assumed that the excellent outcome rates for the DAPT plus argatroban group and the DAPT group would be 70% and 40%, and the END event rates of the 2 groups would be 24% and 55%, respectively. Assuming a 1:1 participant ratio between the 2 groups, we calculated the required sample sizes for both END and excellent outcome. A sample size of 80 patients (40 per group) would provide 80% statistical power to detect a significant difference at a 1-sided α of 5% for both primary outcomes. With a 20% dropout rate assumed, we plan to enroll 100 patients (50 per group).

Statistical Analysis

All analyses were performed based on the modified intention-to-treat population, a predefined group that included patients who received at least 1 study protocol treatment and at least 1 efficacy assessment after randomization, excluding those who voluntarily withdrew or were lost to follow-up. As we analyzed complete cases for all outcomes, there was no need to impute missing data. Continuous variables are expressed as mean±SD or as median and interquartile range. Categorical data are presented as frequencies (percentages).

Initially, the primary and secondary outcomes analyses were unadjusted. We utilized a generalized linear model to analyze the following outcomes: END, excellent functional outcome (mRS score of 0–1) at 90 days; early neurological improvement, favorable functional outcome (mRS score of 0–2) at 90 days; changes in NIHSS score between admission and 7 days; and safety events. The treatment effects for the above outcomes are presented in terms of risk differences (RDs) and risk ratios (RRs), along with their corresponding 95% CIs. In addition, ordinal logistic regression was used to compare the mRS score at 90 days, with results presented as odds ratios along with 95% CIs. Furthermore, we conducted covariate-adjusted generalized linear model analysis for all outcomes, considering 3 predefined prognostic factors: age, sex, and baseline NIHSS score.

Subgroup analysis (predefined for age, sex, hypertension, diabetes, hyperlipidemia, smoking, NIHSS score, and onset-to-randomization) was performed to assess differences in the primary outcome between the randomized groups. A generalized linear model was used to examine the subgroup effects. Statistical significance was set at $P<0.05$. SPSS, version 25.0 software and R software, version 4.1.0 were used for the statistical analyses.

RESULTS

Baseline Characteristics

From May 18, 2021 to February 8, 2023, a total of 111 patients were enrolled and randomly allocated to the study groups. Among these patients, 2 experienced a delay of >48 hours from the onset of symptoms to receiving treatment after randomization, and 1 encountered a randomization error. Four patients withdrew consent, 2 did not complete the argatroban treatment, 1 was excluded for vascular stenosis exceeding 50%, and another was excluded due to loss of follow-up. Ultimately, 100 patients met the criteria for the modified intention-to-treat population (49 in the argatroban plus DAPT group and 51 in the DAPT group). The detailed explanation of the incomplete procedures is provided in Figure 1.

The baseline characteristics and demographic features of the 2 groups of patients in the modified intention-to-treat population remained well-balanced (Table 1). The median age of the 100 assessable patients for the primary outcome was 64 years (range, 55–74), and there were 63 (63.0%) male patients. Upon admission, the median NIHSS score was 2.0 (range, 1.5–4.0) for the argatroban plus DAPT group and that of the DAPT group was 2.0 (range, 1.0–3.0). The median (interquartile range) time from symptom onset to randomization was 20.45 (12.92–33.47) hours for the argatroban plus DAPT group and 21.35 (8.92–33.27) hours for the DAPT group.

Primary Outcomes

Ten patients (20.4%) who received argatroban plus DAPT experienced END within 7 days. In contrast, 24 patients (47.1%) who received DAPT alone experienced END within the same period (unadjusted RD, 26.7% [95% CI, 14.1–39.2]; RR, 2.31 [95% CI, 1.49–3.58]; P=0.006; Table 2). In the argatroban plus DAPT group, 43 patients (87.8%) had mRS score of 0 to 1 at 90 days, compared with 35 patients (68.6%) in the DAPT group (unadjusted RD was −19.1 percentage points [95% CI, −30.3 to −8.0] and risk ratio was 0.78 [95% CI, 0.67–0.91]; P=0.025; Table 2; Figure 2).

After adjusting for the predefined covariates, the results remained statistically significant (for END: adjusted RD, 24.4% [95% CI, 11.7–37.0]; RR, 2.14 [95% CI, 1.39–3.30]; P=0.014; for mRS score of 0–1: adjusted RD, −17.3% [95% CI, −28.5 to −6.2]; RR, 0.80 [95% CI, 0.69–0.93]; P=0.037; Table 2).

Secondary Outcomes

Among the 49 patients treated with argatroban plus DAPT, 11 (22.4%) achieved early neurological improvement within 7 days, which is a significantly better outcome than the 3.9% (2 out of 51 patients) of those

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Table 1. Baseline Characteristics in the Modified Intention-to-Treat Population of Argatroban Plus DAPT Versus DAPT

Characteristics	Arg+DAPT (n=49)	DAPT (n=51)
Demographic data		
Age, y; median (IQR)	61 (54–71)	67 (57–76)
Sex, n (%)		
Male	33 (67.3)	30 (58.8)
Female	16 (32.7)	21 (41.2)
Stroke risk factors, n (%)		
Hypertension	41 (83.7)	42 (82.4)
Diabetes	11 (22.4)	22 (43.1)
Hyperlipidemia	25 (51.0)	26 (51.0)
History of stroke	2 (4.1)	5 (9.8)
Coronary artery disease	1 (2.0)	0 (0.0)
Atrial fibrillation	1 (2.0)	0 (0.0)
Smoking	18 (36.7)	20 (39.2)
Drinking	6 (12.2)	9 (17.6)
Antiplatelet agents	3 (6.1)	4 (7.8)
Laboratory examination, median (IQR)		
Blood glucose, mmol/L	5.8 (4.9–7.4)	5.6 (4.8–9.4)
Systolic blood pressure, mm Hg	160 (144–172)	159 (148–175)
Diastolic blood pressure, mm Hg	92 (83–105)	88 (76–98)
Cr, μmol/L	72 (58–84)	71 (58–83)
ALT, U/L	21.5 (17.3–27.8)	20.0 (14.0–27.3)
AST, U/L	22.5 (16.3–31.8)	19.5 (16–22.3)
TG, mmol/L	1.41 (1.00–2.18)	1.52 (1.11–2.17)
TC, mmol/L	4.90 (4.25–5.68)	5.14 (4.37–6.07)
LDL, mmol/L	2.86 (2.45–3.60)	3.18 (2.37–3.85)
HDL, mmol/L	1.07 (0.89–1.18)	0.98 (0.84–1.21)
Stroke evaluation		
Onset-to-randomization time, h; median (IQR)	20.45 (12.92–33.47)	21.35 (8.92–33.27)
Baseline NIHSS score, median (IQR)	2.0 (1.5–4.0)	2.0 (1.0–3.0)
mRS score at admission		
No symptoms (score of 0), n (%)	44 (89.8)	46 (90.2)
Symptoms without any disability (score of 1), n (%)	5 (10.2)	5 (9.8)
Location of stroke, n (%)		
Internal capsule	27 (55.1)	30 (58.8)
Lower segment of the pons	4 (8.2)	8 (15.7)
LSA posterior type	18 (36.7)	11 (21.6)
Multiple infarctions	0 (0.0)	2 (3.9)

ALT indicates alanine transaminase; Arg, argatroban; AST, acid transferase; Cr, creatinine; DAPT, dual antiplatelet therapy; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LSA, lenticulostriate artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TC, total cholesterol; TG, triglycerides; and UA, uric acid.

treated with DAPT alone (unadjusted RD, −18.5% [95% CI, −27.5 to −9.5]; RR, 0.17 [95% CI, 0.06–0.49]; *P*=0.014; Table 2). At the time of enrollment, all patients were functionally independent. At 90 days, 45 patients (91.8%) in the argatroban plus DAPT group achieved an mRS score of 0 to 2, whereas 43 patients (84.3%) in the DAPT group achieved this score (unadjusted RD, −7.5% [95% CI, −16.4 to 1.4]; RR, 0.92 [95% CI, 0.83–1.02]; *P*=0.255; Table 2; Figure 2). Furthermore, after accounting for predefined prognostic factors, no significant difference was observed in the risk of early neurological improvement and an mRS score of 0 to 2 between the 2 groups.

The NIHSS score between the 2 groups was similar at admission. However, a statistically significant difference emerged at 7 days and discharge (Table 3). The changes in the NIHSS score during hospitalization are shown in Figure S1. Moreover, from baseline to day 7, there were significant differences in the proportion of patients with NIHSS score changes of at least +1, +3, or −1 between the 2 groups. After adjusting for variables, no significant difference was observed in the proportion of patients with NIHSS score changes of at least +3 (Table 2). In addition, no new vascular events were observed within 90 days in either group.

Safety Outcomes

The safety outcomes were similar in both groups. No patients in either treatment group experienced moderate-to-severe bleeding events or death. In the argatroban plus DAPT group, the incidence of minor bleeding was 2.0% (1/49), characterized by a hemoglobin drop of 2 g/L on the third day of argatroban administration compared with admission level. In the DAPT group, the incidence of minor bleeding was 2.0% (1/51), with a hemoglobin decrease of 4 g/L observed on the fifth day compared with admission level. In addition, during the subsequent 3 days of follow-up, neither patient experienced further decreases in hemoglobin levels. By the final assessment before discharge, hemoglobin levels had partially recovered. The difference in safety events between the 2 groups did not reach statistical significance, regardless of whether variables were adjusted (Table 2). A detailed list of safety events is provided in Table S1.

Subgroup Analysis

The subgroup analysis suggested that factors including age, sex, hypertension, diabetes, hyperlipidemia, smoking, NIHSS score, and onset-to-randomization time did not significantly impact the primary outcome of patients between the 2 groups (Figures S2 and S3).

DISCUSSION

This study indicated that the incidence of END was significantly lower, and the 90-day functional outcome

Table 2. Primary Analysis of Outcomes in the Modified Intention-to-Treat Population

	N (%)		Unadjusted			Adjusted*		
Outcomes	Arg+DAPT (n=49)	DAPT (n=51)	Risk difference (95% CI)	Risk ratio (95% CI)	*P* value	Risk difference (95% CI)	Risk ratio (95% CI)	*P* value
Primary outcomes								
END†‡	10 (20.4)	24 (47.1)	26.7 (14.1 to 39.2)	2.31 (1.49 to 3.58)	0.006	24.4 (11.7 to 37.0)	2.14 (1.39 to 3.30)	0.014
mRS score 0–1 at 90 d‡§	43 (87.8)	35 (68.6)	−19.1 (−30.3 to −8.0)	0.78 (0.67 to 0.91)	0.025	−17.3 (−28.5 to −6.2)	0.80 (0.69 to 0.93)	0.037
Secondary outcomes								
ENI‡‖	11 (22.4)	2 (3.9)	−18.5 (−27.5 to −9.5)	0.17 (0.06 to 0.49)	0.014	−13.6 (−22.5 to −4.8)	0.28 (0.11 to 0.70)	0.063
mRS score 0–2 at 90 d‡	45 (91.8)	43 (84.3)	−7.5 (−16.4 to 1.4)	0.92 (0.83 to 1.02)	0.255	−9.7 (−18.6 to −0.7)	0.90 (0.81 to 0.99)	0.151
NIHSS score change of ≤−1, 7 d‡¶	20 (40.8)	7 (13.7)	−27.1 (−38.9. to −15.3)	0.34 (0.16 to 0.72)	0.003	−22.2 (−34.1 to −10.3)	0.41 (0.20 to 0.86)	0.017
NIHSS score change of ≥1, 7 d‡	7 (14.3)	21 (41.2)	26.9 (15.1 to 38.7)	2.88 (1.35 to 6.16)	0.004	25.0 (13.1 to 36.9)	2.67 (1.26 to 5.63)	0.008
NIHSS score change of ≥3, 7 d‡	5 (10.2)	14 (27.5)	17.3 (6.7 to 27.8)	2.69 (1.05 to 6.91)	0.034	14.6 (4.1 to 25.2)	2.31 (0.92 to 5.76)	0.064
NIHSS score change of ≥4, 7 d‡	4 (8.2)	8 (15.7)	7.5 (−1.4 to 16.5)	1.92 (0.62 to 5.97)	0.255	4.6 (−4.3 to 13.5)	1.49 (0.49 to 4.47)	0.473
mRS score distribution at 90 d#	0 (0 to 1)	1 (0 to 2)	Odds ratio, 2.18 (1.04 to 4.59)		0.040	Odds ratio, 4.20 (1.20 to 14.70)		0.025
New vascular events within 90 d	0	0	NA	NA	NA	NA	NA	NA
Safety events	1 (2.0)	1 (2.0)	−0.1 (−4.0 to 3.8)	0.96 (0.14 to 6.69)	0.977	−0.6 (−4.5 to 3.3)	0.75 (0.11 to 5.24)	0.841

Arg indicates argatroban; DAPT, dual antiplatelet therapy; END, early neurological deterioration; ENI, early neurological improvement; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Adjusted for prespecified prognostic variables (age, sex, and baseline NIHSS score).

†END was defined as an increase of ≥2 points in NIHSS score within 7 d.

‡Analyzed using a generalized linear model.

§The mRS is a global stroke disability scale with scores ranging from 0 (no symptoms) to 6 (death).

‖ENI was defined as a decrease of ≥2 points in NIHSS score within 7 d.

¶The NIHSS score was used to evaluate the severity of neurological deficits. A decrease in score indicates neurological improvement, whereas an increase in score indicates neurological deterioration.

#The mRS score at 90 d was assessed by an ordinal logistic regression.

was significantly better in patients with BAD treated with argatroban plus DAPT versus DAPT alone, with no predefined safety events observed. Furthermore, the difference in the primary end point outcome remained significant even after adjusting for predefined prognostic factors.

In a prospective multicenter, single-group trial, 144 patients diagnosed as probable BAD were treated with DAPT with cilostazol plus 1 oral antiplatelet drug (aspirin or clopidogrel), 76.4% of whom also received argatroban treatment. This cohort exhibited a significantly reduced rate of clinical progression at 2 weeks—defined as an increase of ≥1 points on the NIHSS or mRS from baseline—compared with a group of 142 matched historical control patients who received either cilostazol, aspirin, or clopidogrel as single antiplatelet therapy (only 5.6% of whom received argatroban), with rates of 9.7% versus 33.8%, respectively.[24] Another study from Japan suggested that patients with penetrating artery infarctions, including lacunar infarctions and BAD, who were receiving treatment with a combination of argatroban and DAPT (aspirin and clopidogrel) experienced a significantly lower rate of stroke progression, defined as an increase in NIHSS score by 1 or 2 points or more within 7 days of admission.[14] However, notably, less than half of the participants in the study were diagnosed with BAD, and the control group was treated with argatroban and aspirin, not DAPT.

In our study, patients with BAD in the control group in our study received DAPT comprising aspirin and clopidogrel, with an initial loading dose of 300 mg. Recent clinical studies have confirmed that short-term use of DAPT can reduce the risk of stroke recurrence in patients with mild to moderate AIS (NIHSS score ≤5) or high-risk transient ischemic attack.[25–28] Guidelines for the secondary prevention of stroke in numerous countries

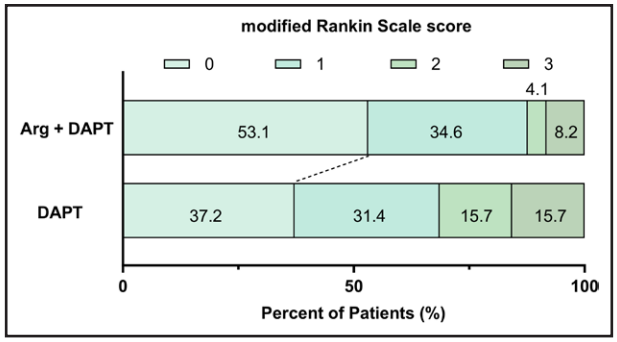

Figure 2. Distribution of modified Rankin Scale (mRS) score at 90 days in the modified intention-to-treat population.
Functional outcome was assessed by mRS score. Score ranged from 0 to 6, with 0 indicating no symptoms; 1, symptoms without clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. Arg indicates argatroban; and DAPT, dual antiplatelet therapy.

have advocated the early administration of DAPT after the onset of acute mild to moderate noncardioembolic ischemic stroke.[18,29] In this study, by using DAPT as a control, we found that treatment with argatroban plus DAPT significantly reduced the risk of END in patients with BAD. To our knowledge, this was the first study to confirm that short-term treatment with argatroban plus DAPT can safely and effectively reduce the risk of END and improve functional outcome in patients with BAD.

We noted that compared with previous observational studies, the proportion of patients who experienced END in our trial was greater, and the difference in END occurrence rates between the argatroban plus DAPT group and the DAPT group was smaller. This is potentially due to our selection of patients with BAD at greater risk of END. The inclusion criteria of our study included certain modifications to the BAD diagnostic criteria proposed by Japanese scholars Adachi and Takagi in 2006.[30] We

Table 3. Comparison of NIHSS Score and mRS Score Between the Modified Intention-to-Treat Population

Variables, median (IQR)	DAPT+Arg (n=49)	DAPT (n=51)	*P* value
NIHSS score at admission	2.0 (1.5–4.0)	2.0 (1.0–3.0)	0.134
24 h NIHSS score	2.0 (2.0–4.5)	3.0 (2.0–4.0)	0.534
48 h NIHSS score	2.0 (1.5–4.5)	3.0 (2.0–5.0)	0.350
7 d NIHSS score	2.0 (1.0–3.0)	3.0 (2.0–5.0)	0.015
NIHSS score at discharge	1.0 (0.0–2.5)	2.0 (1.0–4.0)	0.009
mRS score at admission	0 (0–0)	0 (0–0)	0.604
mRS score at discharge	1 (0–2)	1 (1–3)	0.072
mRS score at 3 mo	0 (0–1)	1 (0–2)	0.040

Arg indicates argatroban; DAPT, dual antiplatelet therapy; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

excluded infarctions in the upper and middle segments of the pons, as lesions located in the lower segment of the pons have been identified as an independent predictor of END in patients with BAD (odds ratio, 3.768), whereas other parts of the pons and brainstem do not correlate with END.[31] In addition, patients with posterior type LSA infarctions were included, as studies have indicated that posterior type LSA infarctions, rather than the number of layers involved in the lesion, are an independent predictor of END (odds ratio, 14.83).[16] Hence, the patients with BAD enrolled in this study predominantly presented with infarct sites at high risk for END, which may account for the greater incidence of END in both groups.

Currently, there is a lack of accurate tools for predicting END in patients with BAD. From a clinical standpoint, selecting patients with BAD at high risk of END for aggressive antithrombotic therapy by imaging examinations appears reasonable, potentially avoiding unnecessary bleeding hazards associated with aggressive antithrombotic treatment in patients at lower risk of END.

In this study, we intentionally excluded patients at high risk of hemorrhage, such as elderly patients, those with lacunar states, or severe leukoencephalopathy (Blennow score of 3 or modified Fazekas score of 3) as shown by computed tomography or magnetic resonance imaging. Although activated partial thromboplastin time monitoring was not conducted, no serious safety events, including moderate-to-severe bleeding or death from any cause, were observed in the argatroban plus DAPT group, similar to the findings of other studies.[12,14,32] Each group had 1 patient who experienced minor bleeding but without further deterioration. This suggests that short-term administration of argatroban plus DAPT among these specific patients with BAD is safe.

The underlying mechanism driving the occurrence of END in patients with BAD remains unclear. A study utilizing whole-brain vessel-wall imaging technology revealed that for single subcortical infarctions, atherosclerotic plaques in the ipsilateral middle cerebral artery, located proximal to the LSA origin, serve as an independent predictor of END, with an odds ratio of 3.87.[33] Given the high sensitivity of penetrating artery orifices to hemodynamic shifts induced by adjacent arterial lesions, it is speculated that END might result from diminished perfusion due to arteriosclerotic lesions at these orifices or from local thrombosis formation and extension, which further exacerbates ischemia.[34,35] Argatroban, a direct thrombin inhibitor, can selectively and reversibly bind to and inactivate thrombin. This action further blocks a series of reactions catalyzed or triggered by thrombin, such as fibrin formation, activation of coagulation factors (factors V, VIII, and XIII), activation of protein C, and platelet aggregation, thereby exerting anticoagulant effects.[9,36–38] We hypothesized that, compared with the use of DAPT alone, the application of argatroban plus DAPT had the potential to further enhance antithrombotic efficacy. This

combination strategy effectively prevented the formation and extension of thrombosis at the orifices of penetrating arteries, thereby preventing the exacerbation of ischemia and the occurrence of END due to hemodynamic disturbances in the penetrating arteries.

In this study, we also observed early improvement in neurological function (a decrease in the NIHSS score of ≥2 points within 7 days) in patients with BAD treated with argatroban plus DAPT, suggesting that argatroban might exert an effect similar to that of thrombolysis by inhibiting thrombin activity within the thrombus, which facilitates the exposure of penetrating artery orifices, and improving perfusion, thereby contributing to the rescue of the ischemic penumbra. In addition, animal experiments have demonstrated that argatroban could dissolve microthrombi and improve perfusion in ischemic areas, thus diminishing the size of infarcts and improving functional outcome.[39–41]

Limitations

This study has several limitations that need to be considered. First, due to the adoption of an open-label design, the concealment of treatment plans from participants and physicians was not possible, potentially affecting the objectivity of the outcomes. Nonetheless, we used a blinded evaluation approach for the study end points to minimize measurement biases and ensure the objectivity of our primary end points. Second, patients who received intravenous thrombolysis were excluded, which may limit the general applicability of the findings. Third, this study excluded specific etiologies like cardioembolic ischemic stroke, resulting in the study population mainly composed of atherosclerotic-type patients. Consequently, we could not perform a detailed etiological classification of BAD, and the findings are mainly applicable to the atherosclerotic subtype of patients with BAD. Fourth, although no safety events such as intracranial hemorrhage were observed, coagulation parameters were not dynamically monitored in patients using argatroban, nor were the doses adjusted according to the individual patient's condition, which may lead to other potential impacts. Notably, given the individual variability in ischemic stroke, the geographic limitation of our participants in Southwest China, and the relatively small sample size, the generalizability of our results is limited. Therefore, further validation across national and international regions, as well as stratified analysis by center is needed.

Conclusions

For patients with BAD at high risk of END who have not undergone intravenous thrombolysis, the administration of argatroban plus DAPT significantly reduced the occurrence of END and improved the 90-day functional outcome without increasing bleeding risk.

ARTICLE INFORMATION

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Author Contributions

J. Xu performed the studies, collected the data, and drafted the manuscript. Y. Liu collected the data, performed the data analysis, and assisted in drafting the manuscript. R. Sun and H. Wang participated in the data acquisition and data analysis. Dr Zhao, X. Liu, and Y. Li provided administrative and technical support. Dr Yang generated the random allocation sequence and performed the data analysis and interpretation. B. Zhang, Dr He, Dr Gong, Dr Ding, and X. Xu revised the manuscript and provided administrative and technical support. R. Xu provided administrative and material support and supervised the trial. J. Wang secured funding, designed the entire trial and supervised its process, managed the data, and revised the manuscript.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Table S1
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CONSORT Checklist

REFERENCES

1. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. *Neurology*. 1989;39:1246–1250. doi: 10.1212/wnl.39.9.1246
2. Kim JS, Yoon Y. Single subcortical infarction associated with parental arterial disease: important yet neglected sub-type of atherothrombotic stroke. *Int J Stroke*. 2013;8:197–203. doi: 10.1111/j.1747-4949.2012.00816.x.
3. Deguchi I, Takahashi S. Pathophysiology and optimal treatment of intracranial branch atheromatous disease. *J Atheroscler Thromb*. 2023;30:701–709. doi: 10.5551/jat.RV22003
4. Tatsumi S, Yamamoto T. An autopsied case of an apparent pontine branch atheromatous disease. *Eur Neurol*. 2010;63:184–185. doi: 10.1159/000290248
5. Petrone L, Nannoni S, Del Bene A, Palumbo V, Inzitari D. Branch atheromatous disease: a clinically meaningful, yet unproven concept. *Cerebrovasc Dis*. 2016;41:87–95. doi: 10.1159/000442577
6. Deguchi I, Hayashi T, Kato Y, Nagoya H, Ohe Y, Fukuoka T, Maruyama H, Horiuchi Y, Tanahashi N. Treatment outcomes of tissue plasminogen activator infusion for branch atheromatous disease. *J Stroke Cerebrovasc Dis*. 2013;22:e168–e172. doi: 10.1016/j.jstrokecerebrovasdis.2012.10.012
7. Yamamoto Y, Ohara T, Hamanaka M, Hosomi A, Tamura A, Akiguchi I. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. *J Neurol Sci*. 2011;304:78–82. doi: 10.1016/j.jns.2011.02.006
8. Xu J, Xu X, Wang H, He L, Liu Q, Du Y, Wang J. Dual antiplatelet therapy plus argatroban prevents early neurological deterioration in branch atherosclerosis disease. *Stroke*. 2022;53:e19–e20. doi: 10.1161/STROKEAHA.121.036356

9. Jeske WP, Fareed J, Hoppensteadt DA, Lewis B, Walenga JM. Pharmacology of argatroban. *Expert Rev Hematol*. 2010;3:527–539. doi: 10.1586/ehm.10.53
10. Barreto AD, Alexandrov AV, Lyden P, Lee J, Martin-Schild S, Shen L, Wu TC, Sisson A, Pandurengan R, Chen Z, et al. The argatroban and tissue-type plasminogen activator stroke study: final results of a pilot safety study. *Stroke*. 2012;43:770–775. doi: 10.1161/STROKEAHA.111.625574
11. Barreto AD, Ford GA, Shen L, Pedroza C, Tyson J, Cai C, Rahbar MH, Grotta JC; ARTSS-2 Investigators. Randomized, multicenter trial of ARTSS-2 (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke). *Stroke*. 2017;48:1608–1616.
12. Zhou LS, Li XQ, Zhou ZH, Chen HS. Effect of argatroban combined with dual antiplatelet therapy on early neurological deterioration in acute minor posterior circulation ischemic stroke. *Clin Appl Thromb Hemost*. 2020;26:107602962090413.
13. Nagakane Y, Tanaka E, Ashida S, Kojima Y, Ogura S, Maezono K, Yamamoto Y. [Safety of dual antiplatelet therapy with argatroban in patients with acute ischemic stroke]. *Brain Nerve*. 2018;70:557–562. doi: 10.11477/mf.1416201038
14. Nishi R, Mano T, Kobayashi Y, Matsuo K, Kobayashi Y. [Argatroban, aspirin, and clopidogrel combination therapy for acute penetrating artery infarction: a pilot study]. *Brain Nerve*. 2016;68:181–189. doi: 10.11477/mf.1416200370
15. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Open Med*. 2010;4:e60–e68. doi: 10.1016/S0140-6736(05)71879-1
16. Ohara T, Yamamoto Y, Tamura A, Ishii R, Murai T. The infarct location predicts progressive motor deficits in patients with acute lacunar infarction in the lenticulostriate artery territory. *J Neurol Sci*. 2010;293:87–91. doi: 10.1016/j.jns.2010.02.027
17. Zhang X, Zhong W, Xue R, Jin H, Gong X, Huang Y, Chen F, Chen M, Gu L, Ge Y, et al. Argatroban in patients with acute ischemic stroke with early neurological deterioration. *JAMA Neurol*. 2024;81:118–125. doi: 10.1001/jamaneurol.2023.5093
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, 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:e344–e418. doi: 10.1161/STR.0000000000000211
19. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
20. Siegler JE, Samai A, Semmes E, Martin-Schild S. Early neurologic deterioration after stroke depends on vascular territory and stroke etiology. *J Stroke*. 2016;18:203–210. doi: 10.5853/jos.2016.00073
21. Huang ZX, Wang QZ, Dai YY, Lu HK, Liang XY, Hu H, Liu XT. Early neurological deterioration in acute ischemic stroke: a propensity score analysis. *J Chin Med Assoc*. 2018;81:865–870. doi: 10.1016/j.jcma.2018.03.011
22. Karaszewski B, Wyszomirski A, Jabłoński B, Werring DJ, Tomaka D. Efficacy and safety of intravenous rtPA in ischemic strokes due to small-vessel occlusion: systematic review and meta-analysis. *Transl Stroke Res*. 2021;12:406–415. doi: 10.1007/s12975-021-00890-9
23. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.
24. Kimura T, Tucker A, Sugimura T, Seki T, Fukuda S, Takeuchi S, Miyata S, Fujita T, Hashizume A, Izumi N, et al. Ultra-early combination antiplatelet therapy with cilostazol for the prevention of branch atheromatous disease: a multicenter prospective study. *Cerebrovasc Dis Extra*. 2016;6:84–95. doi: 10.1159/000450835
25. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
26. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration; Neurological Emergencies Treatment Trials Network; POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
27. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383:207–217. doi: 10.1056/NEJMoa1916870
28. Gao Y, Pan Y, Han S, Chen W, Jing J, Wang C, Yang Y, Wang T, Meng X, Zhao X, et al; INSPIRES Investigators. Rationale and design of a randomised double-blind 2×2 factorial trial comparing the effect of a 3-month intensive statin and antiplatelet therapy for patients with acute mild ischaemic stroke or high-risk TIA with intracranial or extracranial atherosclero. *Stroke Vasc Neurol*. 2023;8:249–258. doi: 10.1136/svn-2022-002084
29. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467. doi: 10.1161/STR.0000000000000375
30. Adachi T, Takagi M. [The clinical differences between lacunar infarction and branch atheromatous disease]. *Nihon Rinsho*. 2006;64(Suppl 8):155–159.
31. Oh S, Bang OY, Chung CS, Lee KH, Chang WH, Kim GM. Topographic location of acute pontine infarction is associated with the development of progressive motor deficits. *Stroke*. 2012;43:708–713. doi: 10.1161/STROKEAHA.111.632307
32. Li X, Hou X, Cui Y, Tian X, Wang X, Zhou Z, Chen H. Safety and preliminary efficacy of argatroban plus dual antiplatelet therapy for acute mild to moderate ischemic stroke with large artery atherosclerosis. *Brain Behav*. 2022;12:e2664.
33. Yan Y, Jiang S, Yang T, Yuan Y, Wang C, Deng Q, Wu T, Tang L, Wu S, Sun J, et al. Lenticulostriate artery length and middle cerebral artery plaque as predictors of early neurological deterioration in single subcortical infarction. *Int J Stroke*. 2023;18:95–101. doi: 10.1177/17474930221081639
34. Alawneh JA, Moustafa RR, Baron JC. Hemodynamic factors and perfusion abnormalities in early neurological deterioration. *Stroke*. 2009;40:e443–e450. doi: 10.1161/STROKEAHA.108.532465
35. Seners P, Hurford R, Tisserand M, Turc G, Legrand L, Naggara O, Mas JL, Oppenheim C, Baron JC. Is unexplained early neurological deterioration after intravenous thrombolysis associated with thrombus extension? *Stroke*. 2017;48:348–352. doi: 10.1161/STROKEAHA.116.015414
36. LaMonte MP, Brown PM, Hursting MJ. Alternative parenteral anticoagulation with argatroban, a direct thrombin inhibitor. *Expert Rev Cardiovasc Ther*. 2005;3:31–41. doi: 10.1586/14779072.3.1.31
37. Rössig L, Genth-Zotz S, Rau M, Heyndrickx GR, Schneider T, Gulba DCL, Desaga M, Buerke M, Harder S, Zeiher AM; ARG-E04 Study Group. Argatroban for elective percutaneous coronary intervention: the ARG-E04 multi-center study. *Int J Cardiol*. 2011;148:214–219. doi: 10.1016/j.ijcard.2010.02.044
38. Imiya M, Matsuo T. Inhibition of collagen-induced platelet aggregation by argatroban in patients with acute cerebral infarction. *Thromb Res*. 1997;88:245–250. doi: 10.1016/s0049-3848(97)00235-1
39. Maclean JAA, Tomkins AJ, Sturgeon SA, Hofma BR, Alwis I, Samson AL, Schoenwaelder SM, Jackson SP. Development of a carotid artery thrombolysis stroke model in mice. *Blood Adv*. 2022;6:5449–5462. doi: 10.1182/bloodadvances.2021006008
40. Kawai H, Yuki S, Sugimoto J, Tamao Y. Effects of a thrombin inhibitor, argatroban, on ischemic brain damage in the rat distal middle cerebral artery occlusion model. *J Pharmacol Exp Ther*. 1996;278:780–785.
41. Lyden P, Pereira B, Chen B, Zhao L, Lamb J, Lei I, Rajput P. Direct thrombin inhibitor argatroban reduces stroke damage in 2 different models. *Stroke*. 2014;45:896–899. doi: 10.1161/STROKEAHA.113.004488.