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Efficacy of combined atorvastatin and argatroban therapy in acute cerebral infarction

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Abstract: **Background**: Acute cerebral infarction (ACI) is a disease which seriously affects the people's health. **Objectives**: To investigate the efficacy of combined atorvastatin and argatroban therapy in patients with ACI and its effects on cerebral hemodynamics, coagulation, endothelial function and inflammation. **Methods**: Eighty ACI patients were assigned into the atorvastatin group (n = 40) and atorvastatin + argatroban group (n = 40), which received the treatment using atorvastatin and atorvastatin combined with argatroban for one month, respectively. After treatment, the overall efficacy was evaluated. Before and after treatment, the cerebral blood flow indexes and blood indexes were determined. **Results**: Compared to the atorvastatin group, the atorvastatin + argatroban group showed the increased overall effective rate (95.00% vs. 80.00%, $p < 0.05$). In the atorvastatin + argatroban group the significant improvements were also observed in cerebral hemodynamics (increased mean blood flow quantity and velocity, decreased pulsatility index and resistance), coagulation function (prolonged prothrombin time, thrombin time and activated partial thromboplastin time, reduced fibrinogen), endothelial function (increased nitric oxide and vascular endothelial growth factor, decreased endothelin-1) and inflammation (reduced hypersensitive C-reactive protein, tumor necrosis factor α and interleukin 6) compared to the atorvastatin group (all $p < 0.05$). **Conclusion**: Atorvastatin combined with argatroban can effectively improve the cerebral hemodynamics, coagulation and endothelial function and reduce the inflammation in ACI patients, thus exerting a good therapeutic efficacy.

Keywords: Acute cerebral infarction; Atorvastatin; Argatroban; Coagulation; Endothelial; Inflammation

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INTRODUCTION

Acute cerebral infarction (ACI) is one of the common clinical diseases of the nervous system, characterized by rapid progression. In the early stage, patients may maintain a certain degree of consciousness, but with the progression of the disease, further necrosis of brain tissue can lead to impaired consciousness and movement, seriously threatening the patient's life safety and quality of life (Beauchamp and Bryan, 1998; Li *et al*., 2023). ACI not only causes serious damage to the nervous system but also imposes a heavy burden on the patient's family and society. With the aging of the population and the changes in lifestyle, the incidence of ACI is increasing year by year (Liang *et al*., 2023). Therefore, exploring more effective treatment methods for ACI has become an urgent need in clinical practice. At present, clinical individualized treatment plans for ACI patients mainly rely on conventional drugs such as antiplatelet and anti-free radical drugs, but the prognosis is poor and the neurological impairment caused by brain tissue necrosis cannot be effectively and timely improved (Wo *et al*., 2020). Atorvastatin is a lipid-lowering drug that significantly reduces the synthesis of endogenous cholesterol and has been used in the treatment of ACI (Xie *et al*., 2020; Yu *et al*., 2025). However, studies have shown that the therapeutic effect of atorvastatin alone is not ideal.

Argatroban is a new anticoagulant drug that has emerged in the clinic in recent years. It is a derivative of L-arginine and a thrombin inhibitor. It can inhibit thrombin catalysis to promote anticoagulation (Geli *et al*., 2022), improve cerebral blood flow and restore blood supply to brain tissue (Yamashita *et al*., 2000). Previous studies have shown that argatroban has a certain therapeutic effect on ACI (Ma *et al*., 2017; Yamashita *et al*., 2000). However, these studies either use argatroban alone or in combination with other thrombolytic drugs and there are few studies on the combination of argatroban with atorvastatin, a commonly used lipid-lowering and vascular protective drug, for the treatment of ACI. In addition, existing studies on argatroban in the treatment of ACI have not comprehensively evaluated its effects on cerebral blood flow, coagulation function, vascular endothelial function and inflammation at the same time. Atorvastatin has been widely used in the prevention and treatment of cardiovascular and cerebrovascular diseases due to its lipid-lowering, anti-

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inflammatory and vascular protective effects. Argatroban, as a new type of thrombin inhibitor, has shown good anticoagulant and thrombolytic effects in the treatment of thrombotic diseases. However, the therapeutic effect of single-drug treatment is still limited. The combination of different types of drugs with complementary mechanisms may be a promising direction for the treatment of ACI. Given that atorvastatin alone has limited efficacy in treating ACI and argatroban has unique advantages in anticoagulation and improving cerebral blood flow, combining these two drugs may have a synergistic effect, thereby enhancing the therapeutic effect on ACI. Therefore, there is a gap in the research on whether the combination of atorvastatin and argatroban can exert a synergistic effect, comprehensively improve the above indicators and enhance the therapeutic efficacy of ACI. This study was designed to fill this gap and explore the efficacy of atorvastatin combined with argatroban in the treatment of ACI and its effects on cerebral blood flow, coagulation function, vascular endothelial function and inflammation in patients.

MATERIALS AND METHODS

Study design

This is a single-center retrospective observational study. A total of 89 ACI patients admitted to The First Affiliated Hospital of Shihezi University from March 2023 to March 2024 were enrolled and nine patients were excluded due to incomplete follow-up or missing laboratory data (n = 4), resulting in 80 eligible patients. This sample size was consistent with similar retrospective ACI studies (Ma *et al*., 2017; Wang Z *et al*., 2020). The study period included patient admission (March 2023-March 2024) and a one-month follow-up (data extracted from electronic medical records up to April 2024). The data collection focused on pre-treatment (admission day) and post-treatment (one month after admission) indicators. Given the retrospective nature, the blinding was not applicable to treatment allocation (data were extracted from pre-existing records). However, the outcome assessors (e.g., radiologists for cerebral blood flow detection, laboratory technicians for coagulation tests) were blinded to patient grouping to minimize bias.

Subjects and grouping

Included 80 patients were assigned into the atorvastatin group (n = 40) and the atorvastatin + argatroban group (n = 40). The atorvastatin group included 23 males and 17 females. The ages were 40-72 years (61.23±10.12 years). Among the patients, 15 cases had hypertension, 9 cases had diabetes and 16 cases had hyperlipidemia. The atorvastatin + argatroban group included 26 males and 14 females, with ages of 42-69 years (60.08±8.74 years). Among the patients, 13 cases had hypertension, 12 cases had diabetes and 15 cases had hyperlipidemia. Comparing the above data, two groups had no significant difference ($p > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients diagnosed with ACI in accordance with the diagnostic criteria of the "Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2021" (Wang *et al*., 2021). The diagnostic features of ACI included: sudden onset of neurological deficit symptoms; the head computed tomography or magnetic resonance imaging examination showed no evidence of cerebral hemorrhage and there were corresponding ischemic lesions in the brain; the onset time was clear and the symptoms lasted for more than 24 h (except for patients with transient ischemic attack). (2) Patients admitted to the hospital within 24 h from the onset of symptoms. (3) First onset of ACI. (4) Patients with obvious clinical signs (such as limb weakness, speech disturbance, facial paralysis, etc.). (5) Patients aged 40-75 years.

Exclusion criteria: (1) Cerebral hemorrhage. (2) Blood system diseases (such as hemophilia, thrombocytopenia, etc.). (3) Lesions of important organs (such as severe liver and kidney function damage, heart failure, etc.). (4) Immune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, etc.). (5) History of allergy to the studied drugs (atorvastatin or argatroban).

Treatments

After admission, both groups were given routine treatments such as dehydration, blood pressure reduction, sugar control, oxygen inhalation, brain nourishing, etc.. In addition, the atorvastatin group was treated with atorvastatin (Pfizer Pharmaceuticals Co., Ltd. YN, USA; 30 mg/time, once/day) (Xie *et al*., 2020) by oral administration for one month. The atorvastatin + argatroban group was treated with atorvastatin combined with argatroban. The use of atorvastatin was the same as that of the control group. A 10 mg of argatroban (Sailong Pharmaceutical Group Co., Ltd., Yueyang, China) was dissolved in 150 ml 0.9% sodium chloride solution and was continuously pumped into the vein within 4 h, once every 6 h. After two days of continuous administration, the frequency of medication was reduced to 2 times/day and the medication was continued for 7 days. The argatroban dosage and administration regimen were based on the recommendations of clinical studies (Geli *et al*., 2022). During the treatment, the vital signs were measured twice daily; the routine blood, coagulation and liver/kidney function tests were performed every three days. The adverse events were recorded in detail. For missing data, the last observation carried forward method was used and no significant missing data were observed.

Evaluation of overall efficacy

Overall efficacy of treatment was evaluated based on NIHSS (Lee and Xiang, 2018). The NIHSS score reduction ≥ 46% was considered significant effect, the 18% ≤ reduction ≤ 46% was considered effective and the reduction <18% was considered ineffective. Significant effective rate + effective rate = overall effective rate.

Determination of cerebral blood flow indexes

Cerebral blood flow indexes were detected using carotid artery color Doppler ultrasound (Philips IU22, Netherlands). The mean blood flow quantity (Q_{mean}), mean blood velocity (V_{mean}) and peripheral resistance (PR) were recorded. In addition, the multi-row computed tomography (Siemens Somatom Definition Flash, Germany) was used to detect the pulsatility index (PI).

Determination of blood indexes

Fasting venous blood (5 ml) was collected from each patient before and after treatment, centrifuged at 3000 rpm for 10 min and the supernatant was separated and stored at -80 °C for testing. The coagulation function indexes (prothrombin time, thrombin time, activated partial thromboplastin time (APTT), fibrinogen) were measured using the fully automatic coagulation analyzer (Sysmex CA-7000, Japan). The vascular endothelial function indexes (nitric oxide, vascular endothelial growth factor (VEGF), endothelin-1) and inflammatory cytokines (hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor α (TNF-α), interleukin 6) were detected by enzyme-linked immunosorbent assay using commercial kits (purchased from R&D Systems, USA). The operation was strictly in accordance with the kit instructions.

Statistical analysis

SPSS 23.0 statistical software was adopted for analysis of data. The measurement data were expressed as mean ±standard deviation and comparison between groups was performed using the independent samples t test; comparison before and after treatment within the group was performed using the paired samples t test. The count data were expressed as number of cases (percentage) and comparison between groups was performed using the chi-square test. $p < 0.05$ indicated statistically significant difference.

RESULTS

Overall efficacy

As shown in table 1, the atorvastatin +argatroban group obtained the overall effective rate of 95.00%, significantly higher than the atorvastatin group with 80.00% ($p < 0.05$).

Cerebral blood flow indexes

After treatment, both groups showed a significant increase in Q_{Mean} and V_{mean} and a significant decrease in PI and PR ($p < 0.05$). These changes were more pronounced in the atorvastatin +argatroban group compared to the atorvastatin group (all $p < 0.05$, Fig. 1).

Coagulation function indicators

Compared to baseline, the prothrombin time, thrombin time and APTT were prolonged and the fibrinogen level was reduced in both groups after treatment. These changes were more significant in the atorvastatin + argatroban group than in the atorvastatin group (all $p < 0.05$, Fig. 2).

Vascular endothelial function indexes

After treatment, in each group the nitric oxide and VEGF levels significantly increased and the endothelin-1 level significantly decreased. Compared with the atorvastatin group, in the atorvastatin +argatroban group the nitric oxide and VEGF levels were significantly higher, while the endothelin-1 level was further reduced (all $p < 0.05$, Fig. 3).

Inflammatory cytokines

After the treatment, in each group the hs-CRP, TNF-α and interleukin 6 significantly decreased and those in the atorvastatin +argatroban group showed a greater reduction compared to the atorvastatin group (all $p < 0.05$, Fig. 4).

Safety profile

During the treatment, no bleeding events (e.g., cerebral hemorrhage, gastrointestinal bleeding) or other adverse reactions (e.g., liver/kidney damage, allergies) occurred in either group. Both regimens showed good safety profiles.

DISCUSSION

ACI is mainly caused by the interruption or reduction of local brain tissue blood flow due to thrombosis and hypoperfusion in the cerebral blood vessels. ACI can lead to the sudden neurological damage and the timely treatment measures are needed to control the condition. Conventional treatment for ACI is mainly the antiplatelet aggregation and use of statins to control the blood lipids and stabilize the plaques (Li *et al*., 2023). At the same time, the treatments such as improving cerebral circulation and controlling blood pressure and blood sugar are taken, but the treatment effect is limited.

This study investigated the efficacy of atorvastatin combined with argatroban for ACI. After comparative analysis of the overall efficacy, cerebral blood flow indexes and coagulation function indicators of two groups, it was found that, comparing to the atorvastatin group, in the atorvastatin +argatroban group the overall effective rate, Q_{mean} and V_{mean} significantly increased, the PI and PR significantly decreased. In addition, comparing to the atorvastatin group, in the atorvastatin +argatroban group the prothrombin time, thrombin time and APTT were further prolonged and the fibrinogen was further reduced. This indicates that the additional use of argatroban can effectively improve the patient's cerebral blood circulation and coagulation function in the treatment of ACI, further improving the treatment efficacy. The improvement of cerebral blood flow by the combination of atorvastatin and argatroban may be due to the synergistic effect of the two drugs.

Table 1: Overall efficacy.

Group	n	Remarkably effective (n)	Effective (n)	Ineffective (n)	Overall effective rate (%)
Atorvastatin	40	17	15	8	80.00
Atorvastatin +argatroban	40	21	17	2	95.00
χ^2					4.114
p					0.042

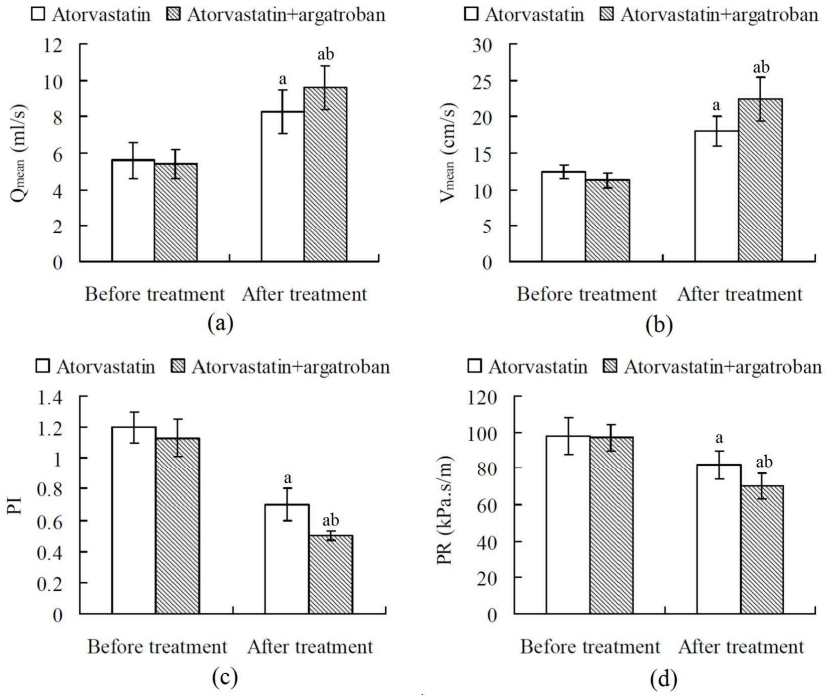

Fig. 1: Cerebral blood flow indexes: (a) Q_{mean}, (b) V_{mean}, (c) PI, (d) PR. Q_{mean}: mean blood flow quantity; V_{mean}: mean blood velocity; PI: pulsatility index; PR: peripheral resistance. $^{a}p < 0.05$ comparing to before treatment; $^{b}p < 0.05$ comparing to atorvastatin group.

Atorvastatin can stabilize atherosclerotic plaques, reduce vascular stenosis and improve vascular compliance, while argatroban can inhibit thrombin activity, prevent thrombosis and dissolve existing microthrombi. Together, they expand the cerebral blood vessels, increase blood flow and reduce peripheral resistance, thereby improving cerebral blood circulation. In terms of coagulation function, atorvastatin can reduce the levels of coagulation factors and inhibit platelet aggregation to a certain extent and argatroban can directly inhibit thrombin, which is a key enzyme in the coagulation process. The combination of the two drugs can more effectively inhibit the coagulation cascade reaction, prolong the coagulation time and reduce the formation of fibrin clots, thus improving the coagulation function of ACI patients.

Our study results are consistent with the findings of Ma *et al*., (2017), who found that argatroban can improve cerebral blood flow in ACI patients. Xie *et al*., (2020) also reported that atorvastatin has a certain protective effect on vascular endothelial function in ACI patients. However, compared with their single-drug studies, our study shows that the combination of the two drugs has a more significant effect on improving cerebral blood flow, coagulation function and vascular endothelial function, which further confirms the synergistic effect of the combined therapy.

In contrast, a study by Beer *et al*., (2012) found that the therapeutic effect of atorvastatin alone in ACI patients was not ideal, which is consistent with our observation that the overall effective rate of the atorvastatin group was only 80.00%. However, they did not explore the combination of atorvastatin with argatroban, which is the innovation of our study. Although our study shows that the combination of atorvastatin and argatroban is effective and safe, there are also some studies with inconsistent results. For example, a small number of studies have reported that high-dose atorvastatin may increase the risk of liver damage, but in our study, no liver function damage was found in the atorvastatin +argatroban group, which may be related to the dosage of atorvastatin (30 mg/day) we used, which is a moderate dosage and has a good safety profile.

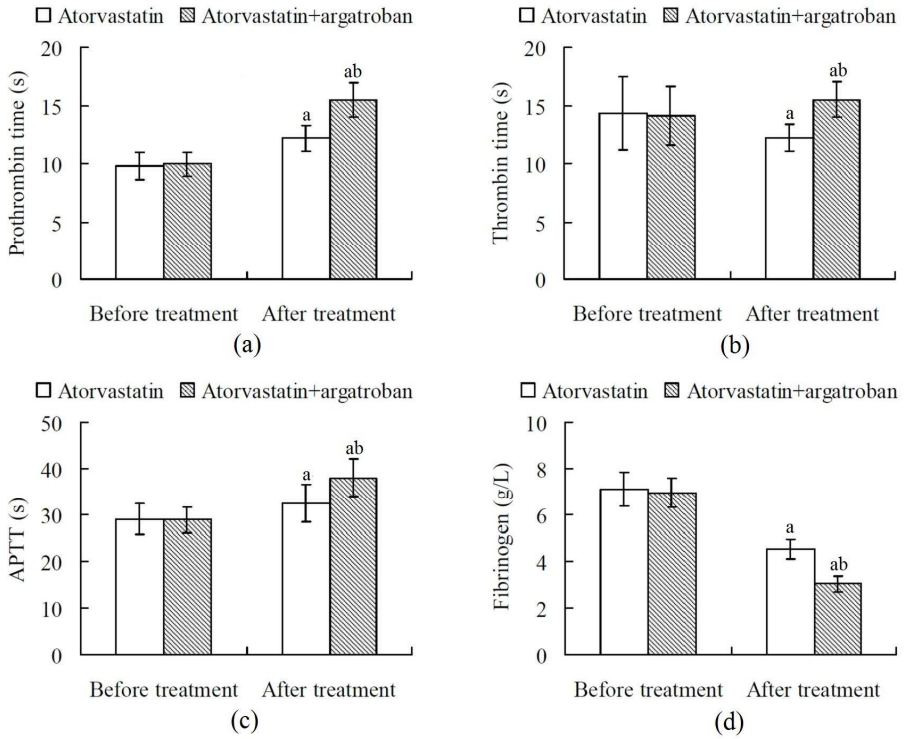

Fig. 2: Coagulation function indicators: (a) prothrombin time, (b) thrombin time, (c) APTT, (d) fibrinogen. APTT: activated partial thromboplastin time. [a]$p < 0.05$ comparing to before treatment; [b]$p < 0.05$ comparing to atorvastatin group.

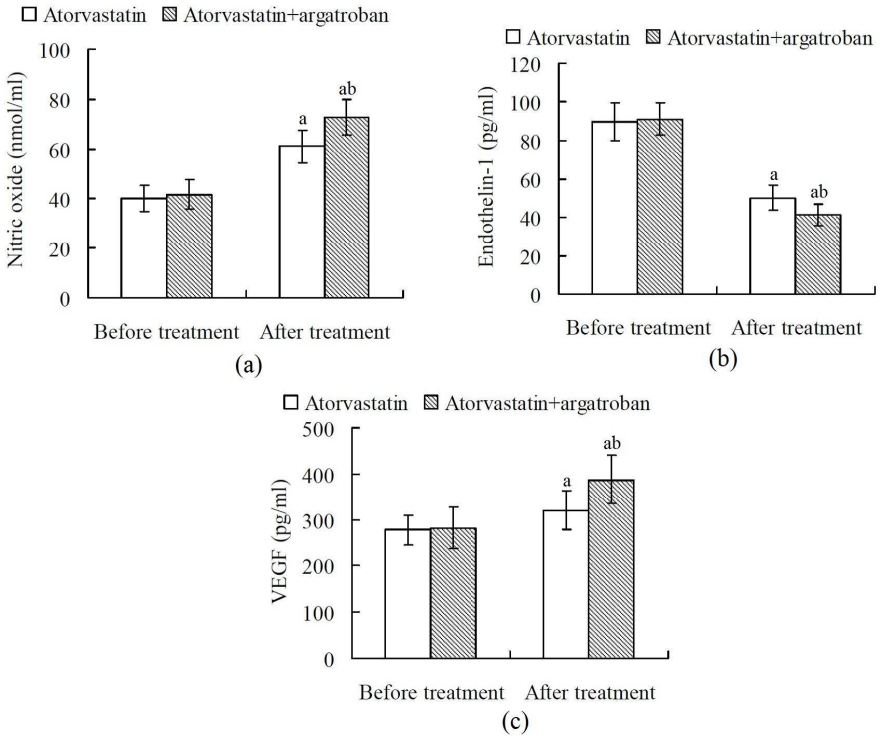

Fig. 3: Vascular endothelial function indexes: (a) nitric oxide, (b) endothelin-1, (c) VEGF. VEGF: Vascular endothelial growth factor. [a]$p < 0.05$ comparing to before treatment; [b]$p < 0.05$ comparing to atorvastatin group.

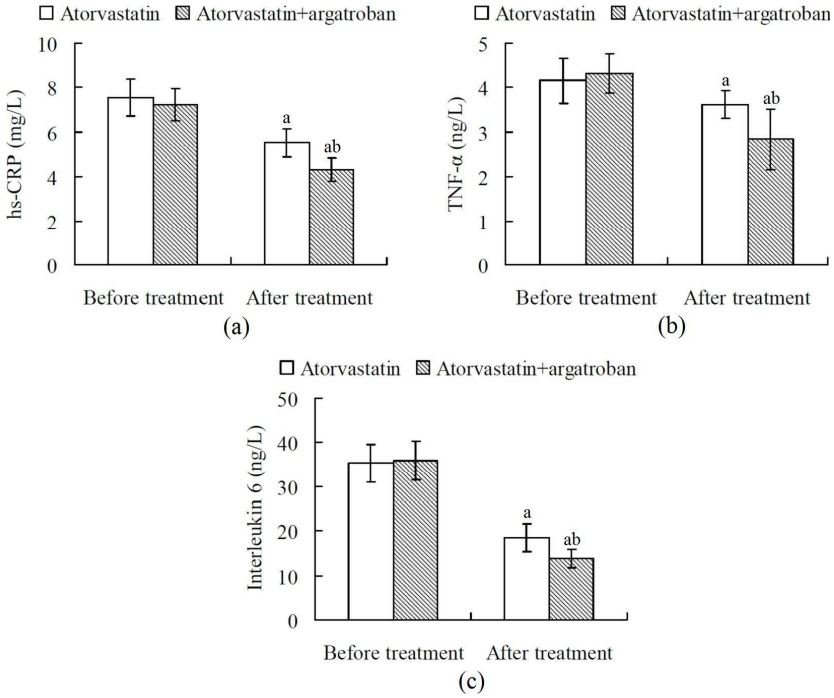

Fig. 4: Inflammatory cytokines: (a) hs-CRP, (b) TNF-α, (c) interleukin 6. hs-CRP: Hypersensitive C-reactive protein; TNF-α: tumor necrosis factor α. [a]$p < 0.05$ comparing to before treatment; [b]$p < 0.05$ comparing to atorvastatin group.

In addition, some studies have suggested that argatroban may increase the risk of bleeding, but in our study, no bleeding events occurred, which may be due to the strict selection of patients (excluding patients with bleeding tendency and blood system diseases) and close safety monitoring during the treatment period.

Most patients with ACI have symptoms of hypertension. The high blood flow shear force caused by hypertension can disrupt the endocrine function of vascular endothelial cells (Cao *et al*., 2020; Ma *et al*., 2023). Nitric oxide, a key endothelium-derived vasodilator, can reach the smooth muscle through the cell membrane to promote the smooth muscle relaxation, thus effectively dilating the blood vessels (Manjunathan *et al*., 2025). Endothelin-1 is a peptide secreted by endothelial cells. ACI leads to the increased secretion of endothelin-1 and its increased neurotoxicity (Luo and Grammas, 2010). VEGF is highly expressed in myocardial ischemia, acute cerebral infarction and other pathological conditions. It can promote the endothelial proliferation and repair the damaged microcirculation, thus restoring the neurological function (Zhang *et al*., 2018). In the study, it was found that, at the end of treatment, comparing to the atorvastatin group, in the atorvastatin +argatroban group the nitric oxide and VEGF further increased and the endothelin-1 further decreased. It is suggested that the additional use of argatroban can improve the endothelial function of patients in treating ACI. The mechanism may be that atorvastatin can up-regulate the expression of endothelial nitric oxide synthase, promote the synthesis and release of nitric oxide and argatroban can reduce the damage of thrombin to vascular endothelial cells, inhibit the secretion of endothelin-1 by endothelial cells and promote the expression of VEGF. The combination of the two drugs can better repair damaged vascular endothelial cells, improve endothelial function and maintain vascular homeostasis. Wang *et al*., (2022) also found in their meta-analysis that the combination of argatroban and statins can significantly increase the level of nitric oxide and decrease the level of endothelin-1 in ACI patients, which is consistent with our study results.

Occurrence of ACI can cause the release of inflammatory cytokines, thereby aggravating the damage to nerves (Liang *et al*., 2023). Clinically, hs-CRP is closely related to the cerebrovascular diseases caused by chronic inflammation (Moutachakkir *et al*., 2017). TNF-α can promote the infiltration and aggregation of leukocytes in the ischemic area of patients, thereby aggravating the occurrence of local inflammation in brain tissue (Jang *et al*., 2021). Interleukin 6 is a lymphokine secreted by T cells and fibroblasts. It can participate in the body's inflammatory response through various pathways (Yao *et al*., 2014). Therefore, the above indicators can be used as the control of inflammatory response in cerebrovascular diseases. In our study, in each group, after the treatment hs-CRP, TNF-α and interleukin 6 significantly decreased and those in the atorvastatin +argatroban group further decreased than the atorvastatin group. This indicates that

in the treatment of ACI, atorvastatin combined with argatroban can better reduce the local inflammatory response. The mechanism behind this may be that atorvastatin inhibits the activation of nuclear factor-κB, a key transcription factor in the inflammatory response, thereby reducing the expression of inflammatory cytokines such as TNF-α and IL-6 (Chen *et al*., 2021). Argatroban, on the other hand, can inhibit the activation of platelets and leukocytes, reducing the release of inflammatory mediators and the infiltration of inflammatory cells into the ischemic brain tissue (Geli *et al*., 2022). The combination of the two drugs exerts a synergistic anti-inflammatory effect, further reducing the inflammatory response in ACI patients. This is consistent with the findings of Liang *et al*. (2023), who reported that effective anticoagulant and lipid-lowering therapy can reduce the level of inflammatory cytokines in ACI patients.

This study has several limitations that need to be acknowledged. Firstly, the grouping relied on clinical decisions rather than randomization, introducing potential selection bias; the unmeasured confounders (e.g., patient compliance, concurrent herbal use) may also impact the results. Secondly, the single-center data restrict the generalizability of findings to other healthcare settings or populations. Thirdly, the short follow-up duration prevents assessment of long-term outcomes such as ACI recurrence and one-year mortality. Fourthly, the small sample size may lead to missed detection of rare adverse events. Future multi-center retrospective studies with larger sample sizes and extended follow-up are needed to validate our results.

CONCLUSION

In the treatment of ACI, atorvastatin combined with argatroban can effectively improve the cerebral blood circulation, coagulation function and vascular endothelial function and reduce the inflammation, thus exerting good therapeutic efficacy. No obvious adverse reactions occurred, indicating good short-term safety. However, due to certain limitations, future multi-center retrospective studies with larger sample sizes, optimized drug dosage and extended follow-up are needed to validate the results, for providing more personalized treatment options for clinical practice.

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Authors' contributions
Weihua Xu designs the study; Ni Zhai and Yanan Wang collect the data; Jie Chen performs the statistical analysis; Licang Zhu writes the manuscript; Zhiwei Li revises the manuscript.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (20240507-2). Given the retrospective nature and use of de-identified data, the ethics committee waived the requirement for individual informed consent.

Conflict of interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors have no conflicts of interest to disclose.

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