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Efficacy of argatroban plus alteplase versus intravenous alteplase according to diabetes mellitus in acute ischemic stroke

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We conducted a post hoc analysis of the ARAIS (Argatroban Plus Recombinant Tissue-Type Plasminogen Activator for AIS) trial to investigate whether diabetes mellitus (DM) affects the efficacy of argatroban plus alteplase in patients with acute ischaemic stroke (AIS). Patients were categorized into DM and non-DM subgroups. In each subgroup, outcomes were compared between the argatroban plus alteplase group and the alteplase alone group. Additionally, the interaction between DM and treatment efficacy was assessed. The primary outcome was excellent functional outcome at 90 days, which was defined as a modified Rankin Scale score of 0–1. A total of 696 patients were included in this study. Regarding the primary outcome, the treatment effect was comparable between the argatroban plus alteplase group and the alteplase alone group both in the DM subgroup (58.4% versus 63.0%; adjusted risk difference, 1.1%; 95% CI, -13.8% to 16.1%; P = 0.88) and the non-DM subgroup (65.8% versus 65.3%; adjusted risk difference, 0.9%; 95% CI, -6.9% to 8.7%, P = 0.81). No significant interaction was observed between DM and treatment effect on the primary outcome (P = 0.93). Compared with alteplase alone, the efficacy of argatroban plus alteplase in achieving excellent functional outcomes at 90 days did not differ by DM status in patients with AIS.

Keywords Acute ischemic stroke, Argatroban, Alteplase, Diabetes mellitus

As the most effective treatments for acute ischaemic stroke (AIS), reperfusion therapies including intravenous thrombolysis and endovascular intervention are recommended[1]. Intravenous thrombolysis remains the first-line treatment due to its rapid administration and widespread availability, especially within 4.5 h of symptom onset[2]. Endovascular therapy is primarily indicated for patients with large vessel occlusions (LVO) and has demonstrated significant benefits in reducing disability when performed promptly[3]. Despite its efficacy, the adoption of endovascular therapy in clinical practice has been constrained by dependencies on specialized equipment, advanced imaging capabilities, and the availability of experienced clinicians.

Alteplase exerts its thrombolytic effect by binding to fibrin through its lysine residues and activating fibrin-bound plasminogen, converting it into plasmin[4]. The benefits of alteplase in AIS are associated with the speed and extent of clot dissolution and vessel recanalization[5]. In practice, approximately 30% of patients achieve complete recanalization of the occluded vessel after thrombolysis[6]. Besides, 14–34% of patients experience re-occlusion after initial recanalization, which may primarily stem from alteplase's very short half-life[6,7]. This suggests that combining antithrombotic therapy with thrombolysis is necessary to prevent re-thrombosis.

Argatroban, a direct thrombin inhibitor, has been shown to be effective in the treatment of AIS in Asian countries without increasing the risk of bleeding[8,9]. The ARTSS-2 trial found that the combined application of argatroban and alteplase could improve the recanalization rate in acute anterior circulation infarction, enhance clinical outcomes, and did not significantly increase bleeding tendency[10]. However, the Argatroban Plus Recombinant Tissue-Type Plasminogen Activator for AIS (ARAIS) trial showed that combining argatroban with intravenous alteplase did not significantly improve the rate of excellent functional outcome at 90 days compared to alteplase alone in patients treated within 4.5 h from symptom onset[11].

Diabetes mellitus (DM) exerts differential effects on pathological processes and therapeutic responsiveness following AIS relative to non-DM status, a phenomenon supported by clearly characterized biological mechanisms and supported by increasing experimental evidence. Hyperglycemia, the key feature of DM, induces

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persistent oxidative stress via excessive reactive oxygen species (ROS) production and impaired antioxidant defense systems, which in turn activates the NF-κB signaling pathway to trigger inflammatory responses[12,13]. Additionally, variable degrees of insulin resistance and pancreatic β-cell dysfunction in diabetic individuals disrupt the expression of key glycolipid metabolism regulators, leading to specific metabolic dysregulation and variable functional recovery outcomes after AIS[14,15]. Moreover, DM-associated vascular complications may alter cerebral blood perfusion and the local ischemic microenvironmental homeostasis, further amplifying the differential responsiveness of the AIS to treatment[16]. These mechanisms establish strong biological plausibility for the differential effects of DM in AIS.

Studies have shown that the efficacy of intravenous thrombolysis was influenced by DM[17,18]. Although the ARAIS trial demonstrated that argatroban plus alteplase did not significantly improve the rate of excellent functional outcome at 90 days[11], it remains unclear whether DM influences the efficacy of the combination therapy in patients with AIS. Given the biological rationale that DM influences the efficacy of AIS treatment, we conducted this exploratory, hypothesis-generating analysis to assess the influence of DM on treatment outcomes with argatroban plus alteplase and to identify which subgroups of AIS patients might benefit from this combination therapy.

Methods

Study design and participants

The ARAIS study, a multicenter, open-label, endpoint-blinded randomized clinical trial, aimed to evaluate the efficacy of argatroban combined with alteplase for AIS patients within 4.5 h of symptom onset. Previous studies have detailed its design and outcomes[11,19]. A total of 817 patients with AIS were enrolled between 18 January 2019 and 30 October 2021. The trial was registered in ClinicalTrials.gov (Registration No.: NCT03740958, first posted date: 20/02/2022). All methods were performed in accordance with the relevant guidelines and regulations. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The trial received ethical approval from the Ethics Committee of the General Hospital of Northern Theater Command (Approval No.: k [2018] 45). Informed consent was obtained from all human participants and/or their legal guardians for study participation in this study. All patient names have been completely removed from all text, figures, tables and images.

Patients were eligible for enrollment if they presented with AIS and had a National Institutes of Health Stroke Scale (NIHSS) score ≥ 6 at the time of randomization. Exclusion criteria included a preexisting disability (modified Rankin Scale [mRS] score ≥ 2), a history of intracranial hemorrhage, gastrointestinal or urinary tract bleeding in the last 30 days, or a requirement for anticoagulant therapy other than argatroban[19].

Procedures

Within this study, patients were stratified into DM and non-DM subgroups based on prior diagnosis. Within each subgroup, patients were further categorized into two treatment groups according to randomization. Eligible patients received intravenous alteplase within 4.5 h after symptom onset. Patients randomized to the argatroban plus alteplase group were administered an intravenous argatroban bolus over 3–5 min within 1 h following the alteplase bolus. This was followed by a continuous argatroban infusion at 1.0 μg/kg/min for 48 h. The specific administration method was described in the ARAIS trial[11].

Clinical characteristics were recorded at randomization. The NIHSS score was used to assess neurologic status at baseline, 48 h, and 14 days after randomization. At the 90-day follow-up, the mRS score was assessed, along with any vascular or bleeding events. All data were obtained from the electronic data capture system provided by Beijing Zhinan Medical Technology Co.

Outcomes

The primary outcome was excellent functional outcome at 90 days, indicated by an mRS score of 0–1. The secondary outcomes included favorable functional outcome at 90 days (mRS score 0–2), the shift analysis of ordinal mRS scores at 90 days, early neurological improvement (ENI) at 48 h (defined as a reduction in the NIHSS score of ≥ 2 points from admission[20], early neurological deterioration (END) at 48 h (defined as an increase in NIHSS score of ≥ 4 points from admission[21], changes in NIHSS scores at 14 days compared with admission, and stroke[22] or other vascular events occurring within 90 days.

The pre-defined safety outcomes included symptomatic intracranial hemorrhage (sICH), parenchymal hematoma type 2 (PH2), and major systemic bleeding occurring during the study. sICH was defined as any intracranial hemorrhage detected on head CT, accompanied by clinically significant neurological deterioration (an increase of ≥ 4 points in the NIHSS score) determined by the clinical investigator or an independent safety monitor[23]. PH2 was defined as confluent hemorrhage involving > 30% of the infarct volume with substantial mass effect[24]. Major systemic bleeding was identified as a decrease in hemoglobin level by ≥ 2 g/dL or transfusion of ≥ 2 units of blood. Follow-up head CT scans were conducted on the alteplase alone group 24 h after randomization, and on the argatroban plus alteplase group at 48 h, or at any time if neurological deterioration occurred.

Statistical analysis

The analyses were conducted on a subset of participants from the full analysis set of the ARAIS trial. Continuous variables are presented as median (interquartile range [IQR]), and categorical variables as frequencies (percentages). Baseline characteristics were compared between groups using the Mann-Whitney U test or the chi-square test. Excellent functional outcome, favorable functional outcome, ENI, END, and safety outcomes were evaluated using the risk difference (RD). Odds ratios (ORs) for mRS score shift distribution, geometric mean ratios (GMRs) for NIHSS score changes, and hazard ratios (HRs) for stroke or other vascular events were used to assess other treatment effects, all of which were presented with 95% confidence intervals (CIs).

We assessed the association between treatments and outcomes within the DM subgroups. Generalized linear models were applied for binary outcomes (excellent functional outcomes, favorable functional outcomes, ENI, END, and safety outcomes) as well as the continuous changes in NIHSS score. An ordinal logistic regression model was used to analyze the ordinal outcome of mRS scores, and a Cox regression model was applied to analyze the time to stroke or other vascular events.

Both unadjusted and adjusted models were conducted to assess treatment effects across DM subgroups. Covariates corresponding to baseline variable differences between treatment groups with a P value < 0.1 were adjusted. Interactions between DM and treatment effect were evaluated by adjusting for unbalanced baseline variables between DM subgroups. A two-sided P value < 0.05 was defined as statistically significant. Statistical analyses were carried out with SPSS (version 26.0; IBM Corp) and R (version 4.1.0; R Foundation for Statistical Computing).

Results

After excluding 64 participants who violated the ARAIS trial criteria, 696 individuals were included in the analysis. The 696 patients comprised 162 participants in the DM subgroup and 534 in the non-DM subgroup. The patient screening process is detailed in Fig. 1. The baseline characteristics of participants were comparable between the current study and the full analysis set of the ARAIS trial (Table S1).

Among the non-DM subgroup, 27 (5.1%) participants had elevated baseline random blood glucose at admission, defined as a level ≥ 11.1 mmol/L[25]. Baseline characteristics of the DM and non-DM subgroups are listed in Table S2. Compared with the non-DM subgroup, the DM subgroup had a higher proportion of hypertension (P < 0.01) and a lower proportion of patients with a baseline mRS score of 0 (P = 0.01). No statistically significant differences were observed in the other baseline variables between the two subgroups. Further details on baseline characteristics of participants are presented in Table 1. In the DM subgroup, 89 participants were assigned to the argatroban plus alteplase group, and 73 received alteplase alone. NIHSS score at randomization was higher in the argatroban plus alteplase group compared to the alteplase alone group (9 [7–13] versus 8 [6–11], P = 0.01). In the non-DM subgroup, 240 participants were assigned to the argatroban plus alteplase group, and 294 received alteplase alone. Between the two treatment groups, imbalances were observed in age (66 [57–71] years versus 62 [55–70] years, P = 0.08), and diastolic blood pressure at admission (90 [82–100] mmHg versus 90 [80–100] mmHg, P = 0.05).

For the primary outcome, participants receiving argatroban plus alteplase had comparable odds of achieving an mRS score of 0–1 at 90 days compared with alteplase alone. In the DM subgroup, the proportions were 58.4% versus 63.0% (adjusted RD [95% CI]: 1.1% [−13.8% to 16.1%], P = 0.88); and in the non-DM subgroup, the proportions were 65.8% versus 65.3% (adjusted RD [95% CI]: 0.9% [−6.9% to 8.7%], P = 0.81). Furthermore, no significant interaction effects were detected between the treatment groups and the DM subgroups (P_{int} = 0.93).

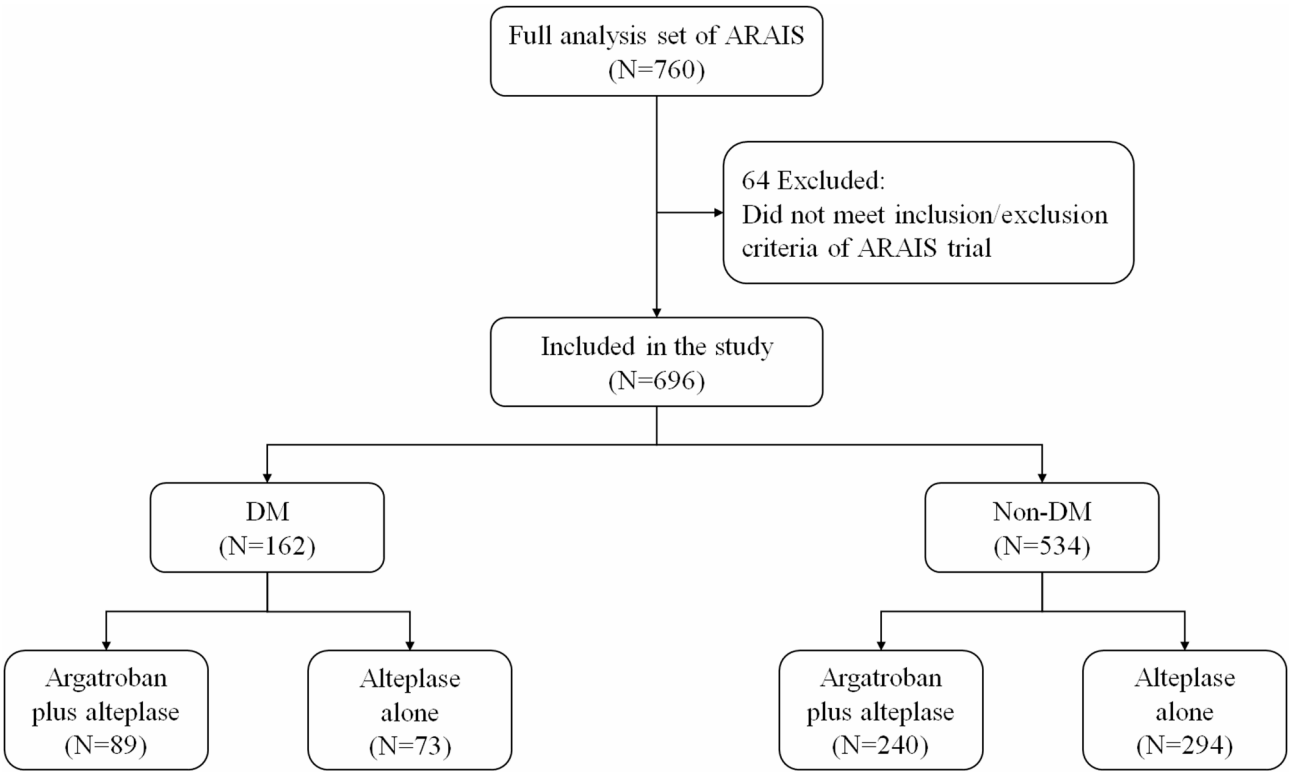


Fig. 1. Flow diagram.

Variables	Diabetes mellitus			Non-diabetes mellitus		
	Argatroban plus alteplase (*N* = 89)	Alteplase alone (*N* = 73)	P value	Argatroban plus alteplase (*N* = 240)	Alteplase alone (*N* = 294)	P value
Age, years	64 (58–72)	63 (55–70)	0.12	66 (57–71)	62 (55–70)	0.08
Male	60 (67.4)	52 (71.2)	0.60	166 (69.2)	216 (73.5)	0.27
Female	29 (32.6)	21 (28.8)		74 (30.8)	78 (26.5)	
Current smoking	25 (28.1)	29 (39.7)	0.12	95 (39.6)	108 (36.7)	0.50
Current drinking*	13/86 (15.1)	10/71 (14.1)	0.86	52/233 (22.3)	53/289 (18.3)	0.26
Hypertension	64 (71.9)	52 (71.2)	0.92	130 (54.2)	156 (53.1)	0.80
Atrial fibrillation	2/88 (2.3)	6/73 (8.2)	0.14	15/236 (6.4)	15/289 (5.2)	0.57
Previous stroke‡	24 (27.0)	12 (16.4)	0.11	46 (19.2)	52 (17.7)	0.66
Previous transient ischemic attack	0 (0.0)	1 (1.4)	0.45	3 (1.3)	3 (1.0)	1.00
Hyperlipidemia	1 (1.1)	0 (0.0)	1.00	2 (0.8)	3 (1.0)	1.00
Systolic	157 (140–170)	151 (131–168)	0.16	157 (140–170)	150 (140–168)	0.11
Diastolic	90 (80–96)	87 (80–95)	0.29	90 (82–100)	90 (80–100)	0.05
Blood glucose at randomization, mmol/L	10.6 (8.6–13.6)	10.8 (8.1–13.4)	0.87	6.1 (5.5–7.4)	6.4 (5.6–7.7)	0.28
NIHSS score at randomization§	9 (7–13)	8 (6–11)	0.01	9 (7–12)	8 (6–12)	0.58
0	68 (76.4)	51 (69.9)	0.35	195 (81.3)	244 (83.0)	0.60
1	21 (23.6)	22 (30.1)		45 (18.8)	50 (17.0)	
Time from symptom onset to alteplase, min	157 (116–206)	151 (120–209)	0.86	158 (115–204)	154 (109–191)	0.28
Undetermined cause	54/87 (62.1)	48 (65.8)	0.80	159/238 (66.8)	207/293 (70.6)	0.60
Large artery atherosclerosis	22/87 (25.3)	15 (20.5)		42/238 (17.6)	54/293 (18.4)	
Small artery occlusion	7/87 (8.0)	5 (6.8)		23/238 (9.7)	21/293 (7.2)	
Cardioembolic	4/87 (4.6)	5 (6.8)		13/238 (5.5)	10/293 (3.4)	
Other determined cause	0 (0.0)	0 (0.0)		1/238 (0.4)	1/293 (0.3)	
Anterior	36/44 (81.8)	30/41 (73.2)	0.34	105/134 (78.4)	112/146 (76.7)	0.35
Posterior	8/44 (18.2)	9/41 (22.0)		24/134 (17.9)	32/146 (21.9)	
Anterior and posterior	0/44 (0.0)	2/41 (4.9)		5/134 (3.7)	2/146 (1.4)	

Table 1. Baseline characteristics grouped according to diabetes mellitus status and treatment. The data were shown with median (IQR) for continuous characteristic or frequency (percentages) for categorical characteristic. mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale. *Defined as consuming alcohol at least once a week within 1 year prior to the onset of the disease. †The comorbidities were based on the patient or family report. ‡Previous ischaemic stroke referred only to the patients with prestroke mRS ≤ 1. §Patients with NIHSS scores ≥ 6 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit. ¶Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). No symptoms indicate scoring 0, and symptoms without disability indicates scoring 1. **The presumed stroke cause was classified according to the Trial of Org 10,172 in Acute Stroke Treatment classification system using clinical findings, brain imaging and laboratory tests. Other determined causes included pulmonary embolism, peripheral vessel incident and cardiovascular incident.

For the secondary and safety outcomes, no significant differences or interaction effects were found between the treatment groups across the DM subgroups. The distributions of the mRS score at 90 days, stratified by DM for each treatment group, are presented in Fig. 2. Detailed results are shown in Table 2.

Discussion

This post-hoc analysis of the ARAIS trial assessed the influence of DM on the efficacy of argatroban plus alteplase. The findings indicate that DM had no effect on the probability of achieving an excellent functional outcome (mRS 0–1) at 90 days with the combination therapy versus alteplase alone.

Baseline comparisons between DM and non-DM subgroups showed a higher proportion of hypertension and a lower rate of baseline mRS score 0 in the DM group, with no significant differences in other variables including the baseline NIHSS score. The lower proportion of mRS 0 in the DM patients is consistent with the expected poorer baseline functional status in this population[26,27], a clinical characteristic inherent to DM patients rather than a confounding imbalance. Together with the well-balanced core neurological deficit indicator (NIHSS score) between the two subgroups, these baseline differences reflect the natural clinical profile of the DM population and do not introduce substantial bias to the comparative analysis of treatment efficacy.

Patients with DM frequently exhibit more pronounced vascular endothelial dysfunction, heightened platelet activation, and abnormalities in coagulation mechanisms[28–30]. These factors contribute to a substantially elevated risk of thrombosis relative to non-diabetic individuals. As a result, DM is widely regarded as a significant factor associated with worse functional outcomes in ischaemic stroke patients after reperfusion

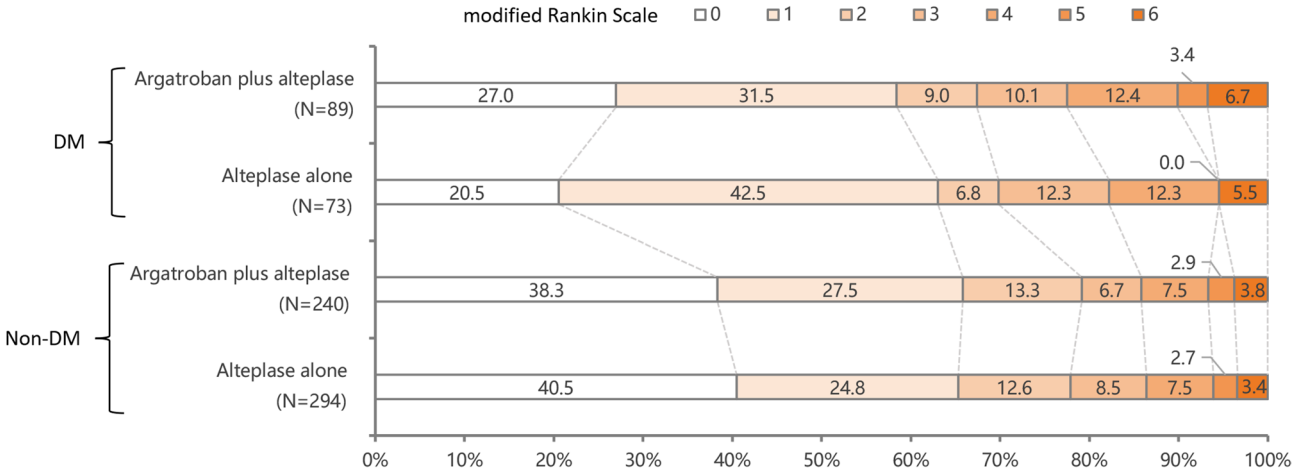


Fig. 2. Distribution of modified Rankin scale scores at 90 days.

Variables	Subgroup	Argatroban plus alteplase (*N* = 329)	Alteplase alone (*N* = 367)	Treatment effect metric	Unadjusted model*		Adjusted model†		P_{int} value
					Treatment difference (95% CI)	P value	Treatment difference (95% CI)	P value	
mRS 0–1 at 90 days‡	DM	52/89 (58.4)	46/73 (63.0)	RD§	−4.6 (−20.0 to 10.5)	0.55	1.1 (−13.8 to 16.1)	0.88	0.93
	Non-DM	158/240 (65.8)	192/294 (65.3)		0.5 (−7.6 to 8.6)	0.90	0.9 (−6.9 to 8.7)	0.81	
mRS 0–2 at 90 days‡	DM	60/89 (67.4)	51/73 (69.9)	RD§	−2.5 (−16.8 to 11.9)	0.74	4.1 (−10.4 to 18.5)	0.58	0.68
	Non-DM	190/240 (79.2)	229/294 (77.9)		1.3 (−5.7 to 8.3)	0.72	1.5 (−5.2 to 8.2)	0.66	
mRS at 90 days‡	DM	NA	NA	OR¶	0.99 (0.57 to 1.72)	0.96	1.25 (0.70 to 2.25)	0.45	0.31
	Non-DM	NA	NA		0.96 (0.71 to 1.31)	0.82	0.96 (0.70 to 1.31)	0.79	
Early neurologic improvement at 48 h#	DM	57/89 (64.0)	45/73 (61.6)	RD§	5.6 (−8.2 to 19.4)	0.43	4.5 (−9.6 to 18.6)	0.53	0.73
	Non-DM	177/240 (73.8)	216/294 (73.5)		−2.5 (−10.2 to 5.2)	0.52	−2.0 (−9.8 to 5.8)	0.62	
Early neurologic deterioration at 48 h**	DM	5/89 (5.6)	4/73 (5.5)	RD§	4.0 (−4.2 to 12.2)	0.33	3.7 (−4.7 to 12.2)	0.38	0.82
	Non-DM	8/240 (3.3)	14/294 (4.8)		0.4 (−2.9 to 3.7)	0.80	0.2 (−3.1 to 3.6)	0.90	
Change in NIHSS at 14 days††	DM	−0.48 (−1.61 to −0.10)	−0.81 (−1.95 to 0.00)	GMR§	0.92 (0.68 to 1.26)	0.61	0.90 (0.66 to 1.25)	0.54	0.86
	Non-DM	−0.85 (−1.61 to −0.37)	−0.85 (−1.95 to −0.34)		0.98 (0.84 to 1.14)	0.78	0.99 (0.85 to 1.16)	0.93	
Stroke or other vascular events within 90 days	DM	0/89 (0.0)	0/73 (0.0)	HR‡‡	NA	NA	NA	NA	1.00
	Non-DM	1/240 (0.4)	1/294 (0.3)		0.81 (0.05 to 13.0)	0.88	0.88 (0.05 to 14.24)	0.93	
Symptomatic intracranial hemorrhage	DM	2/89 (2.2)	0/73 (0.0)	RD§	10.4 (NA to NA)	1.00	11.1 (NA to NA)	1.00	1.00
	Non-DM	5/240 (2.1)	6/294 (2.0)		1.2 (−1.4 to 3.8)	0.35	1.5 (−1.2 to 4.2)	0.25	
Parenchymal hematoma type 2	DM	1/89 (1.1)	0/73 (0.0)	RD§	21.5 (NA to NA)	1.00	22.4 (NA to NA)	1.00	1.00
	Non-DM	5/240 (2.1)	8/294 (2.7)		0.5 (−2.1 to 3.0)	0.72	0.6 (−2.0 to 3.2)	0.65	
Major systemic bleeding	DM	1/89 (1.1)	0/73 (0.0)	RD§	0.0 (NA to NA)	1.00	0.0 (NA to NA)	1.00	1.00
	Non-DM	0/240 (0.0)	1/294 (0.3)		−6.5 (NA to NA)	1.00	−6.5 (NA to NA)	1.00	

Table 2. Association of diabetes mellitus with outcomes. The data were shown with median (IQR) for continuous characteristic or frequency (percentages) for categorical characteristic. *Crude analysis in the model. †Adjusted for covariates compared between argatroban plus alteplase and alteplase alone treatment groups with P value < 0.1 in each subgroup. ‡Scores on the mRS of functional disability 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. §Calculated using the generalized liner model. ¶ A shift measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression. #Early neurologic improvement was defined as a decrease between baseline and 48 h of 2 on the NIHSS score[17]. **Early neurological deterioration was defined as an increase between baseline and 48 h of 4 on the NIHSS score, but not as a result of cerebral hemorrhage[18]. ††Patients with NIHSS scores ≥ 6 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit. The log (NIHSS + 1) was analyzed using generalized linear model. ‡‡Calculated using the Cox regression model. DM, diabetes mellitus; GMR, geometric mean ratio; HR, hazard ratio; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; RD, risk difference.

therapy[31,32]. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial had indicated that aspirin combined with low-dose rivaroxaban reduces major cardiovascular events in patients with stable atherosclerosis versus aspirin alone, and the absolute risk reductions are numerically larger in those with DM[33]. However, a secondary analysis of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial revealed that DM did not significantly affect the efficacy of antiplatelet therapy in preventing stroke recurrence[34].

Different from the ARTSS-2 trial[10], no significant differences were observed in primary or secondary outcomes between the two treatment groups in either DM or non-DM subgroups. The negative results may be attributed to the low proportion of enrolled patients with large artery occlusion in the current study (37/160, 23.1%). This is because promising outcomes of argatroban plus alteplase have been observed in patient cohorts with a high proportion of large artery occlusion in previous study with positive results (16/53, 30.2%)[35]. Specifically, argatroban plus alteplase may enhance recanalization and reduce re-occlusion rates in such cases, thereby leading to better neurological improvement. Regarding safety endpoints, the rates of sICH, PH2, and major systemic bleeding were comparable between the treatment groups. Although DM is an independent risk factor for cerebral hemorrhage[35,36], and combination therapy may increase bleeding risk, this phenomenon has not been observed in our study. This finding should be interpreted with caution and requires further validation through large-sample, prospective studies.

Our study has several limitations. First, the diagnosis of DM was based on patients' prior medical history rather than the results of blood glucose measurements or glycated hemoglobin (HbA1c) tests, which may impair the diagnostic accuracy. This is because we only obtained baseline random blood glucose results, did not measure HbA1c, and the fasting status of patients was inconsistent and unconfirmed (some were fasting, others had eaten with an unknown interval since their last meal). Therefore, fasting blood glucose, postprandial blood glucose, and HbA1c should be additionally measured in future studies to enable more accurate diagnosis and subgroup stratification of DM. Second, we regret that mechanistic data, including acute-phase glycemic profiles, inflammatory or coagulation biomarkers, were not collected in the original ARAIS trial, which limits further mechanistic interpretation. Future prospective studies should incorporate comprehensive biological and pathophysiological data to better characterize diabetic populations and explore the underlying mechanisms. Third, the proportion of patients with large artery occlusion enrolled in this trial was lower than that in previous studies, which may largely explain the negative results. Therefore, the efficacy of alteplase plus argatroban in patients with large artery occlusion needs further investigation in future trials. Fourth, due to data limitations, we were unable to adjust for several DM-related confounding factors, such as type of DM, disease duration, hypoglycemic treatments, and the presence or severity of diabetic complications prior to AIS. These variables are potential confounders that might have influenced the observed outcomes. Finally, the small sample size of the DM subgroup ($N = 162$) may potentially reduce the statistical power of our analysis, which may limit the ability to detect subtle differences in treatment effects by DM status if such differences exist. Thus, the efficacy of argatroban plus alteplase in patients with DM needs further evaluation in adequately powered future trials, and the present findings should be interpreted with caution.

In conclusion, this post hoc analysis of the ARAIS trial indicates that DM did not significantly affect the neuroprotective effect of argatroban plus alteplase. However, these findings should be interpreted with caution and need to be validated in future studies.

Data availability

Data are available from the corresponding author upon reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

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