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ORIGINAL RESEARCH

Analysis of the preliminary findings of rivaroxaban plus *Danshen* polyphenolic acid in the treatment of patients with atrial fibrillation during the recovery period of cardiogenic cerebral infarction

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Abstract

This study aimed at exploring the clinical efficacy of rivaroxaban plus *Danshen* polyphenolic acid for treating atrial fibrillation in patients recuperating from cardiogenic cerebral infarction. The data of 80 patients with atrial fibrillation in the recovery phase (subacute rehabilitation stage) of cardiogenic cerebral infarction, who underwent treatment at the Second People's Hospital of Anhui Province between January 2020 and October 2023, were retrieved and assessed. They were randomly divided into two groups (a control and study group; 40 cases/group) using the random number table method. The control group received anticoagulant treatment with rivaroxaban, while the study group received a combination of rivaroxaban and *Danshen* polyphenolic acid. Then, the symptom scores, neutrophil-to-lymphocyte ratio (NLR), coagulation function indicators, vascular endothelial function indicators, and adverse reactions between the two groups of patients were compared and analyzed. Before treatment, there were no significant differences observed in The National Institute of Health Stroke Scale (NIHSS) score, D-Dimer (D-D), fibrinogen (FIB), antithrombin-III (AT-III), C-reactive protein (CRP), and soluble intercellular adhesion molecule-1 (sICAM-1) between the two groups ($p > 0.05$). After treatment, both groups exhibited a significant reduction in NIHSS scores, D-D, FIB, CRP and sICAM-1 levels, with the study group demonstrating significantly lower values compared to the control group ($p < 0.05$). Moreover, after treatment, both groups had a significant increase in AT-III levels, with the study group exhibiting significantly higher levels than the control group ($p < 0.05$). The incidence of adverse reactions in the study group was 5.00%, significantly lower than the 20.00% observed in the control group ($p < 0.05$). We conclude that, using rivaroxaban plus *Danshen* polyphenolic acid for treating patients with atrial fibrillation during the recovery phase of cardiogenic cerebral infarction could effectively enhance coagulation function, diminish inflammatory response status, facilitate symptom recovery, and enhance clinical prognosis.

Keywords

Rivaroxaban; *Danshen* polyphenolic acid; Cardiogenic cerebral infarction; Atrial fibrillation; Clinical efficacy

1. Introduction

Atrial fibrillation stands as a prevalent form of rapid arrhythmia primarily affecting individuals aged 60 and above, accompanying various clinical challenges. Its incidence increases with age, leading to decreased quality of life, increased economic burden, and sustained demand for social healthcare resources, among other complexities [1]. Cardiogenic cerebral infarction, commonly known as ischemic stroke, is characterized by the softening and necrosis of local brain tissues due to blood circulation disorders, ischemia and hypoxia. It presents with a high recurrence rate, severe manifestations and poor prognoses. Cardiac embolism represents the primary cause of cerebral infarction, with individuals having atrial fibrillation exhibiting a fivefold higher stroke risk compared to those without it [2]. Currently, targeted treatments for atrial fibrillation during cardiogenic cerebral infarction recovery are lacking, with symptomatic management and anticoagulation being the mainstay of treatment [3]. Rivaroxaban indicated for treating venous thrombosis in adults, is characterized by its bioavailability as a factor Xa inhibitor, stable drug properties, and low risk of causing additional bleeding [4]. *Danshen*

derived from traditional Chinese medicine (Salvia miltiorrhiza), possesses antioxidative, antiplatelet aggregation, and antithrombotic effects, effectively addressing symptoms such as hemiplegia and facial asymmetry, such as tilting of the mouth and tongue [5]. Building upon prior research [5], which suggests that the clinical efficacy of solely relying on Western medicine to treat atrial fibrillation in the recovery stage of cardiogenic cerebral infarction could be enhanced, we designed this present study to investigate the combined utilization of Western medicine (rivaroxaban) and traditional Chinese medicine (*Danshen* polyphenolic acid) for treating patients with atrial fibrillation.

2. Information and methods

2.1 Clinical data

Eighty patients diagnosed with atrial fibrillation during the recovery phase of cardiogenic cerebral infarction who underwent treatment at the Second People's Hospital of Anhui Province between January 2020 and October 2023 were selected for this study. Using a random number table method, they were divided into two groups: a study group and a control group, each comprising 40 cases. Table 1 compares general information between the groups, indicating no significant differences ($p > 0.05$).

2.1.1 Inclusion criteria

(1) Patients meeting the relevant clinical diagnostic criteria for cardiogenic cerebral infarction combined with atrial fibrillation; (2) Patients in the subacute recovery stage (14–60 days after disease onset); (3) Patients or their family members have provided informed consent.

2.1.2 Exclusion criteria

(1) Patients with contraindications to the use of relevant drugs; (2) Patients with an expected survival period of less than 6 months; (3) Patients with a significant bleeding tendency following evaluation.

2.2 Treatment methods

Both groups of patients received conventional drug therapy aimed at antiplatelet aggregation, microcirculation improvement, dehydration, and reduction of cranial pressure.

2.2.1 Control group

Patients in this group were administered rivaroxaban (specification: 10 mg; manufacturer: Bayer AG; manufacturing address: Kaiser-Wilhelm-Allee, 51368 Leverkusen, Germany; imported drug registration certificate No.: H20181081) orally at a therapeutic dose of 20 mg per time, once daily (initial dose). The patients' creatinine clearance was dynamically monitored, and the dose was adjusted accordingly.

2.2.2 Study group

Patients in this group received treatment with *Danshen* polyphenolic acid in addition to rivaroxaban. *Danshen* Polyphenolic Acid (specification: 0.13 g (100 mg *Danshen* Polyphenolic Acid) per bottle; Manufacturer: Tianjin Tianshili Lixili Zhijiao Pharmaceutical Company Limited, Beichen Science and Technology Park, Tianjin, China; State Drug License Z20110011) was administered to patients *via* intravenous drip, mixed into 300 mL of 0.9% sodium chloride injection, once daily.

Both groups of patients received continuous medication for one month to examine and compare overall efficacy.

2.3 Observation indexes

2.3.1 National Institutes of Health Stroke Scale (NIHSS) Score

The NIHSS is an 11-item scale ranging from 0 to 42, with higher scores indicating more severe neurologic deficits.

2.3.2 Neutrophil-to-lymphocyte ratio (NLR)

Venous blood samples were collected from patients while fasting in the early morning. These samples were then analyzed using a hematology analyzer to determine lymphocyte count and neutrophil count and to calculate the NLR.

2.3.3 Coagulation function indices

Venous blood samples were obtained from patients and analyzed using a coagulation analyzer to determine levels of D-dimer (D-D), fibrinogen (FIB), and antithrombin-III (AT-III).

2.3.4 Vascular endothelial function indicators

Venous blood samples from the patients were collected and placed in a centrifuge set to parameters of 3000 revolutions per minute (r/min) with a radius (R) of 8 centimeters (cm). Following centrifugation for 15 minutes, the serum was separated. Enzyme-linked immunosorbent assay (ELISA) was employed to analyze the levels of C-reactive protein (CRP) and vascular endothelial function (VEF). Additionally, levels of soluble intercellular adhesion molecule-1 (sICAM-1) were measured.

2.3.5 Adverse effects

The main adverse effects observed included bleeding gums, itchy skin and bleeding under the skin.

3. Results

3.1 Comparison of symptom scores

The NIHSS scores of both groups showed a significant decrease, with the study group displaying notably lower scores compared to the control group ($p < 0.05$), as shown in Table 2 and Fig. 1.

3.2 Comparison of coagulation function indices

After treatment, the levels of D-D and FIB in both groups notably decreased, with the study group exhibiting significantly lower levels compared to the control group ($p < 0.05$). Additionally, the level of AT-III significantly increased in both groups post-treatment, with the study group demonstrating significantly higher levels than the control group ($p < 0.05$), as illustrated in Table 3 and Figs. 2,3,4.

TABLE 1. Comparison of general information between the two groups.

Group	n	Gender (Male/Female)	Age (yr)	BMI (kg/m^2)	NIHSS score (points)	Type of atrial fibrillation (n, %)			TOAST staging of cardiogenic cerebral infarction (n, %)			
						Paroxysmal	Persistent	Permanent	Atherosclerotic stroke	Cardiac cerebral embolism	Small artery occlusion	Other
Study group	40	16/24	58.05 ± 1.43	20.45 ± 1.12	19.35 ± 1.03	3, 7.50	16, 40.00	21, 52.50	10, 25.00	12, 30.00	9, 22.50	9, 22.50
Control group	40	15/25	57.93 ± 1.47	20.83 ± 1.15	19.33 ± 1.07	3, 7.50	15, 37.50	22, 55.00	11, 27.50	12, 30.00	8, 20.00	9, 22.50
χ^2/t	—	0.053	0.385	0.701	0.107		0.056			0.106		
p	—	0.819	1.497	0.138	0.915		0.973			0.991		

BMI: Body Mass Index; TOAST: Trial of Org 10172 in Acute Stroke Treatment; NIHSS: National Institute of Health Stroke Scale.

TABLE 2. Comparison of symptom scores ($\bar{x} \pm s$).

Indicators	Study group (n = 40)	Control group (n = 40)	*t* value	*p*-value
NIHSS score (points)				
Before treatment	18.43 ± 0.50	18.46 ± 0.51	−0.266	0.396
After treatment	8.55 ± 0.50	12.58 ± 0.55	−34.290	<0.001
t value	88.369	49.580	—	—
p	<0.001	<0.001	—	—

NIHSS: National Institute of Health Stroke Scale.

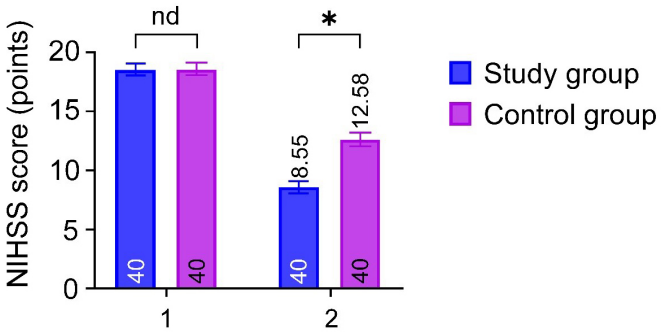

FIGURE 1. Comparison of NIHSS scores between the control and study groups. NIHSS: National Institute of Health Stroke Scale. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

TABLE 3. Comparison of coagulation function indices ($\bar{x} \pm s$).

Indicators	Study group (n = 40)	Control group (n = 40)	*t* value	*p*-value
D-D (mg/L)				
Before treatment	0.75 ± 0.11	0.76 ± 0.09	−0.011	0.991
After treatment	0.33 ± 0.06	0.53 ± 0.08	−12.894	<0.001
t value	25.345	12.598	—	—
p-value	<0.001	<0.001	—	—
FIB (g/L)				
Before treatment	4.18 ± 0.36	4.15 ± 0.39	0.325	0.746
After treatment	2.67 ± 0.22	3.19 ± 0.28	8.439	<0.001
t value	8.515	13.241	—	—
p-value	<0.001	<0.001	—	—
AT-III (%)				
Before treatment	65.35 ± 6.15	65.44 ± 6.09	−0.073	0.942
After treatment	90.70 ± 4.21	75.25 ± 7.22	11.803	<0.001
t value	−20.893	−5.746	—	—
p-value	<0.001	<0.001	—	—

D-D: D-Dimer; FIB: fibrinogen; AT-III: antithrombin-III.

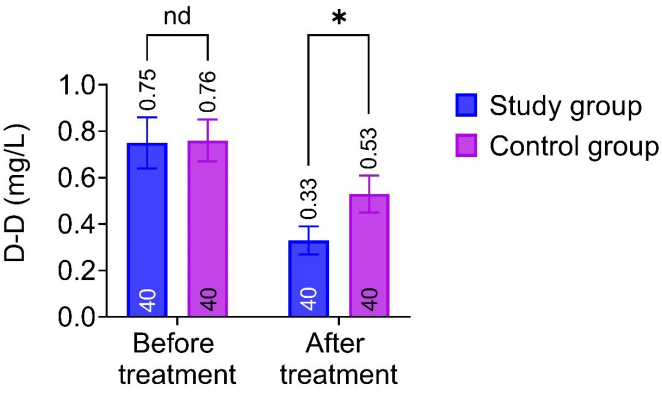

FIGURE 2. Comparison of D-D between the two groups. D-D: D-Dimer. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

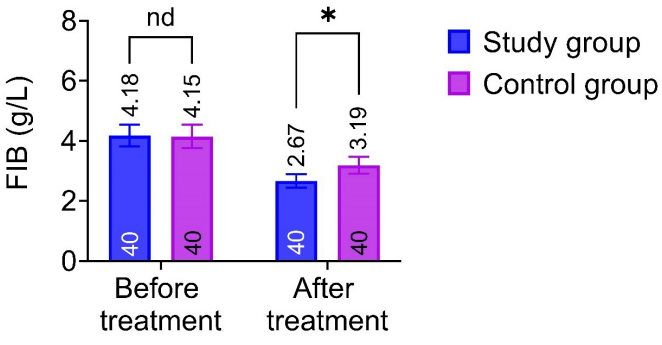

FIGURE 3. Comparison of FIB between the two groups. FIB: fibrinogen. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

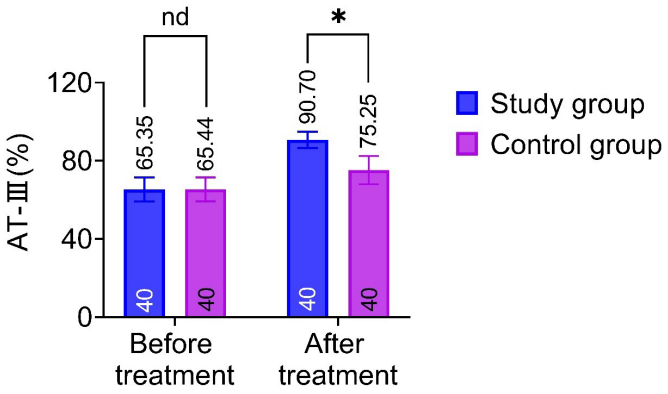

FIGURE 4. Comparison of AT-III between the two groups. AT-III: antithrombin-III. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

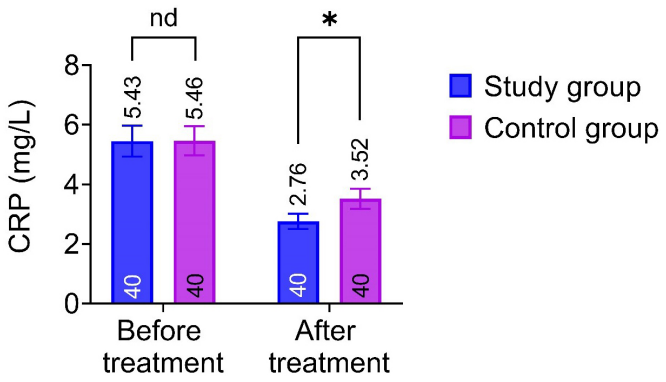

FIGURE 5. Comparison of CRP between the two groups. CRP: C-reactive protein. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

3.3 Comparison of serologic indices

After treatment, the levels of CRP and sICAM-1 in the two groups were significantly reduced, with the study group showing significantly lower levels compared to the control group ($p < 0.05$) (Table 4 and Figs. 5,6).

TABLE 4. Comparison of serologic indices ($\bar{x} \pm s$).

Indicators	Study group (n = 40)	Control group (n = 40)	*t* value	*p*-value
CRP (mg/L)				
Before treatment	5.43 ± 0.52	5.46 ± 0.49	−0.268	0.789
After treatment	2.76 ± 0.26	3.52 ± 0.34	−11.257	<0.001
t value	30.957	21.413	—	—
p value	<0.001	<0.001	—	—
sICAM-1 (ng/mL)				
Before treatment	578.35 ± 45.36	579.09 ± 46.05	−0.073	0.942
After treatment	306.25 ± 32.06	381.25 ± 33.69	−10.201	<0.001
t value	28.760	20.633	—	—
p value	<0.001	<0.001	—	—

CRP: C-reactive protein; sICAM-1: soluble intercellular adhesion molecule-1.

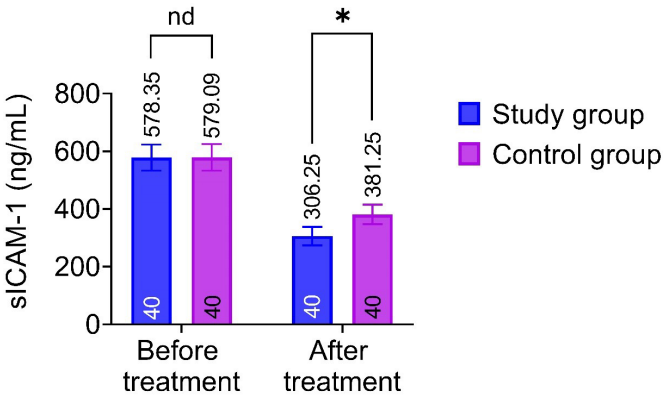

FIGURE 6. Comparison of sICAM-1 between the two groups. sICAM-1: soluble intercellular adhesion molecule-1. Note: nd: $p > 0.05$, the difference is not statistically significant; *: $p < 0.05$, the difference was statistically significant.

3.4 Comparison of adverse reactions

Further analysis showed that the incidence of adverse reactions in the study group was 5.00%, which was significantly lower than the 20.00% recorded in the control group ($p < 0.05$) (Table 5).

TABLE 5. Comparison of adverse reactions (n, %).

Groups	n	Bleeding gums	Itchy skin	Subcutaneous bleeding	Adverse reactions
Study group	40	1, 2.50	1, 2.50	0, 0.00	2, 5.00
Control group	40	2, 5.00	3, 7.50	3, 7.50	8, 20.00
t value	—		—		4.114
p	—		—		0.043

4. Discussion

The results of this study revealed that patients receiving rivaroxaban plus *Danshen* polyphenolic acid exhibited lower NIHSS scores, decreased levels of D-D, FIB, CRP and sICAM-1, and higher levels of AT-III after treatment compared to those receiving rivaroxaban alone. Additionally, the incidence of adverse events in the study group was found to be significantly lower at 5.00% compared to 20.00% in the control group. Taken together, these findings align with both Chinese and international reports. It has been reported that atrial fibrillation is one of the most prevalent and perilous factors contributing to stroke [5]. The pathogenesis of cerebral infarction involves various factors acting on cerebral blood vessels, leading to obstruction, ischemia, and hypoxia of brain tissue, thereby impairing neurological function. Cardio embolism commonly results in infarctions of the middle cerebral artery and anterior cerebral artery (ACA) regions. Clinical experience indicates that cerebral infarction significantly increases the risk of death or disability in patients with atrial fibrillation [6]. The formation of thrombi due to a large number of adherent red blood cells on vessel walls leads to cardiogenic embolism [7]. When such emboli occlude cerebral arteries, the affected brain tissue becomes ischemic. Without compensatory collateral circulation, this ischemic event results in tissue death, and this scenario is particularly critical in patients experiencing atrial fibrillation during the recovery period following cerebral infarction as it prolongs hospital stays, increases the risk of complications, and significantly reduces patient survival and quality of life [8]. In current medical practice, anticoagulation and symptomatic therapy are used as the standard approach to managing atrial fibrillation in conjunction with cerebral infarction [9].

Rivaroxaban is an orally administered anticoagulant drug utilized in the treatment of venous thrombosis in adults, effectively preventing endogenous and exogenous blood clot formation [10]. *Danshen* Polyphenolic Acid, derived from the ancient Chinese medicine *Danshen,* constitutes a class of polyphenolic compounds. Among its biochemical constituents are protocatechuic aldehyde and rosmarinic acid, which contribute to cardiovascular and cerebrovascular disease recovery. *Danshensu*, scientifically known as 3-(3,4-dihydroxyphenyl)-L-lactic acid or Salvia divinorum, is a naturally occurring phenolic acid compound with beneficial properties. Similarly, 3,4-dihydroxybenzaldehyde, or protocatechuic aldehyde, is a naturally occurring phenolic chemical found in various plants such as Chenpi, Salvia miltiorrhiza, and hawthorn. It exhibits diverse biological actions, including anticancer, antibacterial, anti-inflammatory, and antioxidant properties. Additionally, rosmarinic acid, present in several plants including thyme, perilla, and rosemary, possesses pharmacological actions such as anti-inflammatory, antibacterial, antioxidant, and anti-tumor properties. These active components collectively contribute to improving blood flow to the brain [11].

This study investigates the efficacy of rivaroxaban in combination with *Danshen* polyphenolic acid for treating atrial fibrillation concomitant with cerebral infarction through a comprehensive review and analysis of prior research. Relevant data suggests that concurrently administering these two drugs can significantly safeguard and restore brain neural tissues, surpassing the effects of either drug used in isolation. The diagnostic and therapeutic mechanism is attributed to *Danshen* polyphenolic acid's ability to attenuate cellular oxidative aging reactions, thereby mitigating brain tissue injury [12, 13]. It has been suggested that thrombosis in patients with cerebral infarction correlates with vascular endothelial impairment and blood hypercoagulability [14]. D-D is a valuable indicator of abnormal coagulation in the body. FIB, a glycoprotein synthesized by hepatocytes, contributes to hypercoagulability, with elevated levels associated with thrombosis. AT-III actively participates in the body's anticoagulation processes, and a reduction in its levels increases thrombotic risk [15]. Furthermore, there exists a positive correlation between the inflammatory response and the occurrence of brain damage in patients with atrial fibrillation concomitant with cerebral infarction [16]. sICAM-1 plays a crucial role in promoting inflammatory factors by inducing leukocyte adhesion to damaged tissues, thereby delaying organism repair and exacerbating brain damage [17]. CRP, a non-specific inflammatory marker, further contributes to inflammation [18]. In this study, combination therapy effectively lowered sICAM-1 and CRP levels, attenuating the inflammatory response, promoting cellular healing, and reducing brain tissue damage. Experimental data also revealed that *Danshen* polyphenolic acid not only countered ischemia-reperfusion injury but also inhibited inflammation, thereby significantly enhancing the speed and quality of bodily repair.

NLR is used as a predictor for disease prognosis, and its value has been reported to be inversely correlated with prognostic outcomes [19–21]. The results of our present study indicate that patients treated with *Danshen* polyphenolic acid plus rivaroxaban exhibit lower NLR levels compared to those receiving monotherapy, suggesting that the combined treatment significantly reduces NLR levels and improves prognosis. Moreover, no serious adverse reactions were observed in either research group, and the differences between groups were not statistically significant, thus supporting the safety analysis results of this study.

Furthermore, rehabilitation has a significant favourable impact on the recovery of cardiogenic cerebral infarction associated with atrial fibrillation. Rehabilitation therapy can help patients recover limb function, linguistic function, cognitive function, and so on, as well as improve their overall quality of life. At the same time, rehabilitation therapy can assist patients in managing atrial fibrillation and lowering the incidence of atrial fibrillation and death. Physical therapy, occupational therapy, speech therapy, and cognitive therapy are some of the specialized approaches of rehabilitation. Physical therapy can assist patients recover limb function while also improving limb flexibility and coordination.

Occupational therapy can help patients regain daily function and improve their quality of life. Speech therapy can help individuals restore language function and improve their communication skills. Cognitive therapy can assist patients in regaining cognitive function and improving their thinking skills. It should be emphasized that rehabilitation therapy must develop an individualized rehabilitation treatment plan based on the specific needs of patients. Simultaneously, rehabilita-

tion therapy must be continued for an extended period of time, and patients and their families must actively collaborate with the doctor's treatment to improve patient recovery.

This study has certain limitations, notably its single-center design, which may restrict the generalizability of its findings across different research settings. Future research directions should focus on investigating the safety and tolerability of rivaroxaban combined with *Danshen* polyphenolic acid in treating patients with atrial fibrillation and cerebral infarction. Additionally, there is a need for thorough drug interaction studies to elucidate potential interactions between rivaroxaban, *Danshen* polyphenolic acid, and commonly prescribed medications like antiplatelet and antiarrhythmic drugs. Furthermore, it is imperative to refine efficacy assessment criteria, incorporating parameters such as cognitive function and cerebrovascular health. Lastly, longitudinal studies are warranted to evaluate the long-term efficacy and prognosis of rivaroxaban plus *Danshen* polyphenolic acid in individuals with atrial fibrillation and cardiogenic cerebral infarction during the recovery phase.

5. Conclusions

The combination of rivaroxaban and *Danshen* polyphenolic acid in treating patients with atrial fibrillation during the recovery phase of cardiogenic cerebral infarction effectively enhances coagulation function, reduces inflammatory response status, promotes symptom recovery, and improves clinical prognosis.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

DJZ and CY—designed the study and carried them out; prepared the manuscript for publication, and reviewed the draft of the manuscript. DJZ—supervised the data collection, analyzed and interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Second People's Hospital of Anhui Province (Approval no. (R)2024-002). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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