Effect of Argatroban Plus Intravenous Alteplase vs Intravenous Alteplase Alone on Neurologic Function in Patients with Acute Ischemic Stroke: The ARAIS Randomized Clinical Trial

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Key Points

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

Findings In this randomized clinical trial that included 808 patients with acute ischemic stroke, excellent neurologic function at 90 days in those randomized to argatroban plus intravenous recombinant tissue-type plasminogen activator compared with intravenous recombinant tissue-type plasminogen activator alone occurred in 63.8% vs 64.9%, a difference that was not statistically significant.

Meaning Among patients with acute ischemic stroke who receiving intravenous recombinant tissue-type plasminogen activator, argatroban was not associated with better neurologic function.

Abstract

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

OBJECTIVE To assess the efficacy and safety of argatroban plus r-tPA for AIS.

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

INTERVENTIONS Eligible patients were randomly assigned within 4.5 hours of symptom onset into argatroban plus r-tPA group: 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 r-tPA (0.9 mg/kg; maximum dose 90 mg, 10% administered as 1-minute bolus, remaining infused over 1 hour), or r-tPA alone group: intravenous r-tPA alone. Both groups received guideline-based treatments.

MAIN OUTCOMES AND MEASURES The primary end point was an excellent functional outcome, defined as a modified Rankin Scale score of 0 to 1 at 90 days. All end points had blinded assessment and were analyzed on a modified intention-to-treat population.

RESULTS Among 808 eligible patients with AIS who were randomized (mean age, 64 [10.3]; 238 [29.5%] women), 696 (86.1%) completed the trial. At 90 days, 210 (63.8%) in the argatroban plus r-tPA group versus 238 (64.9%) in the r-tPA alone group had an excellent functional outcome (risk difference, -1.0% [95% CI, -8.1% - 6.1%]; crude relative risk, 0.98 [95% CI, 0.88 - 1.10, P =.78). The proportion of symptomatic intracerebral hemorrhage was 0.3% (1/383) in the argatroban plus r-tPA group and 0.3% (1/397) in the r-tPA alone group.

CONCLUSIONS AND RELEVANCE: Argatroban is safe but does not improve functional outcome at 90 days in Chinese patients with AIS treated with r-tPA.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03740958

Introduction

Current guidelines recommend reperfusion therapies such as intravenous thrombolysis and endovascular thrombectomy as the most effective strategies for acute ischemic stroke (AIS).[1] Vessel recanalisation is strongly associated with lower mortality and improved functional outcome of reperfusion therapies in patients with AIS.[2] However, only 30% of patients achieved complete recanalisation through intravenous thrombolysis,[3] while approximately 30% of patients with large artery occlusion did not achieve successful reperfusion after endovascular thrombectomy.[4] Although endovascular therapy has been shown to be effective in AIS with large artery occlusion,[4] its use in clinical practice is limited due to a reliance on device availability and experienced clinicians. In addition, 14%–34% of the population with initial recanalisation undergoes reocclusion after recombinant tissue-type plasminogen activator (r-tPA) thrombolysis and has clinical deterioration and poor outcomes.[3,5] Thus, an effective and simple method is needed to improve vessel recanalisation, prevent reocclusion, and reduce AIS disability.

Argatroban, a selective thrombin inhibitor, directly inhibits free and clot-associated thrombin as well as thrombin-induced events and has been widely used to treat AIS, particularly in Asian countries such as China and Japan.[6,7] Growing evidence from preclinical studies has demonstrated the effect of argatroban plus r-tPA in ischemic stroke by enhancing and sustaining arterial recanalisation.[8-9] Translating into clinical practice, early phase trials have demonstrated the safety and possible efficacy of argatroban plus r-tPA in patients receiving intravenous thrombolysis and endovascular treatments.[10-12] There is a lack of robust evidence for the effect of argatroban plus r-tPA in AIS patients because of small sample sizes. In this context, we designed a prospective, multicenter, open-label, blinded-end point, randomized trial to explore the efficacy and safety of argatroban plus r-tPA for AIS

within 4.5 hours from onset.

Methods

Study Design

Argatroban plus r-tPA for AIS (ARAIS) was a multicenter, open-label, blinded-end point, randomized controlled trial to assess the efficacy and safety of argatroban plus r-tPA in patients with AIS within 4.5 hours from symptom onset. The study protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2. The trial was conducted at 50 medical sites (Supplement 3 eAppendix 1) in China. Details of the study design and rationale have been published elsewhere.[13] The trial protocol was approved by the appropriate regulatory and ethical authorities of the Ethics Committee of the General Hospital of Northern Theatre Command and other participating hospitals. An independent data monitoring committee (Supplement 3 eAppendix 2) monitored the progress of the trial every 6 months. Signed informed consent was obtained from patients or their legally authorized representatives.

Participants

Eligible patients were adults aged between 18-80 years old with AIS at the time of randomization (baseline National Institutes of Health Stroke Scale [NIHSS] scores of more than 6; range 0 to 42, with higher scores indicating greater stroke severity), and were enrolled up to 4.5 hours after the onset of stroke symptoms (the time the patient last seen was well). Whole-head computed tomography or magnetic resonance imaging was performed on admission to identify patients with ischemic stroke. Key exclusion criteria were as follows: presence of disability in the community

(modified Rankin Scale [mRS] scores ≥ 2; range 0 [no symptoms] to 6 [death]) before the stroke; history of intracerebral hemorrhage; gastrointestinal or urinary tract bleeding in the last 30 days; and need for concomitant use of anticoagulants other than argatroban. A full list of inclusion and exclusion criteria is available in the study protocol (Supplement 1).

Randomization and masking

In the trial, eligible patients were randomly assigned to either the argatroban plus r-tPA group or the r-tPA alone group using a block randomization method with a block size of four, through a computer-generated random sequence that was centrally administered via a password-protected web-based program at http://console.tt.zhinanmed.com (Beijing Zhinan Medical Technology Co., Ltd). The study team members were blinded to the treatment allocation.

Procedures

In both treatment groups, intravenous r-tPA (0.9 mg/kg; maximum dose 90 mg, 10% administered as a 1-minute bolus, the remaining infused over 1 hour; Boehringer Ingelheim Co., Ltd) was administered within 4.5 hours after symptom onset. Patients in the argatroban plus r-tPA group received a 100 μg/kg intravenous argatroban (Tianjin Institute of Pharmaceutical Research Co., Ltd) bolus over 3 to 5 minutes within 1 hour of the r-tPA bolus, followed by an argatroban infusion of 1.0 μg/kg per minute for 48 hours. Standard treatments based on current guidelines were also received by the patients in both groups.[1]

Argatroban infusion rates were adjusted to achieve a target activated partial thromboplastin time (APTT) of 1.75 × baseline (±10%). A dosing algorithm was developed so that standardized

increments or decrements of argatroban infusion rate took place in response to the APTT.[14] APTT was monitored at baseline and at 2, 6, 12, 24, and 48 hours after initiation of argatroban; within 2 to 4 hours of any argatroban infusion adjustment, and in the event of major systemic bleeding. Argatroban infusion was terminated immediately if major systemic bleeding or symptomatic intracerebral hemorrhage was suspected.

The NIHSS was used to assess neurologic status at baseline, 24 hours, 48 hours, 7 days, and 14 days after randomization. A detailed flowchart of the assessment schedule is provided in the study protocol (Supplement 1). Data on demographic and clinical characteristics was obtained at randomization. Follow-up data was collected at 7 days, 14 days (or at hospital discharge if earlier), and 90 days after randomization. Remote and on-site quality control monitoring and data verification were conducted throughout the study.

Outcomes

The primary end point was whether there was excellent functional outcome at 90 days, defined as a score of 0–1 on the mRS for the evaluation of neurologic disability, assessed in person or, if an in-person visit was not possible, through a structured interview for telephone assessment, by personnel certified in the scoring of the mRS at 90 days after randomization (Supplement 3 eMethods).

The secondary end points were the favorable functional outcome (mRS scores 0–2) at 90 days; the occurrence of early neurologic improvement (ENI), compared with baseline at 48 hours, defined as more than or equal to 2 NIHSS score decrease;[15] the occurrence of early neurologic deterioration (END), compared with baseline at 48 hours, defined as more than or equal to 4 NIHSS score increase;[16] change in NIHSS score compared with baseline at 14 days; and the occurrence of

stroke[17] or other vascular events within 90 days. In addition, a shift in measures of functioning according to the full range of mRS scores at 90 days was analyzed as secondary outcome, which was included in the statistical analysis.

The pre-specified safety outcomes were symptomatic intracerebral hemorrhage, parenchymal hematoma type 2, and major systemic bleeding that occurred during the study. Symptomatic intracerebral hemorrhage was defined as any evidence of bleeding on the head CT scan associated with clinically significant neurologic deterioration (NIHSS score ≥ 4 points increase) in the opinion of the clinical investigator or independent safety monitor.[18] Parenchymal hematoma type 2 was defined as confluent bleeding occupying more than 30% of the infarct volume and causing significant mass effect.[19] Major systemic bleeding was defined as a drop in the hemoglobin level by ≥2 g/dL or a transfusion of ≥2 U of blood.

The baseline and follow-up NIHSS scores were evaluated by the same neurologist, who was not blinded to the treatment allocation. Final follow-up was performed at 90 days in person or, if an in-person visit was not possible, a structured interview for telephone assessment was performed by a trained and certified staff member in each centre who was unaware of the randomized treatment assignment. A training course was held for all the investigators at each centre to ensure the validity and reproducibility of the evaluation. Central adjudication of clinical outcomes and adverse events was also performed by assessors unaware of treatment allocation or clinical details. If there was disagreement between local and central assessors, a consensus was reached by discussion. The local assessor retained control of the final mRS score following any discussion. Finally, there was no disagreement between the central adjudicator and the local assessor.

Sample Size Calculation

Power calculations were based on the estimated treatment effects based on a binary assessment of excellent functional outcomes at 90 days. In the Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke (ARTSS-2) study,[11] argatroban plus r-tPA resulted in a 9% improvement in the primary end point compared to r-tPA alone. Therefore, 9% was chosen as the minimal detectable difference in this study. This was based on the assumption that proportions with excellent functional outcomes were 30% in the argatroban plus r-tPA group and 21% in the r-tPA alone group (equivalent to a risk ratio [RR] = 1.43), a sample size of 734 (367 per group) was estimated to provide more than 80% power (using a two-sided $\alpha = 0.05$) to detect the 9% greater excellent functional outcome in the argatroban plus r-tPA group. Assuming a 10% loss to follow-up, the total sample size was 808. Therefore, this study included 808 participants (404 participants per group).

Statistical Analysis

Statistical analyses were performed on a modified intention-to-treat (ITT) basis, which included all randomized participants with at least one post-baseline efficacy evaluation. Generalized linear models (GLMs) were performed for the analyses of the primary and secondary outcomes of favorable functional outcomes at 90 days, the occurrence of early neurologic improvement, and early neurologic deterioration. The treatment effects for the above outcomes are presented as odds ratio (OR), RR, and risk differences (RD) with their 95% confidence intervals (CIs). In sensitivity analyses, missing values in the primary outcome were imputed using the last observation carried forward method, as well as the worst-case scenario and best-case scenario approaches. No interim analyses were performed in this study.

The mRS score at 90 days was compared using ordinal logistic regression via GLM with treatment effect presented as OR with 95% CI. A GLM was also used to compare changes in log (NIHSS score) between admission and 14 days, and geometric mean ratio with 95% CI was calculated between the argatroban plus r-tPA and r-tPA alone groups. Time-to-event outcomes of stroke and other vascular events were compared using Cox regression models, and the corresponding treatment effects are presented as hazard ratios (HR) with 95% CI. The proportionality assumption was tested by including a time-treatment interaction in the Cox model.

The primary analyses of the primary and secondary outcomes were unadjusted. Covariate adjusted GLM analyses were also performed for all outcomes, adjusting for six prespecified prognostic factors: age, sex, NIHSS score at randomization, time from symptom onset to thrombolysis, premorbid function (mRS score 0 or 1), and history of stroke or transient ischemic attack. Endovascular therapy and large artery occlusion were planned in the covariate adjusted analyses but were excluded due to skewed distribution or large proportion of missing values (Supplement 2).

Subgroup analysis of the primary outcome was performed using GLM on eight prespecified subgroups (age [<65 years or ≥65 years], sex [female or male], NIHSS score at randomization [6-9 or >9], endovascular therapy [yes or no], large artery occlusion [yes or no], time from symptom onset to thrombolysis [<3 hours or 3-4.5 hours], premorbid function (mRS score), and history of stroke or transient ischemic attack. Assessment of the homogeneity of the treatment effect by a subgroup variable was conducted using a GLM with the treatment, subgroup variable, and their interaction term as independent variables, and the p value for the interaction term was presented. Detailed statistical analyses are described in the statistical analysis plan (Supplement 2).

In addition, per-protocol analyses for primary and secondary outcomes were performed on

patients who received complete intervention as specified in the protocol. A 2-sided p value of less than 0.05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for secondary outcome analyses should be interpreted as exploratory. SPSS software (version 23) and R software (version 4.1.0) were used for the statistical analyses.

Results

Trial Population

Between January 18, 2019, and October 30, 2021, 828 patients were enrolled, and 808 were randomly assigned to the argatroban plus r-tPA group (397 patients) or the r-tPA alone group (411 patients) after excluding 20 patients due to randomization errors or lack of informed consent. A total of 112 (13.9%) patients were further excluded (58 patients withdrew consent due to clinical decisions, 33 withdrew consent due to patients' decisions, 6 for other reasons, and 15 were lost to follow-up). Finally, the modified ITT population included 696 patients (329 in the argatroban plus r-tPA group and 367 in the r-tPA alone group) (Figure 1 and Supplement 3 eFigure 1). The procedure was completed according to the protocol for 692 patients (325 in the argatroban plus r-tPA group and 367 in the r-tPA alone group) and the results were included in the per-protocol analysis. The reasons for the incomplete procedures are provided in Figure 1. The trial was completed in January 2022.

The treatment groups were well balanced with respect to baseline patient characteristics in the modified ITT population (Table 1) and per-protocol analysis (Supplement 3 eTable 1). In the argatroban plus r-tPA group, 325 of 329 patients (98.8%) underwent the complete procedure of argatroban plus r-tPA treatment at a mean of 158.5 minutes from symptom onset to the r-tPA treatment. The remaining four patients did not receive complete argatroban treatment after r-tPA treatment.

Primary Outcome

For the primary outcome, the proportion of patients with mRS scores of 0 to 1 at 90 days was 63.8% (210/329) in the argatroban plus r-tPA group and 64.9% (238/367) in the r-tPA alone group. In the modified ITT population, the risk of having an excellent outcome showed no difference between the argatroban plus r-tPA and r-tPA alone groups (unadjusted RR 0.98; 95% CI 0.88-1.10; *P*=0.78; Table 2, Figure 2). Similar RR results were observed in the last observation carried forward, worst-case scenario, and best-case scenario sensitivity analyses (Supplement 3 eTable 2). The difference in the risks of having a primary outcome remained insignificant after adjustment for pre-specified prognostic variables (RR 1.03; 95% CI 0.86-1.23; *P*=0.78; Table 2). The per-protocol analysis yielded similar results (unadjusted RR 1.00; 95% CI 0.89-1.11; *P*=0.95; adjusted RR 0.98; 95% CI 0.89-1.08; *P*=0.65; Supplement 3 eFigure 2, eTable 3).

Secondary Outcomes

For the secondary outcomes, no significant differences were observed in the secondary outcomes in both the unadjusted and adjusted analysis, including the risks of having an mRS score of 0 to 2, mRS improvement at 90 days, early neurologic improvement within 48 hours, early neurologic deterioration within 48 hours, change in NIHSS score compared with randomization at 14 days, and stroke or other vascular events within 90 days (Table 2). In the per-protocol analysis, similar results were obtained in both unadjusted and adjusted per-protocol analyses (Supplement 3 eTable 3).

Prespecified subgroup analysis showed no evidence of effect modification in the risks of having a primary outcome between the argatroban plus r-tPA and r-tPA alone groups by age, sex,

NIHSS score at randomization, endovascular therapy, large artery occlusion, time from the onset of symptoms to treatment, mRS score at admission, and history of stroke or transient ischemic attack (Supplement 3 eFigure 3). The results of the per-protocol analysis were similar to those of the modified ITT population for the primary outcome (Supplement 3 eFigure 4).

Safety Outcomes

Analyses of safety outcomes were based on the safety population which consists of all randomized subjects who receive at least one dose of study drug. In the safety population, one patient experienced symptomatic intracerebral hemorrhage and one patient experienced major systemic bleeding in the argatroban plus r-tPA group, while one patient experienced symptomatic intracerebral hemorrhage, one patient experienced parenchymal hematoma type 2, and one patient experienced major systemic bleeding in the r-tPA alone group (Table 3 and Supplement 3 eTable 4).

Discussion

To the best of our knowledge, this is the first large-sample, appropriately powered, prospective, multicenter, randomized controlled trial of argatroban plus r-tPA treatment in patients with AIS. We found that treatment with argatroban plus r-tPA, applied as an adjunct to guideline-based treatment, was safe but did not improve the functional outcome at 90 days in AIS after symptom onset when compared with r-tPA alone treatment. Furthermore, there was no evidence of effect modification of prespecified subgroups on the treatment effect on the primary end point.

Although some studies have investigated the effect of argatroban plus r-tPA on AIS,[10-12] there is a lack of strong evidence for this effect. This ARIAS study differed from previous studies in three

major ways.[10-12] First, previous trials had relatively small sample sizes ranging from 10 to 90. To date, the present study, including 828 participants, is the largest randomized controlled trial that provides robust statistical evidence on the effect of argatroban plus r-tPA on AIS. Second, the included patients with median NIHSS scores of 8–9 were less severe than those in previous studies with a median NIHSS score of 13–19.5. Third, the target population was the patients with large artery occlusion in previous studies whereas this was not mandatory in this study. Although previous studies suggested that argatroban plus r-tPA increased the proportion of patients with excellent functional outcomes,[10,11] unexpectedly, argatroban plus r-tPA did not show a significant improvement in neurologic function in the present study. The negative results may be attributed to the fewer enrolled patients with large artery occlusion in the current study (20.8%) because the promising results of argatroban plus r-tPA were found in patients with a high proportion of large artery occlusion (51.1% to 100%)[9-11], while argatroban plus r-tPA may increase recanalisation and decrease the reocclusion rates of large artery occlusion, resulting in better neurologic improvement. Because it is impractical to perform vessel imaging before intravenous thrombolysis in most stroke centers in China, large artery occlusion is not mandatory in the ARIAS design. In addition, the rapid development of endovascular treatment after five clinical trials resulted in more patients with large artery occlusion receiving endovascular treatment.[20] Collectively, these two reasons resulted in a lower proportion of patients with large artery occlusion enrolled in the trial. Having similar profile of enrolled patients and study aim to ARAIS trial, the Multi-arm Optimization of Stroke Thrombolysis (MOST) (ClinicalTrials.gov Identifier: NCT03735979) was ongoing and the results will bring us further evidence about the efficacy and safety of argatroban plus r-tPA therapy.

In this study, we found no effect of argatroban plus r-tPA on early functional outcomes such

as early neurologic improvement at 48 hours, early neurologic deterioration at 48 hours, or change in NIHSS score compared with randomization at 14 days. The lack of a significant effect on early outcomes correlated well with the negative primary outcome because the changes in these early outcomes, such as an increase in early neurologic improvement and a decrease in early neurologic deterioration, will result in the high risk of excellent functional outcome at 90 days. Furthermore, no significant difference in risk of having other secondary outcome, such as stroke or other vascular events within 90 days, was found between the groups.

For the safety outcomes, similar rates of bleeding events were observed between the argatroban plus r-tPA group and the r-tPA alone group, which was consistent with previous studies.[10,11] However, the proportion of bleeding events was lower than in previous studies.[10,11] This could be due to the lower median NIHSS score at risk in the present study.[21]

Limitations

The key strengths of this randomized controlled trial were its large sample size and multicenter recruitment, enhancing the generalizability of the results and the possibility of influencing clinical practice nationwide. Robust methodologies were used to ensure masking during the assessment of key efficacy and safety outcomes. Nonetheless, we acknowledge several potential limitations to our study. One limitation was that the number of patients in the argatroban plus r-tPA group (n=329) did not meet the minimum sample size (n= 367); the lower statistical power and imbalanced sample sizes between the groups cannot be ignored. This may have resulted from more patients dropping out of the argatroban plus r-tPA group. Second, due to the open-label design, we did not conceal the assigned treatment from the participants and physicians. Blinded end point assessments, on the other hand, were used to reduce measurement bias and ensure that the primary end point was measured objectively.

Third, a lower proportion of patients with large artery occlusion was enrolled in the trial, which may be the main cause of the negative results of the ARAIS trial. Thus, the effect of r-tPA plus argatroban in patients with large artery occlusion warrants investigation in future trials. Finally, further confirmation of these conclusions in non-Chinese populations would be welcome, given the differences in body mass, comorbidities, and etiology of AIS patients.

Conclusions

Although argatroban plus r-tPA is safe, it does not improve neurologic function in Chinese patients with AIS within 4.5 hours after symptom onset. These findings do not support the hypothesis that the combination of argatroban and r-tPA in ischemic stroke patients is superior to r-tPA alone in this population, which require further confirmation in future trials.

Author Contributions

HSC 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: HSC and YLW.

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

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: HSC.

Statistical analysis: YC and DLW.

Administrative, technical, or material support: All authors.

Supervision: HSC.

Conflict of Interest Disclosures

We declared no competing interests.

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Role of the Funder/Sponsor

The funder 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 RICAMIS Trial members are listed in Supplement 3 eAppendix 3.

Data Sharing Statement

See Supplement 4.

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Figure Legends

Figure 1 Recruitment, Randomization, and Patient Flow in the ARAIS Randomized Clinical Trial

Baseline characteristics in patients missing primary outcome are shown in eTable 5 in Supplement 3.

IVT indicates intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and r-tPA, recombinant tissue plasminogen activator.

Figure 2 Distribution of Modified Rankin Scale Scores at 90 Days in the modified intention-to-treat population

The raw distribution of scores is shown. Scores ranged from 0 to 6. 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death.

r-tPA indicates recombinant tissue plasminogen activator.

470 **Table 1. Baseline Characteristics of Population in the modified intention-to-treat population**

	Group, No.(%)	
	Argatroban + r-tPA group (n=329)	**r-tPA group (n=367)**
Age, mean (SD), y	64.2 (9.8)	62.4 (10.4)
Sex		
Male	226 (68.7)	268 (73.0)
Female	103 (31.3)	99 (27.0)
Body-mass index, mean (SD), kg/m^2	22.6 (3.0)	23.1 (2.6)
Current smoker	120 (36.5)	137 (37.3)
Current drinker, No./total (%) [a]	65/319 (20.4)	63/360 (17.5)
Comorbidities		
Hypertension	194 (59.0)	208 (56.7)
Diabetes	89 (27.1)	73 (19.9)
Previous ischemic or hemorrhagic stroke [b]	70 (21.3)	64 (17.4)
Atrial fibrillation	17/324 (5.2)	21/362 (5.8)
Hyperlipidemia	3 (0.9)	3 (0.8)
Previous transient ischemic attack	3 (0.9)	4 (1.1)
Time from the onset of symptom to intravenous thrombolysis, mean (SD), min	159.0 (55.3)	154.7 (58.1)
Time to hospital discharge, mean (SD), d	10.4 (5.4)	10.5 (5.5)
Blood pressure at randomization		

Systolic blood pressure, mean (SD), mm Hg	156.7 (25.1)	152.9 (25.7)
Systolic blood pressure > 140 mm Hg	229 (69.6)	238 (64.9)
Diastolic blood pressure, mean (SD), mm Hg	90.9 (13.4)	89.1 (13.8)
Diastolic blood pressure > 90 mm Hg	139 (42.2)	136 (37.1)
Blood glucose, mean (SD), mg/dL	145.8 (66.6)	142.2 (59.4)
Blood glucose > 126 mg/dL	121/267 (45.3)	135/301 (44.9)
NIHSS score at randomization, median (IQR) [c]	9 (7-12)	8 (6-12)
Estimated premorbid function (mRS)		
No symptoms (score 0)	263 (79.9)	295 (80.4)
Symptoms without any disability (score 1)	66 (20.1)	72 (19.6)
Presumed stroke cause, No./total (%) [d]		
Undetermined cause	213/325 (65.6)	255/366 (69.6)
Large-artery atherosclerosis	64/325 (19.7)	69/366 (18.9)
Small-artery occlusion	30/325 (9.2)	26/366 (7.1)
Cardioembolic	17/325 (5.2)	15/366 (4.1)
Other determined cause	1/325 (0.3)	1/366 (0.3)
Location of responsible vessel, No./total (%) [e]		
Anterior circulation stroke	141/178 (79.2)	142/187 (75.9)
Posterior circulation stroke	32/178 (18.0)	41/187 (21.9)
Anterior and posterior circulation stroke	5/178 (2.8)	4/187 (2.2)
Degree of responsible vessel stenosis, No./total (%) [e]		
Mild (< 50%)	107/178 (60.1)	109/187 (58.3)

Moderate (50%-69%)	17/178 (9.5)	8/187 (4.3)
Severe (70%-99%)	24/178 (13.5)	24/187 (12.8)
Occlusion (100%)	30/178 (16.9)	46/187 (24.6)
Endovascular treatment	5/329 (1.5)	12/367 (3.3)

Abbreviations: IQR = interquartile range. NIHSS = National Institutes of Health Stroke Scale. mRS = modified Rankin Scale. r-tPA = recombinant tissue plasminogen activator. SD = standard deviation.

[a] Current drinkers consume alcohol at least once a week within one year before the onset of the disease and consume alcohol continuously for more than one year.

[b] Reported only in patients who did not have prior symptomatic ischemic stroke

[c] Patients with NIHSS scores more than or equal to 6 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurologic deficit.

[d] The presumed stroke cause was classified according to the "Trial of Org 10172 in the Acute Stroke Treatment (TOAST)" classification system.

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

484 **Table 2. Primary and secondary outcomes in the modified intention-to-treat population.**

	Group, No.(%)		**Treatment effect metric**	**Unadjusted**		**Adjusted** [a]	
	Argatroban + r-tPA group (n=329)	**r-tPA group (n=367)**		**Treatment Difference (95% CI)**	***P* value**	**Treatment Difference (95% CI)**	***P* value**
Primary outcome							
mRS score of 0 to 1 within 90 d [b]	210 (63.8)	238 (64.9)	RR [c]	0.98 (0.88 to 1.10)	.78	1.03 (0.86 to 1.23)	.78
			RD,% [c]	-1.0 (-8.1 to 6.1)	.78	-1.0 (-7.6 to 5.7)	.77
			OR [c]	0.96 (0.70 to 1.31)	.78	1.03 (0.74 to 1.43)	.88
Secondary outcomes							
mRS score of 0 to 2 within 90 d [b]	250 (76.0)	280 (76.3)	RR [c]	1.00 (0.92 to 1.08)	.93	0.99 (0.77 to 1.26)	.92
			RD,% [c]	-0.3 (-6.6 to 6.0)	.93	0.9% (-5.2 to 6.9)	.78
mRS score distribution within 90 d [b]			OR [c]	1.06 (0.81 to 1.39)	.66	1.01 (0.58 to 1.76)	.98
Early neurologic improvement within 48 h [d]	234 (71.1)	261 (71.1)	RR [c]	1.00 (0.91 to 1.10)	1.00	0.99 (0.90 to 1.08)	.76
			RD,% [c]	0.0 (-6.7 to 6.8)	1.00	-0.7 (-7.5 to 6.1)	.84
Early neurologic	13 (4.0)	18 (4.9)	RR [c]	0.81 (0.40 to 1.62)	.54	0.78 (0.39 to 1.56)	.48

deterioration within 48 h [e]			RD,% [c]	-0.9 (-4.0 to 2.1)	.54	-1.2 (-4.2 to 1.9)	.46
Change in NIHSS score at day 14 from baseline, median (IQR) [f]	5 (3-7)	5 (2-7)	GMR [c]	0.98 (0.92 to 1.04)	.49	0.98 (0.93 to 1.04)	.58
Stroke or other vascular events within 90 d	1 (0.3)	1 (0.3)	HR [g]	1.12 (0.07 to 17.94)	.94	0.78 (0.04 to 15.16)	.87

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; RR = risk ratio; RD = risk difference; OR = odds ratio; HR= hazard ratio; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range; r-tPA = recombinant tissue plasminogen activator.

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

[b] mRS scores range from 0 to 6:0, 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 between baseline and 48 score of ≥ 2 on the NIHSS score.

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

494 [f] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model.

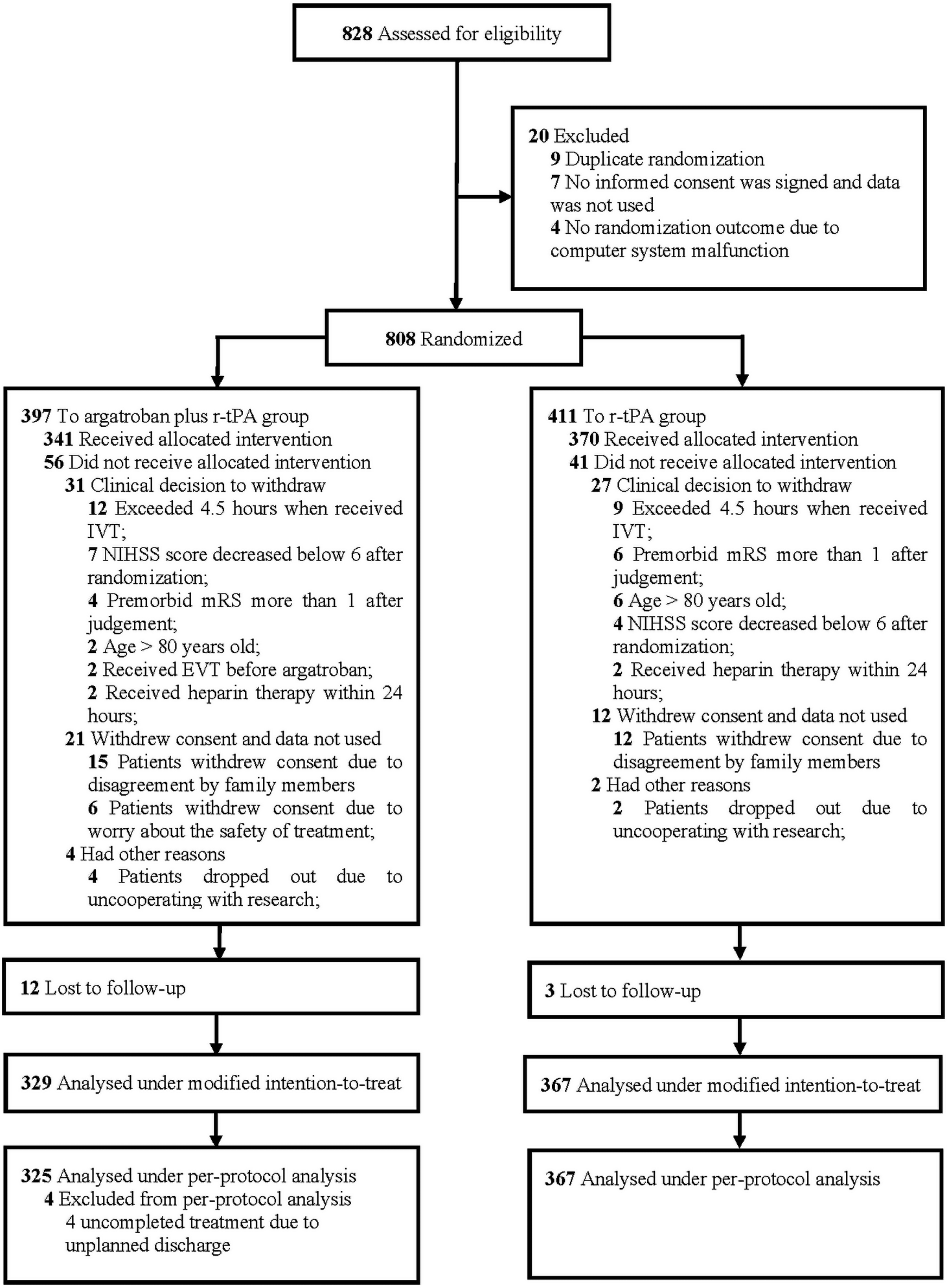
495 [g] Calculated using Cox regression model.

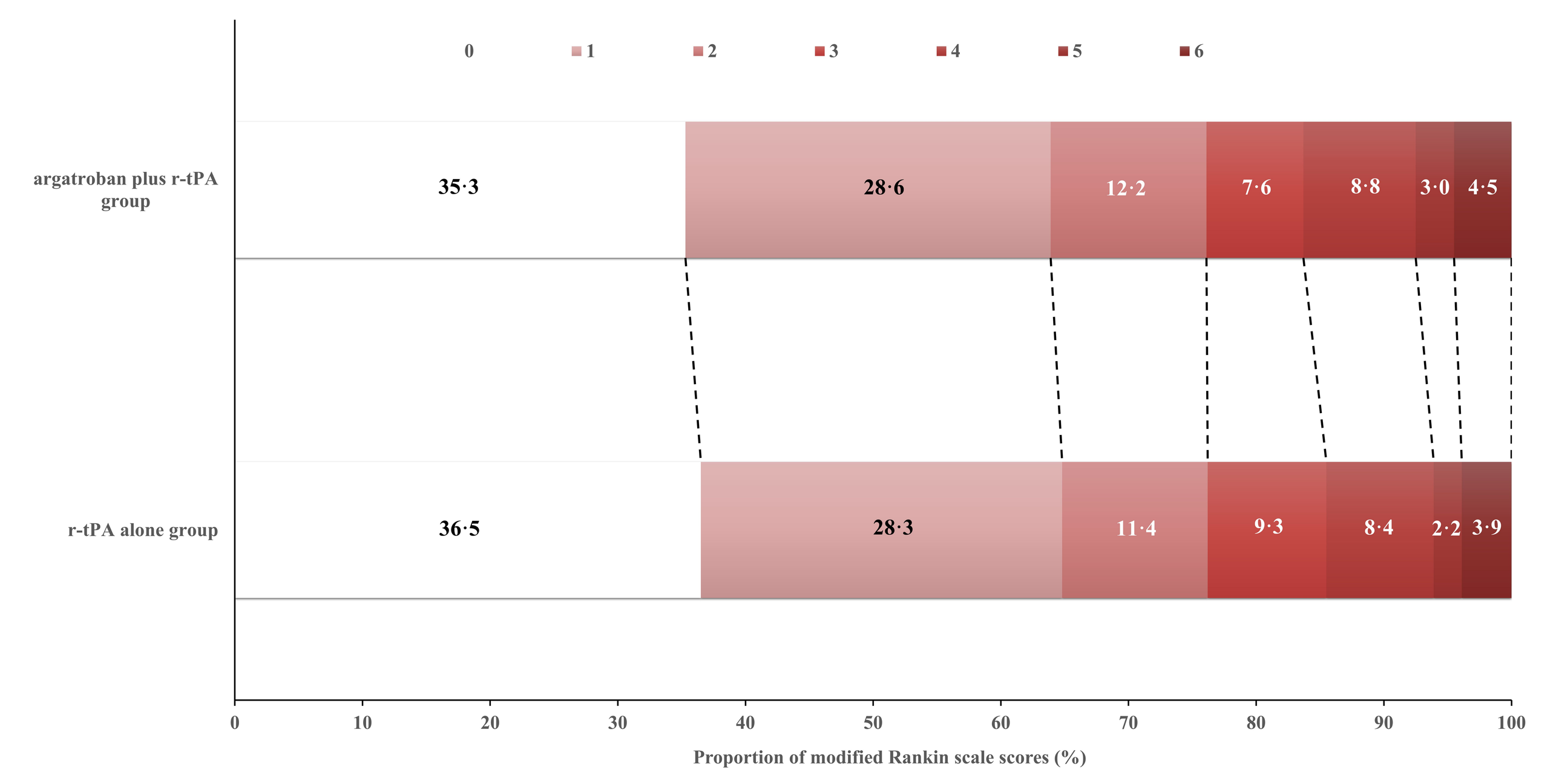
496

Table 3. Safety outcomes in the safety population.

	Group, No.(%)	
	Argatroban + r-tPA group (n=383)	**r-tPA group (n=397)**
Symptomatic intracerebral hemorrhage	1 (0.3)	1 (0.3)
Parenchymal hematoma type 2	0 (0.0)	1 (0.3)
Major systemic bleeding	1 (0.3)	1 (0.3)

Abbreviations: r-tPA=recombinant tissue plasminogen activator.


828 Assessed for eligibility
20 Excluded
9 Duplicate randomization
7 No informed consent was signed and data was not used
4 No randomization outcome due to computer system malfunction
808 Randomized
397 To argatroban plus r-tPA group
341 Received allocated intervention
56 Did not receive allocated intervention
31 Clinical decision to withdraw
12 Exceeded 4.5 hours when received IVT;
7 NIHSS score decreased below 6 after randomization;
4 Premorbid mRS more than 1 after judgement;
2 Age > 80 years old;
2 Received EVT before argatroban;
2 Received heparin therapy within 24 hours;
21 Withdrew consent and data not used
15 Patients withdrew consent due to disagreement by family members
6 Patients withdrew consent due to worry about the safety of treatment;
4 Had other reasons
4 Patients dropped out due to uncooperating with research;
411 To r-tPA group
370 Received allocated intervention
41 Did not receive allocated intervention
27 Clinical decision to withdraw
9 Exceeded 4.5 hours when received IVT;
6 Premorbid mRS more than 1 after judgement;
6 Age > 80 years old;
4 NIHSS score decreased below 6 after randomization;
2 Received heparin therapy within 24 hours;
12 Withdrew consent and data not used
12 Patients withdrew consent due to disagreement by family members
2 Had other reasons
2 Patients dropped out due to uncooperating with research;
12 Lost to follow-up
3 Lost to follow-up
329 Analysed under modified intention-to-treat
367 Analysed under modified intention-to-treat
325 Analysed under per-protocol analysis
4 Excluded from per-protocol analysis
4 uncompleted treatment due to unplanned discharge
367 Analysed under per-protocol analysis


0
1
2
3
4
5
6
argatroban plus r-tPA group
35·3
28·6
12·2
7·6
8·8
3·0
4·5
r-tPA alone group
36·5
28·3
11·4
9·3
8·4
2·2
3·9
0
10
20
30
40
50
60
70
80
90
100
Proportion of modified Rankin scale scores (%)