Study Protocol

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Efficacy and safety of Naoshuantong capsule in high-recurrence-risk patients with acute ischemic stroke (RESPACE)

Study protocol for a multicenter, randomized, double-blind, controlled trial

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Abstract: Ischemic stroke (IS) is a leading cause of death and long-term disability worldwide. The Naoshuantong capsule (NC), a traditional Chinese patent medicine, has been extensively used in the treatment of stroke in China. However, the clinical efficacy and safety of NC have not been finally verified through rigorous randomized controlled trials. Therefore, this randomized, multicenter, double-blinded, placebo-controlled trial is designed to investigate the efficacy and safety of NC in high-recurrence-risk patients with acute IS within 72 h after symptom onset. An estimated 3150 participants at age of 18 to 80 years with Essen stroke risk score ≥ 3 and National Institutes of Health Stroke Scale score ≤ 15 from approximately 100 Chinese hospitals will be randomly assigned in a 1:1 ratio to the NC group (NC 3 capsules 3 times daily for 90 days) or control group (NC placebo 3 capsules 3 times daily for 90 days). Guideline-based standard medical care will be used in both groups. The primary efficacy outcome is any stroke (ischemic or hemorrhagic) within 90 days after symptom onset. The primary safety outcome is severe adverse events within 90 days. To our knowledge, this study is the first double-blind trial to assess the efficacy and safety of NC in patients with acute IS. Findings of the trial will be valuable in improving evidence regarding the clinical application of NC therapy in patients with mild- to moderate-stroke at high risk of recurrence.

Clinical trial registration: The Chinese Clinical Trial Registry (ChiCTR), identifier ChiCTR2300075877.

Keywords: acute ischemic stroke, herbal medicine, protocol, randomized controlled trial, secondary prevention

1. Introduction

Acute ischemic stroke (AIS) carries a significant risk of early recurrence, with approximately 6.5% of patients experiencing a subsequent stroke within 3 months.[1] This risk is substantially elevated in high-risk subgroups, particularly those with an Essen stroke risk score (ESRS) ≥ 3,[2] approximately 7.9%, underscoring the need for more effective secondary prevention strategies in this vulnerable population.[3] The pathogenesis of AIS involves multiple interrelated mechanisms—including excitotoxicity, oxidative and nitrosative stress, apoptosis, and sustained inflammation—which collectively contribute to brain injury and increase susceptibility to recurrent events.[4–7] Targeting these pathways through

Supplemental Digital Content is available for this article.

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Cardiac Research (2026) 2:1

Received: 20 November 2025 / Received in final form: 008 February 2026 / Accepted: 11 March 2026

http://dx.doi.org/10.1097/re9.0000000000000013

neuroprotective interventions represents a promising therapeutic direction.

Traditional Chinese medicine (TCM), with its long history and holistic approach, has been increasingly recognized as a valuable complementary option in stroke management.[8–10] Accumulating preclinical and clinical observations suggest that certain TCM formulations possess anti-inflammatory, antioxidant, and neuroregulatory properties, which may address multifactorial injury processes not fully covered by conventional antithrombotic therapy alone.[11–13] Among these, the Naoshuantong capsule (NC)—a compound preparation derived from five herbal components (Pu Huang, Chi Shao, Yu Jin, Tian Ma, and Lou Lu, for details, see Supplemental Digital of Appendix 1–Appendix 4, https://links.lww.com/CARES/A6)—has shown particular promise. Experimental studies indicate that NC exerts multitarget neuroprotective effects, such as reducing infarct volume, improving neurological function, suppressing apoptosis, modulating inflammatory responses, attenuating excitotoxicity, and enhancing cerebral hemodynamics and metabolism.[14–16]

Despite these encouraging preclinical findings and positive signals from preliminary clinical trials observed for the efficacy of NC in treating ischemic stroke (IS), robust evidence from large-scale, rigorously designed studies remains scarce.[17–19] Currently, there is a lack of high-quality clinical data demonstrating the superior efficacy of NC specifically in high-risk AIS patients, who continue to face substantial residual recurrence risk under standard secondary prevention.

Therefore, the efficacy and safety of NC in high-recurrence-risk patients with acute IS (RESPACE), a well-design clinical trial, will be conducted to evaluate the efficacy and safety of NC in the treatment of patients with IS who are at a high risk of recurrence, which will provide a solid evidence base for its integration into routine care for high-risk AIS patients.

2. Methods

2.1. Study design

The RESPACE trial is a multicenter, randomized, double-blind, parallel, placebo-controlled study, which will enroll patients from emergency departments and neurology wards that receive patients with AIS in China. The study will be conducted in nearly 100 centers in China, and a total of 3150 participants will be recruited and allocated randomly to either the NC treatment group or the control group. Participating centers will be selected based on predefined criteria, including hospital level, stroke unit capabilities, annual stroke volume, qualified personnel, and infrastructure, and will compete for enrollment (see Supplemental Digital of Appendix 5, https://links.lww.com/CARES/A6, for detailed criteria). Both groups will undergo a treatment period of 90 days. Participants will be followed up at 30, 60, 90, and 180 days after randomization (D30, D60, D90, and D180, respectively) to collect efficacy and safety outcomes in person. Participants will be assessed with a relevant scale or laboratory biochemical examination on the scheduled day for each treatment and the follow-up period. The trial is designed according to the principles of the Declaration of Helsinki.

2.2. Ethics

Ethical approval was granted by the research ethics committee of The First Affiliated Hospital of Henan University of Chinese Medicine (approval number: 2023HL-098-02; September 8, 2023), Zhengzhou, China and registered in public clinical trial database, and was approved by the local institutional review boards of all participating sites. Any severe adverse events (AEs) will be reported to the committees immediately, and any revisions to the study design can only be made with the permission of the committees. This study was initiated in September 2023.

2.3. Participant recruitment

We will recruit patients with AIS who are of ages 18 to 80 years, with ESRS ≥ 3 and National Institute of Health Stroke Scale (NIHSS) score ≤ 15, have at least 2 elements of the Diagnostic Scale for Syndrome Elements of IS,[20,21] and can be treated within 72 h of symptom onset. All patients or their legally authorized representatives will provide written informed consent before any study-specific procedure. Table 1 lists the summary of inclusion and exclusion criteria.

2.4. Diagnostic criteria for symptom pattern in TCM practice

The Ischemic Stroke TCM Syndrome Factor Diagnostic Scale (ISTSFDS) can help to classify and diagnose the TCM symptom patterns objectively with the application of syndrome factors. Six syndrome factors are considered, encompassing internal wind, internal fire, phlegm dampness, blood stasis, Qi-deficiency, and Yin-deficiency. For the diagnosis of each syndrome element to be established, a score of 10 or more is required. Patients who will participate in the study must meet the diagnostic criteria for 3 or more of the following syndrome elements: internal wind, internal fire, phlegm-damp, and blood stasis.

2.5. Randomization, allocation, and blinding

Patients will be randomly assigned to the NC group and control group in a 1:1 ratio using block randomization. A randomization allocation sequence will be assigned to each group based on a computer-generated random number table created by an independent statistician using SAS version 9.4 software. All patients will be centrally randomized to the study using an interactive web response system, which links a sequential patient randomization number to the treatment codes. This trial is double-blind; the patient and all those involved in the clinical outcomes and the assessment of outcomes will be blinded to the

Table 1

Inclusion and exclusion criteria of the RESPACE trial.

Inclusion criteria
Meets the diagnosis of acute IS;
ESRS score is ≥ 3 and NIHSS score is ≤ 15;
Meets the diagnostic criteria for "internal wind syndrome, internal fire syndrome, phlegm dampness syndrome, blood stasis syndrome" in the "*Diagnostic Scale for Syndrome Elements of Ischemic Stroke*" with ≥ 2 elements;
Age is between 18 and 80 years old;
Can be treated with the study drug within 72 h of symptom onset;
Informed consent signed.
Exclusion criteria
Received intravenous thrombolysis or endovascular treatment;
History of stroke with residual sequelae that significantly affect the outcome assessment, i.e., a mRS score of ≥ 2 points before the onset of this stroke;
Suspected or known allergy to the ingredients of NC (Pu Huang, Chi Shao, Yu Jin, Tian Ma, and Lou Lu), or individuals with allergic constitution;
Concurrent diseases affecting limb activity function, such as claudication, osteoarthritis, rheumatoid arthritis, and gouty arthritis, which cause limb activity dysfunction affecting neurological examination before treatment;
Inability to understand and/or comply with the study procedures and/or follow-up due to mental illness and/or cognitive or emotional disorders;
History of chronic or severe diseases in the digestive, respiratory, urinary, hematopoietic, reproductive, or other systems, which the investigator deems unsuitable for participation;
Liver dysfunction (ALT, AST values > 2 times the upper limit of normal) or renal insufficiency (serum creatinine > 1.5 times the upper limit of normal);
Participation in other clinical trials within the past 30 days;
Pregnant women, women planning to become pregnant, or nursing mothers.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ESRS = Essen stroke risk score, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale.

treatment group. The two forms of drugs are visually identical and cannot be distinguished in appearance, taste, or packaging.

Emergency unblinding will be permitted only when knowledge of the assigned intervention is essential for the clinical management of an AE. In such cases, the site principal investigator must be immediately notified for approval, followed by prompt notification to the monitor and sponsor. All telephone communications are recorded by the Contract Research Organization (CRO). Following any unblinding event, the investigator must document the date, time, and reason in writing and discontinue the investigational product.

2.6. Treatment

Eligible patients will be randomly assigned to either the experimental group or the control group. The treatment assignments are presented in Figure 1. Participants in the experimental group will receive NC, 3 capsules (0.4 g each), 3 times daily for 90 days. The control group will receive an NC placebo, 3 capsules (0.4 g each), 3 times daily for 90 days. All patients will receive a standard treatment, which is referred to in the current guidelines (Chinese Society of Neurology and Chinese Stroke Society, 2018 for the acute treatment phase, and Chinese Guidelines for the Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack 2022 for the secondary prevention),[22,23] which will be predefined and uniformly implemented across all participating centers (see Supplemental Digital content Appendix 6, https://links.lww.com/CARES/A6 for details).

2.7. Follow-up procedures

Face-to-face follow-up will be conducted at days 30 ± 3, 60 ± 3, and 90 ± 7 after randomization. And telephone or face-to-face long-term follow-up will also be conducted at day 180 ± 14. The contents of each visit are listed in Table 2. Standardized case report forms are used for data collection, and data are then entered by separate data entry personnel via the Electronic Data Capture system.

2.8. Efficacy outcomes

The primary outcome is any stroke (ischemic or hemorrhagic) within 90 days after symptom onset. The secondary outcomes include IS within 90 days, vascular events (IS/hemorrhagic stroke/myocardial infarction/vascular death) within 90 days, the proportion of patients with the mRS score ≤ 1 on day 90, and EuroQol 5-dimension 5-level (EQ-5D-5L) scale scores change from baseline to day 90 after symptom onset. The definitions of outcomes are listed in Table 3.

2.9. Safety outcomes

The primary safety outcome is severe AEs during the treatment period. Other safety outcomes include any AE, all-cause mortality, any bleeding (severe or moderate bleeding and intracerebral hemorrhage), severe or moderate bleeding as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria, and hepatorenal dysfunction during the treatment period.

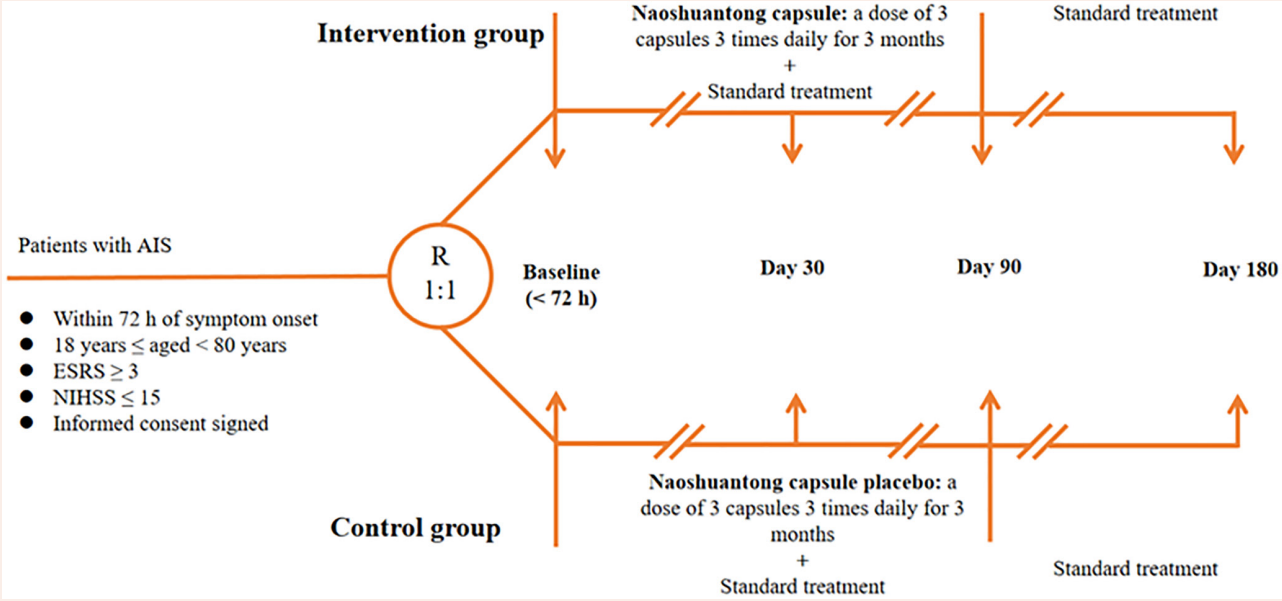

Figure 1. The flowchart of the trial. AIS = acute ischemic stroke, ESRS = Essen stroke risk score, NIHSS = National Institute of Health Stroke Scale.

2.10. Exploratory outcomes

To assess the long-term efficacy of NC, the exploratory outcomes include ISTSFDS change from baseline to day 90 after symptom onset, vascular events within 180 days, the proportion of patients with mRS ≤ 1 on day 180, and EQ-5D-5L scale scores change from baseline to day 180 after symptom onset.

2.11. Data Safety and Monitoring Board (DSMB)

The clinical endpoint events and safety endpoints will be reviewed by an independent clinical event committee blinded to treatment assignment. The Data Safety and Monitoring Board (DSMB) is mandated to convene in accordance with the protocol, overseeing the trial's progress and safety, and to submit regular reports to the committee. Following each session, the DSMB will furnish the Steering Committee with written recommendations. The DSMB holds the responsibility to suggest the premature termination of the study in the event of any unforeseen safety concerns.

2.12. Sample size calculation

According to Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients With Acute Nondisabling Cerebrovascular Events II (CHANCE-2), we assume an 8.0% stroke event rate within 90 days for the control group among AIS patients with ESRS scores of 3 or higher.[3] It is expected that the use of NC will reduce the risk of stroke recurrence by 37.5% compared with the control group, resulting in a 90-day stroke recurrence rate of 5.0%. With a test level of 0.05 (2-sided test), a power of 0.9, and a dropout rate of 10%, the trial will require a total of 3150 subjects, with 1575 in each group.

2.13. Statistical analysis

An intention-to-treat analysis will be performed for statistical analysis. For baseline characteristics, continuous variables will be provided as the mean ± standard deviation or median with interquartile range and compared using a *t* test or a Wilcoxon sum of rank test. Categorical variables will be provided as frequency with percentage and will be compared using either the χ^2 test or the Fisher exact test.

Participants will be censored at their last follow-up assessment when experiencing a clinical event, at the end of the study, or at the time of withdrawal from the study. Statistically, the cumulative risk of stroke will be reported as a Kaplan–Meier estimate during the 90-day follow-up. Cox proportional hazards methods will be used for hazard ratio calculation with 95% confidence interval, with trial centers set as a random effect. The treatment effect will be assessed by the log-rank test. Detailed analysis plans will be given in the statistical analysis plan before the database is locked and the blind is broken. All statistical analyses will be performed using the SAS statistical software, version 9.4 (SAS Institute Inc). A $P < 0.05$ in two tails is considered statistically significant.

3. Discussion

Patients at high risk of stroke recurrence often present with a more complex clinical profile compared with those at lower risk. Notably, comorbidities such as hypertension and diabetes mellitus—frequently observed in this population—have been associated with reduced responsiveness to antiplatelet therapy.[24] Given the elevated recurrence risk in these patients, the development and optimization of effective combination strategies for

Table 2

Follow-up procedures.

Measurements	Screening and enrollment	Enrollment day	Day 30 ± 3	Day 60 ± 3	Day 90 ± 7	Day 180 ± 14	Endpoint event visit*
Demographic characteristics		√					
NIHSS	√		√		√		√
ESRS	√						
mRS	√†	√	√		√	√	√
EQ-5D-5L Scale		√			√	√	√
Diagnostic scale for syndrome elements of IS	√						
Stroke syndrome element evaluation scale		√			√		√
Physical examination	√				√		√
Distribute/collect subject diary card		√	√	√‡	√		√
Medical history	√						
Pre-enrollment treatment		√					
Laboratory tests	√§				√‖		√‖
Cranial CT/MRI	√¶						√#
Stroke etiological subtype (TOAST)		√**					
12-lead ECG	√				√		
Verify inclusion/exclusion criteria	√						
Sign informed consent form	√						
Drug dispensing/collection		√	√	√‡	√		
Adverse events/serious adverse events			√	√	√	√	√
Study drug compliance			√	√	√		√
Concomitant medications during study			√	√	√	√	√

CT = computed tomography, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5-dimension 5-level, ESRS = Essen stroke risk score, MRI = magnetic resonance imaging, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale.

*All patients who experienced a stroke recurrence during the study period will be required to complete the endpoint event visit form, which is specifically designed to document detailed information about the stroke recurrence event. Only when a participant actually experienced an endpoint event requiring adjudication would the investigators and the adjudication committee fill out and utilize the "endpoint event visit" section of the form. For participants who did not experience an event, this section was left blank.

†The mRS score at "screening and enrollment" refers to the prestroke mRS score.

‡For the visit at day 60 ± 3, if the subject has mobility difficulties, the distribution and collection of the subject's diary card and trial drugs can be done via mail or by a family member.

§Laboratory tests should be completed within 7 days after enrollment (including blood routine, urinalysis, liver function, renal function, fasting blood glucose, and lipid profile). Laboratory results after the time of stroke onset can be used as screening results.

‖Laboratory tests, including blood routine, urinalysis, liver function, renal function, fasting blood glucose, and lipid profile, performed at the laboratory of each center.

¶Cranial CT/MRI: Depending on the situation at each participating center, it is strongly recommended to complete a cranial MRI within 3 days of enrollment (cranial MRI should include T1, T2, diffusion-weighted imaging [DWI], fluid-attenuated inversion recovery [FLAIR], apparent diffusion coefficient [ADC], and magnetic resonance angiography [MRA]), and data should be collected in digital imaging and communications in medicine (DICOM) format.

#Cranial CT/MRI: Depending on the situation at each participating center, for IS, it is strongly recommended to complete a cranial MRI at the endpoint event visit (cranial MRI should include T1, T2, DWI, FLAIR, and ADC). All images should be saved in DICOM format; for hemorrhagic stroke, a cranial CT scan is sufficient.

**All enrolled subjects must complete vascular assessment within 7 days of onset and undergo stroke etiological subtyping (Trial of ORG 10172 in Acute Stroke Treatment [TOAST] classification).

secondary prevention remain a critical priority in the management of AIS.[25]

NC, a compound preparation derived from five herbal components including Pu Huang, Chi Shao, Yu Jin, Tian Ma, and Lou Lu, exerts significant neuroprotective effects in IS through a multicomponent, multitarget synergistic mechanism, primarily centered on the suppression of neuroinflammation.[14–16] The integration of its bioactive compounds—such as paeoniflorin, apigenin, and gastrodin—targets key inflammatory pathways in activated microglia, the primary immune cells in the brain.[26] Paeoniflorin downregulates proinflammatory cytokines, curbing microglial proliferation and neuroinflammatory responses. Apigenin operates via dual pathways, inhibiting inducible nitric oxide synthase and cyclooxygenase-2 to reduce nitric oxide and prostaglandin E2 (PGE2) production, while simultaneously suppressing p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) phosphorylation, thereby attenuating microglial overactivation.[27] Gastrodin further modulates the phosphatidylinositol 3-kinase/protein kinase (PI3K/AKT) signaling pathway, leading to decreased expression of critical inflammatory mediators like tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).[28] This coordinated suppression of the inflammatory cascade by NC's components plays a pivotal role in reversing vascular endothelial cell injury, preserving blood–brain barrier integrity, and protecting cerebral parenchyma. Beyond its core anti-inflammatory action, preclinical evidence highlights NC's multitargeted neuroprotective profile, which encompasses mitigating cerebral infarction, ameliorating neurological deficits, inhibiting neuronal apoptosis, reducing excitatory amino acid toxicity, and improving cerebral hemodynamics and metabolism.[15] Collectively, these synergistic mechanisms position NC as a comprehensive therapeutic strategy for IS, addressing the complex pathophysiology of the condition through a holistic pharmacological approach.

Several prior studies have explored the efficacy and safety of NC in patients with AIS. For example, a meta-analysis of 13 randomized controlled trials (RCTs) involving 1360 IS patients demonstrated that

Table 3

Definition of outcomes.

Term	Definition
Stroke	Sudden onset of focal or global brain, spinal cord, or retinal vascular injury, leading to acute neurological deficit symptoms and signs, related to cerebral circulatory disturbance.
IS	Acute focal cerebral or retinal infarction. Criteria: (1) Acute onset of new clinical signs of focal neurological deficit or imaging evidence lasting more than 24 h, excluding other nonischemic causes (such as cerebral infection, brain trauma, brain tumor, epileptic seizure, severe metabolic disease, degenerative neurological disease, and drug side effects); or (2) Acute cerebral or retinal ischemic event, excluding other nonischemic causes, with focal symptoms or signs lasting less than 24 h, but accompanied by imaging evidence of a new infarct; or (3) Progression of pre-existing vascular IS (i.e., an increase in NIHSS score of ≥ 4 points from the baseline IS, excluding hemorrhagic transformation after infarction or symptomatic intracranial hemorrhage) lasting more than 24 h, accompanied by new ischemic changes on head MRI or CT. Etiological classification will be performed according to TOAST criteria.
Hemorrhagic stroke	Hemorrhagic stroke is defined as acute focal or global neurological dysfunction of the brain or spinal cord caused by nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
Myocardial infarction	*Criteria for Acute Myocardial Infarction: Third Universal Definition* (Thygesen 2012) Acute MI should be diagnosed when there is evidence of myocardial necrosis consistent with acute myocardial ischemia. MI is diagnosed when any one of the following criteria is met: 1. Detection of a rise and/or fall of cardiac biomarkers (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL), and with at least one of the following: (1) Symptoms of myocardial ischemia; (2) New ischemic electrocardiogram (ECG) changes, i.e., new ST-T changes or new left bundle branch block (LBBB) (classified as acute ST-segment elevation MI [STEMI] and non-ST-segment elevation MI [NSTEMI] based on the presence or absence of ST-segment elevation); (3) Development of pathological Q waves on ECG; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; (5) Identification of an intracoronary thrombus by angiography or autopsy. 2. Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumed new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography or autopsy, where death occurs before blood samples could be obtained or before cardiac biomarkers could appear in the blood. 3. Percutaneous coronary intervention (PCI)-related MI is defined as: for patients with normal cTn baseline (≤ 99th percentile URL), cTn values increase (> 5 times the 99th percentile URL); or for patients with elevated, stable, or falling baseline values, cTn increases by > 20%. Additionally, at least one of the following must be present: (1) Symptoms suggestive of myocardial ischemia; (2) New ischemic changes on ECG; (3) Angiographic findings consistent with a procedural complication; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 4. Stent thrombosis-associated MI, identified by coronary angiography or autopsy, in patients with myocardial ischemic symptoms and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. 5. Coronary artery bypass grafting (CABG)-related MI is defined as: for patients with normal cTn baseline (≤ 99th percentile URL), cardiac biomarkers increase (> 10 times the 99th percentile URL). Additionally, at least one of the following must be present: (1) New pathological Q waves or new LBBB; (2) Angiographically documented new graft or native coronary artery occlusion; (3) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Vascular death	Vascular death includes death due to stroke, sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, pulmonary embolism, death related to cardiac/cerebrovascular procedures or surgery (unrelated to acute MI), and other cardiovascular causes of death (e.g., arrhythmias unrelated to sudden cardiac death, ruptured aortic aneurysm, or peripheral arterial disease). Any death from unknown/unclear causes occurring within 30 days of a stroke, myocardial infarction, or cardiac/cerebrovascular procedure/surgery will be attributed to death from that stroke, myocardial infarction, or procedure/surgery, respectively.
Adverse event	Any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject who is administered an investigational product and that does not necessarily have a causal relationship with this treatment
Severe adverse event	An event that occurs during the study and meets one of the following criteria: death or life-threatening

CT = computed tomography, MI = Myocardial Infarction, MRI = magnetic resonance imaging, NIHSS = National Institute of Health Stroke Scale, TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

NC was significantly associated with improved overall response rates, enhanced neurological function, elevated blood adiponectin levels, reduced neurological deficits, and decreased atherosclerotic plaque area.[17] Another meta-analysis encompassing 27 RCTs with 3319 patients indicated that NC could improve neurological function across different phases of IS, reduce the risk of cerebrovascular disease recurrence, and enhance quality of life during the acute period, suggesting a potential role for NC in the secondary prevention of IS.[18] Nevertheless, the methodological limitations and notable heterogeneity among the included trials in these meta-analyses underscore the need for further validation of NC's true therapeutic value through well-designed, standardized RCTs.

To our knowledge, the RESPACE trial represents the first and largest randomized controlled double-blind trial in TCM research targeting secondary stroke prevention among patients with high risk of recurrence. While the 90-day treatment duration and 180-day follow-up period were pragmatically designed due to time constraints, this landmark study innovatively investigated the potential therapeutic effects of NC in reducing vascular events.

4. Conclusion

In summary, the RESPACE trial will provide high-quality evidence of NC for the secondary prevention of IS among high-recurrence-risk patients with AIS within 72 h.

Acknowledgements

We thank all study participants, their relatives, and the members of the survey teams of the RESPACE study.

Ethical statement

Ethical approval was granted by the Research Ethics Committee of The First Affiliated Hospital of Henan University of Chinese Medicine (approval number: 2023HL-098-02; September 8, 2023), Zhengzhou, China and registered in the public clinical trial database, and was approved by the local institutional review boards of all participating sites. All patients or their legally authorized representatives will provide written informed consent before any study-specific procedure.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding source

This study is supported by the National Key Research and Development Program of the Ministry of Science and Technology (No.2022YFC3501103) and Guangzhou South China Pharmaceutical Group Co., Ltd. The design, management, analysis, and reporting of the study are entirely independent of the manufacturers.

Data availability statement

Data sharing is not applicable as no datasets were generated and/or analyzed for this article.

Author contributions

Conceptualization: Min Zhao. **Data curation:** Nan Qu, Dan Wang, Jie Zhang, Xiangzhe Liu, Yongkang Sun, Yuxin Zheng. **Formal analysis:** Xue Tian, Anxin Wang. **Methodology:** Ying Gao, Anxin Wang. **Supervision:** Min Zhao. **Manuscript:** Nan Qu, Xue Tian, Ying Gao, Anxin Wang, Min Zhao. **Co–corresponding:** Anxin Wang and Min Zhao.

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