Effect of Remote Ischemic Conditioning vs Usual Care on Neurological Function in Patients with Acute Moderate Ischemic Stroke: The RICAMIS Randomized Clinical Trial

Hui-Sheng Chen, MD; Yu Cui, MM; Xiao-Qiu Li, MD; Xin-Hong Wang, MD; Yu-Tong Ma, MM; Yong Zhao, BSM; Jing Han, MM; Chang-Qing Deng, MM; Mei Hong, BSM; Ying Bao, MM; Li-Hong Zhao, MM; Ting-Guang Yan, BSM; Ren-Lin Zou, BSM; Hui Wang, MM; Zhuo Li, MM; Li-Shu Wan, MM; Li Zhang, BSM; Lian-Qiang Wang, BSM; Li-Yan Guo, MM; Ming-Nan Li, BSM; Dong-Qing Wang, MM; Qiang Zhang, MM; Da-Wei Chang, MM; Hong-Li Zhang, BSM; Jing Sun, BSM; Chong Meng, BSM; Zai-Hui Zhang, BSM; Li-Ying Shen, BSM; Li Ma, MM; Gui-Chun Wang, BSM; Run-Hui Li, MM; Ling Zhang, BSM; Cheng Bi, MM; Li-Yun Wang, BSM; Duo-Lao Wang, PhD; on behalf of the RICAMIS Investigators

Author Affiliations: Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China (Prof HS Chen, Y Cui, XQ Li, XH Wang); Department of Neurology, Beipiao Central Hospital, Beipiao, China (YT Ma); Department of Neurology, Haicheng Chinese Medicine Hospital, Haicheng, China (Y Zhao); Department of Neurology, Panjin Central Hospital, Panjin, China (J Han, Z Li); Department of Neurology, Dandong Central Hospital, Dandong, China (CQ Deng, C Bi); Department of Neurology, China Railway 19th Bureau Group Central Hospital, Liaoyang, China (M Hong); Department of Neurology, Fuxin Second People's Hospital, Fuxin, China (Y Bao); Department of Neurology, Dandong People's Hospital, Dandong, China (LH Zhao); Department of Neurology, Chaoyang Central Hospital, Chaoyang, China (TG Yan); Department of Neurology, Wafangdian Third

Hospital, Dalian, China (RL Zou); Department of Neurology, Chinese People's Liberation Army 230 Hospital, Dandong, China (H Wang); Department of Neurology, Dandong First Hospital, Dandong, China (LS Wan); Department of Neurology, Suizhong County Hospital, Huludao, China (L Zhang); Department of Neurology, Liaoyang County Stroke Hospital, Liaoyang, China (LQ Wang); Department of Neurology, Fushun Second Hospital, Fushun, China (LY Guo); Department of Neurology, Huanren Manchu Autonomous County People's Hospital, Benxi, China (MN Li); Department of Neurology, Panjin People's Hospital, Panjin, China (DQ Wang); Department of Neurology, Fushun Central Hospital, Fushun, China (Q Zhang); Department of Neurology, Sujiatun Stroke Hospital, Shenyang, China (DW Chang); Department of Neurology, Taian County Chinese Medicine Hospital, Anshan, China (HL Zhang); Department of Neurology, Anshan Hospital, The First Affiliated Hospital of China Medical University, Anshan, China (J Sun); Department of Neurology, Liaoyang County Central Hospital, Liaoyang, China (C Meng); Department of Neurology, Xiuyan County Central Hospital, Anshan, China (ZH Zhang); Department of Neurology, Tieling County Central Hospital, Tieling, China (LY Shen); Department of Neurology, The Affiliated Central Hospital of Shenyang Medical College, Shenyang, China (L Ma, RH Li); Department of Neurology, Changtu County Central Hospital, Tieling, China (GC Wang); Department of Neurology, Dengta Central Hospital, Dengta, China (L Zhang); Department of Neurology, Liaoyang Petrochemical General Hospital, Liaoyang, China (LY Wang); Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK (Prof DL Wang).

Correspondence Author:

Prof Hui-Sheng Chen MD,

Department of Neurology,

General Hospital of Northern Theatre Command,

No.83 Wenhua Rd, Shenhe District,

Shenyang, 110016, China.

Email: chszh@aliyun.com.

Tel: +86-13352452086.

Date of revision: April 27th, 2022.

Word count: 3481.

Key Points

Question: Does remote ischemic conditioning improve neurological function in patients with acute moderate ischemic stroke?

Findings: In this randomized clinical trial that included 1893 participants with acute moderate ischemic stroke, excellent neurological function at 90 days in those randomized to remote ischemic conditioning compared with usual care occurred in 67.4% vs 62.0%, a difference that was statistically significant.

Meaning: Although remote ischemic conditioning was associated with better neurological function in patients with acute moderate ischemic stroke, this trial requires replication before concluding efficacy for this intervention.

Abstract

Importance Preclinical and clinical studies have suggested a neuroprotective effect of remote ischemic conditioning (RIC); however, robust evidence in patients with ischemic stroke was still lacking.

Objective To assess the efficacy of RIC for acute moderate ischemic stroke.

Design, Setting, and Participants The multicentre, open-label, blinded-endpoint, randomized, clinical trial including1893 patients with acute moderate ischemic stroke conducted at 55 hospitals in China from December 26, 2018, through April 19, 2021.

Interventions: Eligible patients were randomly assigned within 48 hours after symptom onset to receive treatment with RIC (5 cycles of cuff inflation for 5 minutes and deflation for 5 minutes to the bilateral upper limbs to 200 mmHg) for 10 to 14 days as an adjunct to guideline-based treatment (n=922) or only guideline-based treatment such as antiplatelet or anticoagulant, statin etc (n=971).

Main Outcomes and Measures: The primary endpoint was whether there was an excellent functional outcome at 90 days, defined as a modified Rankin Scale score 0 to 1. All the endpoints were assessed in a blinded manner and analysed on a full analysis set.

Results: Among 1893 eligible patients with acute moderate ischemic stroke who were randomized (mean age, 65; 606 [34.1%] women), 1776 (93.8%) completed the trial. The number with excellent functional outcome at 90 days was 582 (67.4%) in the RIC group and 566 (62.0%) in the control group. The RIC group showed a significant improvement in the odds of having an excellent functional outcome at 90 days over the control group (risk difference 5.4%, 95% confidence interval 1.0%-9.9%). The proportion of patients with any adverse events was 6.8% (59/863) in the RIC group and 5.6% (51/913) in the control group.

Conclusions and Relevance: The study provided some evidence that among adults with acute moderate

ischemic stroke, treatment with remote ischemic conditioning compared with usual care could increase the likelihood of excellent neurological function at 90 days. A further randomized clinical trial is needed to confirm the findings from this study.

Trial Registration: This trial is registered with ClinicalTrials.gov, number NCT03740971.

Introduction

Reperfusion therapies including intravenous thrombolysis and endovascular thrombectomy were recommended as the most effective strategy for acute ischemic stroke (AIS) by current guidelines.[1] About 37% of patients had a good prognosis through intravenous thrombolysis in 2012,[2] while about 46% of patients with large artery occlusion got a good outcome after endovascular therapy in 2016.[3] Nevertheless, only a small proportion of the population can be treated with reperfusion therapies due to the limited therapeutic window and technical requirements. Thus, an area of interest has been a hot topic to find new neuroprotective strategies to reduce the disability of AIS.[4-5]

When Murry et al. first discovered and reported the phenomenon of myocardial ischemic preconditioning,[6] it attracted much attention in the field of preclinical and clinical research.[7] In recent years, growing evidence has demonstrated the neuroprotective action of remote ischemic conditioning (RIC) in preclinical studies, through multiple mechanisms: reducing brain infarction and improving neurologic outcomes.[7-8] Translating into clinical practice, several studies have demonstrated the safety of RIC.[9–11] Although the preclinical evidence from animal studies raised the possibility of benefit and some beneficial effects have been observed in clinical trials, there was a lack of robust evidence for the neuroprotective effect of RIC in AIS patients due to small sample sizes, different RIC procedures, and heterogeneity of patients, with different extent of neurological deficits.[12-15] In this context, a multicentre, open-label, blinded-endpoint, randomized, clinical trial was designed to explore the efficacy of RIC with approximately two weeks' duration for acute moderate ischemic stroke within 48 hours from onset.

Methods

Study Design

Remote ischemic conditioning for acute moderate ischemic stroke (RICAMIS) was a multicentre, open-label, blinded-endpoint, randomized, clinical trial to assess the efficacy of two weeks' RIC in patients with acute moderate ischemic stroke within 48 hours from symptom onset. Details of the study design and rationale is available in Supplement 1, and the statistical analysis plan, in Supplement 2. The trial took place at 55 medical sites (Supplement 3 p 13) in China.

Participants

Eligible patients were adults aged 18 years or older with acute moderate ischemic stroke at the time of randomization (baseline National Institutes of Health Stroke Scale [NIHSS] scores 6 to 16; range 0–42, with higher scores indicating greater stroke severity), who had been functioning independently in the community (modified Rankin Scale [mRS] scores 0 to 1; range 0 [no symptoms] to 6 [death]) before the stroke, and were enrolled up to 48 hours after onset of stroke symptoms (the time the patient was last seen well). Whole head computed tomography or magnetic resonance imaging were done at admission to identify patients with ischemic stroke. Key exclusion criteria were that a patient who received intravenous thrombolysis and/or other endovascular therapy; had an uncontrolled severe hypertension (systolic blood pressure $\geqslant$ 180 mmHg or diastolic blood pressure $\geqslant$ 110 mmHg after agent treatment); had any contraindication for RIC (e.g., upper limb with serious soft tissue injury, fracture or vascular injury, distal upper limb with perivascular lesions.); or had etiology of cardiogenic embolism (e.g., atrial fibrillation) given the high risk of intracranial hemorrhage transformation. A full list of inclusion and exclusion criteria is available from the study protocol in Supplement 1.

The trial protocol was approved by appropriate regulatory and ethical authorities at the ethics committee

of General Hospital of Northern Theatre Command (former General Hospital of Shenyang Military Region) and other participating hospitals. Signed informed consents were obtained from the patients or their legally authorized representative.

Randomization and Masking

In the trial eligible patients were randomly assigned into the RIC group or control group using a simple randomization (1:1) method without stratification through a computer-generated random sequence that was centrally administrated via a password-protected, web-based program at http://ricamis.medsci.cn (Shanghai Meisi Medical Technology Co., Ltd). The study team member was unmasked to the treatment allocation.

Procedures

The cuff of a pneumatic electronic auto-control device (Patent Number: ZL201410834305·2; Device Model: IPC-906; Beijing Renqiao Cardiocerebrovascular Disease Prevention and Treatment Research Jiangsu Co., Ltd), placed around the bilateral upper limbs within 48 hours of symptom onset, was used to deliver the RIC protocol: 5 cycles of cuff inflation (200 mmHg for 5 minutes) and deflation (for 5 minutes), for a total procedure time of 50 minutes, twice daily for 10-14 days. After the blood pressure inflation target was set in the device by a trained nurse, the electronic tourniquet automatically delivered the cycles. In the RIC group, the patients received RIC treatment, in addition to guideline-recommended treatment (such as antiplatelet or anticoagulant, statin etc).[1] In the control group, patients only received guideline-recommended treatment. All the patients completed the RIC treatment in hospital.

Blood pressure was recorded before cuff inflation and at the end of 5 cycles of cuff inflation. In each

hospital the physicians and nurses involved in the clinical trial were trained by the local principal investigator to place the cuff in the middle of the bilateral upper limbs and to enter the target blood pressure into the electronic tourniquet. The completion criteria of RIC in the trial was defined as 80%-120% completion of a 10-14 days RIC treatment program. Patients in both groups received standard care at the discretion of the local investigator at each participating hospital and according to guidelines.

Neurological status, measured with NIHSS, was assessed at baseline, 7 days and 12 days after randomization. A detailed flowchart of the assessment schedule was given in the study protocol.[16] Information on demographic and clinical characteristics was obtained at randomization. Follow-up data were collected at 7 days, 12 days (or at hospital discharge if earlier), and 90 days after randomization. Remote and on-site quality control monitoring and data verification were done throughout the study.

Outcomes

The primary endpoint was whether there was excellent functional outcome at 90 days, defined as a score of 0–1 on the mRS for the evaluation of neurological disability assessed in person or, if an in-person visit was not possible, by personnel certified in the scoring of the mRS at 90 days after randomization through a structured interview for telephone assessment (Supplement 3 p 15).

The secondary endpoints were the favourable functional outcome (mRS scores 0–2) at 90 days; a shift in measures of functioning according to the full range of scores on the mRS at 90 days; occurrence of early neurological deterioration (END), compared with baseline at 7 days, defined as more than 2 NIHSS scores increase, but not result of cerebral hemorrhage (Supplement 3 p 15); occurrence of stroke-associated pneumonia at 12 days (Supplement 3 p 15); change in NIHSS score compared with baseline at 12 days; occurrence of stroke or other vascular events at 90 days; and time from randomization to the

occurrence of death due to any cause within 90 days.

Any adverse events that occurred in the course of the study were recorded. The RIC related adverse events included arm pain assessed by visual scale, redness or swelling of arms, skin petechiae on arms, palpitation, intracerebral hemorrhage, and dizziness which was not present at the beginning of the study. Whether the unexpected adverse event was associated with the RIC treatment were further adjudicated by principal investigator (HSC).

Baseline and follow-up NIHSS scores were evaluated by the same neurologist who was not blinded to treatment allocation. Final follow-up was done at 90 days, in person or by telephone, by one trained and certified staff in each centre who were unaware of the randomized treatment assignment (Supplement 3 p 5-12). To ensure validity and reproducibility of the evaluation, we held a training course for all investigators at each centre. Central adjudication of clinical outcomes and adverse events were also done by assessors unaware of treatment allocation or clinical details. In this trial, the central adjudicator seldom disagreed with the site assessor, which should attribute to the standard training of a structured interview assessment in each site.

Sample Size Calculation

Power calculations were based on the estimated treatment effects on a conventional binary assessment of excellent functional outcome at 90 days. In the European Cooperative Acute Stroke Study III (ECASS III), alteplase administered 3.0–4.5 h after the onset of stroke symptoms resulted in a 7.2% benefit in the primary endpoint (mRS score 0–1) versus placebo,[17] therefore 7% was chosen as the minimal detectable difference used to power the current study. Assuming proportions with excellent functional outcome of 47% in the RIC group and 40% in the control group (equivalent to odds ratio [OR] = 1.18), a sample size

of 1568 (784 per group) was estimated to provide more than 80% power (using a two-sided $\alpha = 0.05$) to detect the 7-percentage point greater excellent functional outcome in the RIC group. In consideration of 10% lost to follow-up, the total sample size was 1742. Therefore, this study finally planned to include 1800 participants (900 per group). No interim analysis was performed in this study.

Statistical Analysis

Primary analyses were performed on full analysis set, which included all randomized subjects with at least one post-baseline efficacy evaluation. We performed binary logistic regression analyses of the primary outcome and secondary outcomes of favourable functional outcome at 90 days, occurrence of early neurological deterioration and stroke-associated pneumonia. The treatment effects for the above outcomes were presented as OR with 95% confidence interval (CI). In addition, risk ratio and risk difference with 95% CIs were calculated for the binary outcomes using generalized linear model. Missing values in the primary outcome were imputed using the last observation carried forward method, worst-case scenario and best-case scenario approaches in the sensitivity analyses.

The score of mRS at 90 days was compared using ordinal logistic regression and odds ratio with 95% CI was calculated. Change in NIHSS score between admission and at 12 days was compared using a generalized linear model and the mean difference between RIC and Control with its 95% CI was derived. Time-to-event outcomes of stroke, other vascular events, and death of any cause, which were experienced by the two groups up to 90 days after randomization, were compared using Cox regression models, and the corresponding treatment effects were presented as hazard ratio (HR) with 95% CI. The assumption of proportionality was tested by adding an interaction between time and treatment in the Cox model.

The primary analyses for primary and secondary outcomes were unadjusted. We also did covariate adjusted analyses of all outcomes adjusting for six pre-specified prognostic factors: age, sex, premorbid function [mRS core 0 or 1], NIHSS score at randomization, history of stroke or transient ischemic attack [TIA], and time from the onset of symptom to RIC. The missing values of baseline variables in covariate adjusted analyses were imputed by mean for continuous variables and mode for categorical variables.

Subgroup analysis of primary outcome was performed on eight prespecified subgroups (age [<65 years or ≥65 years], sex [female or male], NIHSS score at randomization [6-10 or 11-16], time from the onset of symptom to RIC [<24 hours or ≥24 hours], degree of responsible vessel stenosis [mild, moderate, or severe], location of stenosis [anterior circulation stroke, posterior circulation stroke, or anterior and posterior circulation stroke], and stroke etiology [large-artery atherosclerosis, cardioembolic, small-artery occlusion, other determined cause, and undetermined cause]). Assessment of the homogeneity of treatment effect by a subgroup variable was conducted by a logistic regression model with the treatment, subgroup variable, and their interaction term as predictors, and the P value presented for the interaction term.

In addition, we did per-protocol analyses of primary and secondary outcomes restricted to patients who received the complete intervention as specified in the protocol. A two-sided P value of less than 0.05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. An Independent data monitoring committee monitored progress of the trial every 6 months. SPSS software version 23 and R software version 4.1.0 were used for statistical analyses.

Results

Trial Population

Between December 26, 2018, and April 19, 2021, 1893 patients were enrolled and randomly assigned into the RIC group (922 patients) or control group (971 patients). A total of 1[17] (5.9%) patients were excluded (65 patients withdrew due to clinical decision, 16 withdrew consent due to patients' decision, 18 had other reasons, 10 received duplicate randomization, and 8 lost to follow-up). Finally, 1776 patients (863 in the RIC group and 913 in the control group) were included in the full analysis set (Figure 1). The procedure was completed according to protocol for 1707 patients (808 in the RIC group and 899 in the control group), and the results were included in the per-protocol analysis. Reasons for incomplete procedure are provided in Figure 1. The trial has been enrolled to completion in May 2021.

The treatment groups were well balanced with respect to patient baseline characteristic in the full analysis set (Table 1) and per-protocol analysis (Supplement 3 p 20-21). In the RIC group, 808 of 863 patients (93.6%) underwent the complete procedure of 8 to 16 days of RIC treatment at a mean of 24.8 hours from symptom onset to the first cuff inflation. Of the remaining 55 patients, 46 received 1 day of RIC treatment, 1 received 5 days, 1 received 6 days, and 7 received 7 days.

Primary Outcome

For the primary outcome, the proportion with mRS score 0 to 1 at 90 days was 67.4% (582/863) in the RIC group and 62.0% (566/913) in the control group, yielding a risk difference 5.4% (95% CI 1.0%-9.9%; P = 0.02) and a risk ratio 1.17 (95% CI 1.03-1.32; P = 0.02) (Table 2). The odds of having an excellent outcome were significantly higher in the RIC group than in the control group (unadjusted OR 1.27; 95% CI 1.05-1.54; P = 0.02; Table 2, Figure 2) in the full analysis set. Similar results in odds ratio were observed in three sensitivity analyses of primary outcome (Last observation carried forward, worst-

case scenario and best-case scenario. See Supplement 3 p 22). The significant difference in odds of having a primary outcome remained after adjustment for prespecified prognostic variables (OR 1.41; 95% CI 1.14-1.74; P = 0.002; Table 2). Similar results were also obtained in the per-protocol analysis (unadjusted OR 1.32; 95% CI 1.08-1.62; P = 0.007; adjusted OR 1.45; 95% CI 1.17-1.81; P = 0.001; Supplement 3 p 17, 23).

Secondary Outcomes

For the secondary outcomes, full analysis set showed that significant differences in the odds of having an mRS score 0 to 2 and mRS improvement at 90 days were observed in both unadjusted and adjusted analysis (Table 2 and Figure 2). However, no significant differences were observed in the other secondary outcomes in both unadjusted and adjusted full analysis set, including early neurological deterioration within 7 days, stroke-associated pneumonia within 12 days, change in NIHSS score compared with randomization at 12 days, stroke or other vascular events within 90 days, and death from any cause within 90 days (Table 2). In the per-protocol analysis, significant differences in odds of having a mRS score 0 to 2 and mRS improvement within 90 days were also found between groups in both unadjusted and adjusted analysis, while no significant differences were evident in the other secondary outcomes in both unadjusted and adjusted analysis (Supplement 3 p 23-24).

Prespecified subgroup analysis showed no evidence of significant differences in the odds of having a primary outcome between the RIC group and control group by age, sex, NIHSS score at randomization, time from the onset of symptom to RIC treatment, degree of responsible vessel stenosis, location of stenosis, and presumed stroke cause (Supplement 3 p 18). The results of the per-protocol analysis were very similar to those of the full analysis set for the primary outcome (Supplement 3 p 19).

Adverse Events

Adverse events occurred to 59/863 [6.8%] in the RIC group and 51/913 [5.6%] in the control group, including 23 serious adverse events (10/863 [1.2%] in the RIC group and 13/913 [1.4%] in the control group) (Table 3). The results in the per-protocol analysis were shown in Supplement 3 p 25. With respect to the RIC related adverse events in the RIC group, 6 patients experienced adverse events, including 3 patients with redness or swelling in arms, 2 with skin petechiae on arms, and 1 with dizziness.

Discussion

The current study found treatment with RIC performed twice daily for two weeks, applied as an adjunct to guideline-based treatment, could improve excellent functional outcome at 90 days in acute moderate ischemic stroke after symptom onset, when compared with current guideline-recommended treatment.

Many studies have investigated the effect of RIC on ischemic stroke, but there was a lack of strong evidence for the neuroprotective effect of RIC. For the first time, the current study provided some evidence in acute moderate ischemic stroke. There were several obvious differences between this study and previous studies. First, in this study, the target population was acute moderate ischemic stroke within 48 hours, while the specific population was less targeted in the previous studies.[11,13,18-19] The present study argue that targeted stroke patients should be most likely to benefit from neuroprotective therapy,[5] because the neuroprotective effect could be underestimated in patients with mild neurological deficit, while in patients with severe neurological deficit this was mostly due to large artery occlusion and would not be improved by neuroprotective treatment without the help of reperfusion treatment. Second, previous studies had relatively small sample sizes ranging from 20 to 188.[9-11,20-25] To date, the present

study including 1776 participants was the largest randomized clinical trial ever undertaken of RIC treatment in acute ischemic stroke. Third, there were differences in RIC treatment procedures between previous studies and this study. Compared with previous studies (4 cycles of 5 min ischemic and 5 min reperfusion during transportation to hospital),[11] 5 cycles of 5 min ischemic and 5 min reperfusion to bilateral upper limbs, twice daily for two weeks were used in the study, suggesting that longer duration of RIC may exert more neuroprotective effect. The RCI paradigm was supported by two recent studies,[12,18] in which RIC treatment twice daily for two weeks or until discharge with an average duration of 11.2 days was found to be neuroprotective. Additionally, longer duration of RIC treatment (more than 300 days) was also proven to be effective for secondary stroke prevention.[13,26] Finally, binary excellent functional outcome at 90 days was used as the primary outcome in the present study, while surrogate outcomes such as the penumbral salvage and reduction in infarction volume were mainly assessed in the previous studies.[10-11,18,24] Collectively, the positive effect of RIC on AIS should be attributed to the specifically targeted population (moderate neurological deficits, median NIHSS score 7 [6-9]), the larger sample size (1776 participants), and the longer duration of RIC (10 to 14 days vs 1 day).

The present study did not find the effect of RIC on early neurological improvement such as early neurological deterioration at 7 days and change in NIHSS score compared with randomization at 12 days. The absence of significant effect on early outcome vs the positive effect on long-term outcome of RIC in the current study may provide a possible explanation for previous negative results, which mainly focused on the early outcomes. [10,21-22] Furthermore, the present study also found no significant differences between groups in the other secondary outcomes, including stroke-associated pneumonia within 12 days, stroke or other vascular events within 90 days, and death within 90 days. In the current study, the average onset to RIC treatment initiation time (around 24 hours) was longer than the time window of acute

ischemic brain injury (mostly in the first 6 hours after stroke onset). The results suggested that the mechanism of RIC may be more "recovery" effect than neuroprotection, namely, the effect of RIC on 90-day outcome may not be attributed to rescue ischemic penumbra as investigated in most previous studies,[10-11,18,24] but possibly to chronic RIC-induced neurorestorative effect such as angioneurogenesis and neuroplasticity of peri-infarct area.[27-28] The explanation was also supported by one animal study that very delayed RIC (5 days after stroke, repeated for 14 consecutive days) did not yield reduction of infarct volume, but produced neurological improvement at least for 3 months.[29] The underlying mechanism of RIC in this study warranted to be investigated in the future. Also, the future studies should examine additional biomarkers as intermediary outcomes to demonstrate the effect of early vs late RIC in stroke. In addition, the present study also did not observe the effect on recurrence of stroke, which has been reported in previous studies.[13,26] The discrepancy may be due to the difference in RIC duration (300 days vs 14 days).

There was no unexpected RIC-related adverse event in the RIC group, which was consistent with those described in the previous studies, such as redness and skin petechiae on arms.[10,12,18,21,23,30]

The key strength of this randomized clinical trial was its large sample size and multicentre recruitment, which enhanced the generalisability of the results and the possibility of influencing clinical practice nationwide. The present study used robust methodologies to ensure masking during assessment of the key efficacy outcomes.

Limitation

This study had several potential limitations. First, the present study did not mask the assigned treatment to participants and physicians due to the open-label design. However, blinded-endpoint assessments were

used to reduce observer's bias and ensure that the primary and secondary outcomes were measured objectively. In addition, the assessment of the success of outcome blinding was not performed. Second, there may be outcome measurement bias in the full analysis set and selection bias in the exclusion after randomization. Furthermore, the relatively large amount of dropout after randomization may introduce the attrition bias although a similar rate of dropout in RIC vs control group (59/922 (6.4%) vs 58/971 (6.0%), P =0.70). Third, it is regretful that we did not collect the data regarding physiotherapy and speech language therapy in the study. Given their effects on the clinical outcome, the lack of the above data may introduce the possible confounding, although randomization may have balanced their distributions between two arms. Fourth, further confirmation of these conclusions in non-Chinese populations would be needed, given the differences in the body mass, co-morbid factors and patterns of cerebrovascular disease of AIS patients compared with other populations.

Conclusions

The study provided some evidence that among adults with acute moderate ischemic stroke, treatment with remote ischemic conditioning compared with usual care could increase the likelihood of excellent neurological function at 90 days. A further randomized clinical trial is needed to confirm the findings from this study.

Author Contributions

HSC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: HSC.

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

Drafting of the manuscript: All authors.

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

Statistical analysis: YC and DLW.

Administrative, technical, or material support: All authors.

Supervision: HSC.

Conflict of Interest Disclosures

We declared no competing interests.

Funding/Support:

The study was funded by grants 2018225023, 2019JH2/10300027 from the Science and Technology Project Plan of Liao Ning Province and 20-205-4-007 from the Science and Technology Project Plan of ShenYang ().

Role of the Funder/Sponsor:

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the

manuscript for publication.

Group Information:

The RICAMIS Trial members are listed in Supplement 3 and Supplement 4.

Data Sharing Statement

See Supplement 5.

Acknowledgments

We thank the investigators and research staff (Supplement 3 p 5-12) at the participating sites, members of the trial steering and data monitoring committees (Supplement 3 p 4). We also thank the participants, and their families and friends.

REFERENCES

1 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12): e344-e418.

2 IST-3 collaborative group, Sandercock P, Wardlaw JM, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379(9834):2352-2363.

3 Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731.

4 Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke. *Lancet*. 2018;392(10154):1247-1256.

5 Savitz SI, Baron JC, Fisher M; STAIR X Consortium. Stroke Treatment Academic Industry Roundtable X: Brain Cytoprotection Therapies in the Reperfusion Era. *Stroke*. 2019;50(4):1026–1031.

6 Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124-1136.

7 Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning-a new paradigm of self-protection in the brain. *Nat Rev Neurol*. 2015;11(12):698-710.

8 Weir P, Maguire R, O'Sullivan SE, England TJ. A meta-analysis of remote ischaemic conditioning

in experimental stroke. *J Cereb Blood Flow Metab*. 2021;41(1):3-13.

9 England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning After Stroke Trial): A Pilot Randomized Placebo Controlled Phase II Trial in Acute Ischemic Stroke. *Stroke*. 2017;48(5):1412-1415.

10 Pico F, Lapergue B, Ferrigno M, et al. Effect of In-Hospital Remote Ischemic Perconditioning on Brain Infarction Growth and Clinical Outcomes in Patients With Acute Ischemic Stroke: The RESCUE BRAIN Randomized Clinical Trial. *JAMA Neurol*. 2020;77(6):725-734.

11 Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke*. 2014;45(1):159-167.

12 Zhao W, Meng R, Ma C, et al. Safety and Efficacy of Remote Ischemic Preconditioning in Patients With Severe Carotid Artery Stenosis Before Carotid Artery Stenting: A Proof-of-Concept, Randomized Controlled Trial. *Circulation*. 2017;135(14):1325-1335.

13 Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology*. 2012;79(18):1853-1861.

14 Landman TRJ, Schoon Y, Warlé MC, de Leeuw FE, Thijssen DHJ. Remote Ischemic Conditioning as an Additional Treatment for Acute Ischemic Stroke. *Stroke*. 2019;50(7):1934-1939.

15 Zhao W, Li S, Ren C, Meng R, Jin K, Ji X. Remote ischemic conditioning for stroke: clinical data, challenges, and future directions. *Ann Clin Transl Neurol*. 2018;6(1):186-196.

16 Li XQ, Tao L, Zhou ZH, Cui Y, Chen HS; RICAMIS Protocol Steering Group. Remote ischemic conditioning for acute moderate ischemic stroke (RICAMIS): Rationale and design. *Int J Stroke*. 2020;15(4):454-460.

17 Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with

alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.

18 An JQ, Cheng YW, Guo YC, et al. Safety and efficacy of remote ischemic postconditioning after thrombolysis in patients with stroke. *Neurology*. 2020;95(24): e3355-e3363.

19 Wang Y, Meng R, Song H, et al. Remote Ischemic Conditioning May Improve Outcomes of Patients With Cerebral Small-Vessel Disease. *Stroke*. 2017;48(11):3064-3072.

20 Meng R, Ding Y, Asmaro K, et al. Ischemic Conditioning Is Safe and Effective for Octo- and Nonagenarians in Stroke Prevention and Treatment. *Neurotherapeutics*. 2015;12(3):667-677.

21 Che R, Zhao W, Ma Q, et al. rt-PA with remote ischemic postconditioning for acute ischemic stroke. *Ann Clin Transl Neurol*. 2019;6(2):364-372.

22 He YD, Guo ZN, Qin C, et al. Remote ischemic conditioning combined with intravenous thrombolysis for acute ischemic stroke. *Ann Clin Transl Neurol*. 2020;7(6):972-979.

23 Zhao W, Che R, Li S, et al. Remote ischemic conditioning for acute stroke patients treated with thrombectomy. *Ann Clin Transl Neurol*. 2018;5(7):850-856.

24 Poalelungi A, Tulbă D, Turiac E, Stoian D, Popescu BO. Remote Ischemic Conditioning May Improve Disability and Cognition After Acute Ischemic Stroke: A Pilot Randomized Clinical Trial [published online August 30, 2021]. *Front Neurol*. doi: 10.3389/fneur.2021.663400.

25 England TJ, Hedstrom A, O'Sullivan SE, et al. Remote Ischemic Conditioning After Stroke Trial 2: A Phase IIb Randomized Controlled Trial in Hyperacute Stroke. *J Am Heart Assoc*. 2019;8(23): e013572.

26 Hou C, Duan J, Luo Y, et al. Remote limb ischemic conditioning treatment for intracranial atherosclerotic stenosis patients. *Int J Stroke*. 2016;11(7):831-838.

27 Khan MB, Hafez S, Hoda MN, et al. Chronic Remote Ischemic Conditioning Is Cerebroprotective

and Induces Vascular Remodeling in a VCID Model. *Transl Stroke Res*. 2018;9(1):51-63.

28 Ren C, Li S, Wang B, et al. Limb remote ischemic conditioning increases Notch signaling activity and promotes arteriogenesis in the ischemic rat brain. *Behav Brain Res*. 2018; 340: 87-93.

29 Doeppner TR, Zechmeister B, Kaltwasser B, et al. Very Delayed Remote Ischemic Post-conditioning Induces Sustained Neurological Recovery by Mechanisms Involving Enhanced Angioneurogenesis and Peripheral Immunosuppression Reversal. Front Cell Neurosci. 2018;12:383.

30 Li YJ, Liang KK, Zhang L, Pan R, Hu YM, Zhao JH. Remote Ischemic Post-Conditioning may Improve Post-Stroke Cognitive Impairment: A Pilot Single Center Randomized Controlled Trial. *J Stroke Cerebrovasc Dis*. 2020;29(11):105217.

Figure Legends

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

RICAMIS indicates Remote Ischemic Conditioning for Acute Moderate Ischemic Stroke.

Figure 2 Distribution of Modified Rankin Scale Scores at 90 Days in the Full Analysis Set

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

The Odds ratio (95% confidence) was 1.29 (1.09-1.52), and the P value was 0.003; the adjusted odds ratio (95% confidence) was 1.37 (1.16-1.63), and the adjusted P value was <0.001.

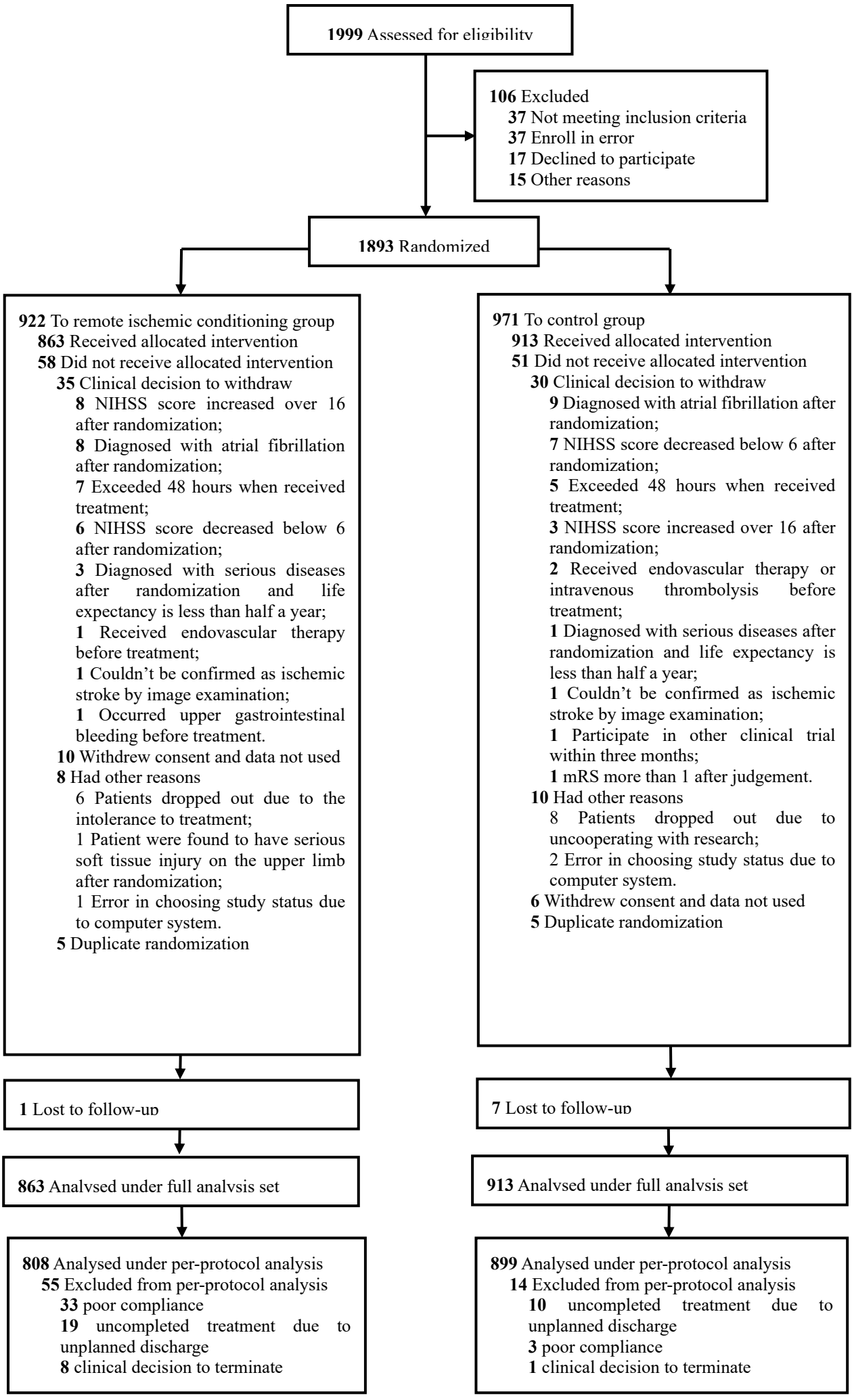

1999 Assessed for eligibility
106 Excluded
37 Not meeting inclusion criteria
37 Enroll in error
17 Declined to participate
15 Other reasons
1893 Randomized
922 To remote ischemic conditioning group
863 Received allocated intervention
58 Did not receive allocated intervention
35 Clinical decision to withdraw
8 NIHSS score increased over 16 after randomization;
8 Diagnosed with atrial fibrillation after randomization;
7 Exceeded 48 hours when received treatment;
6 NIHSS score decreased below 6 after randomization;
3 Diagnosed with serious diseases after randomization and life expectancy is less than half a year;
1 Received endovascular therapy before treatment;
1 Couldn't be confirmed as ischemic stroke by image examination;
1 Occurred upper gastrointestinal bleeding before treatment.
10 Withdrew consent and data not used
8 Had other reasons
6 Patients dropped out due to the intolerance to treatment;
1 Patient were found to have serious soft tissue injury on the upper limb after randomization;
1 Error in choosing study status due to computer system.
5 Duplicate randomization
971 To control group
913 Received allocated intervention
51 Did not receive allocated intervention
30 Clinical decision to withdraw
9 Diagnosed with atrial fibrillation after randomization;
7 NIHSS score decreased below 6 after randomization;
5 Exceeded 48 hours when received treatment;
3 NIHSS score increased over 16 after randomization;
2 Received endovascular therapy or intravenous thrombolysis before treatment;
1 Diagnosed with serious diseases after randomization and life expectancy is less than half a year;
1 Couldn't be confirmed as ischemic stroke by image examination;
1 Participate in other clinical trial within three months;
1 mRS more than 1 after judgement.
10 Had other reasons
8 Patients dropped out due to uncooperating with research;
2 Error in choosing study status due to computer system.
6 Withdrew consent and data not used
5 Duplicate randomization
1 Lost to follow-up
7 Lost to follow-up
863 Analysed under full analysis set
913 Analysed under full analysis set
808 Analysed under per-protocol analysis
55 Excluded from per-protocol analysis
33 poor compliance
19 uncompleted treatment due to unplanned discharge
8 clinical decision to terminate
899 Analysed under per-protocol analysis
14 Excluded from per-protocol analysis
10 uncompleted treatment due to unplanned discharge
3 poor compliance
1 clinical decision to terminate

Table 1. Baseline Characteristics and Procedural Details in the Full Analysis Set

	Remote ischemic conditioning group (n=863)	**Control group (n=913)**
Baseline characteristics		
Age, mean (SD), years	65.3 (10.5)	65.3 (10.1)
Sex		
Male, No. (%)	556/863 (64.4)	614/913 (67.3%)
Female, No. (%)	307/863 (35.6%)	299/913 (32.7%)
Body-mass index, mean (SD), kg/m^2	24.3 (3.0)	24.3 (2.9)
Current smoker, No. (%)	259/839 (30.9%)	246/878 (28.0%)
Current drinker, No. (%) [a]	137/848 (16.2%)	103/887 (11.6%)
Comorbidities, No. (%)		
Hypertension	531/852 (62.3%)	552/901 (61.3%)
Previous ischemic or hemorrhagic stroke	280/858 (32.6%)	289/907 (31.9%)
Diabetes	208/862 (24.1%)	223/908 (24.6%)
Hyperlipidaemia	15/846 (1.8%)	9/898 (1.0%)
Previous TIA	11/861 (1.3%)	11/911 (1.2%)
Time from the onset of symptom to remote ischemic conditioning treatment, mean (SD), hours	24·8 (13.2)	25·0 (13.7)
Time to hospital discharge, mean (SD), days	11.4 (2.4)	11.5 (1.9)
Blood pressure at randomisation, mean (SD), mm Hg		
Systolic	151.3 (18.7)	151.8 (18.8)
No. of patients	569	610
Diastolic	88.6 (11.2)	88.9 (11.4)
No. of patients	478	524
Blood glucose, mean (SD), mg/dL	133.2 (55.8)	135 (59.4)
No. of patients	372	433
NIHSS score at randomisation, median (IQR) [b]	7 (6-9)	7 (6-9)
Estimated premorbid function (mRS), No. (%)		
No symptoms (score 0)	647/863 (75.0%)	685/913 (75.0%)
Symptoms without any disability (score 1)	216/863 (25.0%)	228/913 (25.0%)
Location of responsible vessel stenosis, No. (%) [c]		
Anterior circulation stroke	294/484 (60.7%)	348/551 (63.1%)
Posterior circulation stroke	180/484 (37.2%)	191/551 (34.7%)
Anterior and posterior circulation stroke	10/484 (2.1%)	12/551 (2.2%)
Degree of responsible vessel stenosis, No. (%) [c]		
Mild (< 50%)	195/484 (40.3%)	207/551 (37.6%)
Moderate (50%-69%)	189/484 (39.0%)	236/551 (42.8%)
Severe (70%-99%) or occlusion	100/484 (20.7%)	108/551 (19.6%)
Presumed stroke cause, No. (%) [c]		
Undetermined cause	486/862 (56.3%)	443/911 (48.6%)
Large-artery atherosclerosis	229/862 (26.6%)	287/911 (31.5%)

Intracranial atherosclerosis	204/862 (23.7%)	254/911 (27.9%)
Small-artery occlusion	123/862 (14.3%)	161/911 (17.7%)
Other determined cause	14/862 (1.6%)	8/911 (0.9%)
Cardioembolic	10/862 (1.2%)	12/911 (1.3%)
Procedural details		
Days of complete cycles of Remote ischemic conditioning, No. (%) [d]		
<8	55/863 (6.4%)	NA
8	9/863 (1.0%)	NA
9	124/863 (14.4%)	NA
10	212/863 (24.6%)	NA
11	190/863 (22.0%)	NA
12	135/863 (15.6%)	NA
13	87/863 (10.1%)	NA
14	49/863 (5.7%)	NA
15	1/863 (0.1%)	NA
16	1/863 (0.1%)	NA

Abbreviations: IQR = inter-quartile range. NA = not applicable. NIHSS = National Institute of Health Stroke Scale. mRS = modified Rankin scale. SD = standard deviation.

[a] Current drinker means consuming alcohol at least once a week within one year before onset of the disease, and consuming alcohol continuously for more than one year.

[b] Patients with NIHSS scores 6 to 16 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[c] Diagnosis according to the clinician's interpretation of clinical features and results of investigators at the time of discharge from hospital; the presumed stroke cause was classified according to the "Trial of Org 10172 in Acute Stroke Treatment (TOAST)" classification system.

[d] The complete cycles was defined as that patients continually finished remote ischemic conditioning treatment twice daily.

Table 2. Primary and Secondary Outcomes in the Full Analysis Set.

	Remote ischemic conditioning group (n=863)	Control group (n=913)	Treatment metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	p value	Treatment Difference (95% CI)	p value
Primary outcome							
mRS [b] score 0-1 within 90 days, No. (%)	582/863 (67.4%)	566/913 (62.0%)	OR	1.27 (1.05-1.54)	0.02	1.41 (1.14-1.74)	0.002
			RR [c]	1.17 (1.03-1.32)	0.02	1.18 (1.04-1.34)	0.007
			RD [c]	5.4% (1.0%-9.9%)	0.02	6.2% (2.0%-10.4%)	0.004
Secondary outcomes							
mRS [b] score 0-2 within 90 days, No. (%)	687/863 (79.6%)	689/913 (75.5%)	OR	1.27 (1.01-1.59)	0.04	1.42 (1.11-1.81)	0.005
			RR [c]	1.20 (1.01-1.43)	0.04	1.22 (1.03-1.45)	0.02
			RD [c]	4.1% (0.3%-8.0%)	0.04	4.3% (0.9%-7.8%)	0.01
Early neurological deterioration within 7 days, No. (%) [d]	77/863 (8.9%)	64/913 (7.0%)	OR	1.30 (0.92-1.84)	0.14	1.29 (0.91-1.82)	0.16
			RR [c]	1.27 (0.93-1.75)	0.14	1.26 (0.91-1.73)	0.16
			RD [c]	1.9% (-0.6%-4.4%)	0.14	1.8% (-0.8%-4.3%)	0.17
Stroke-associated pneumonia within 12 days, No. (%) [e]	26/863 (3.0%)	19/913 (2.1%)	OR	1.46 (0.80-2.66)	0.21	1.42 (0.78-2.61)	0.25
			RR [c]	1.45 (0.81-2.60)	0.21	1.48 (0.82-2.65)	0.19
			RD [c]	0.9% (-0.5%-2.4%)	0.21	1.0% (-0.4%-2.5%)	0.17
Change in NIHSS [f] score at day 12 from baseline, median (IQR) [g]	4 (2-6)	4 (2-5)	Mean difference	1.18 (0.80-1.73)	0.40	1.19 (0.81-1.74)	0.37
Stroke or other vascular events within 90 days, No. (%) [h]	7/863 (0.8%)	6/913 (0.7%)	HR	1.24 (0.42-3.68)	0.70	1.21 (0.40-3.61)	0.74
Death within 90 days, No. (%) [h]	7/863 (0.8%)	10/913 (1.1%)	HR	0.74 (0.28-1.94)	0.54	0.63 (0.24-1.70)	0.37

Treatment effect is presented as OR or RR or RD or HR or mean difference (95% CI) of Remote ischemic conditioning versus control group, analyzed by unadjusted and adjusted binary logistic regression.

Abbreviations: OR = odds ratio. RR = risk ratio. RD = risk difference. HR= hazard ratio. CI = confidence interval. mRS = modified Rankin scale. NIHSS = National Institute of Health Stroke Scale. IQR = inter-quartile range.

[a] Adjusted for key prognostic covariates (age; sex; premorbid function [mRS score 0 or 1]; NIHSS score at randomization; history of stroke or TIA; and time from the onset of symptom to Remote ischemic conditioning time).

[b] mRS scores range from 0 to 6: 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death.

[c] Calculated with generalized linear model.

[d] Early neurological deterioration was defined as an increase between baseline and 7 days of ≥ 2 on the NIHSS score, but not result of cerebral hemorrhage (Supplement 3 p 15).

[e] Stroke-associated pneumonia was defined according to the recommendation from the pneumonia in stroke consensus group (Supplement 3 p 15).

[f] NIHSS scores range 0–42, with higher scores indicating greater stroke severity.

[g] Calculated with general linear model.

[h] Calculated with Cox regression model.

Table 3. Adverse Events in the Full Analysis Set.

	Remote ischemic conditioning group (n=863)	**Control group (n=913)**
All the adverse events, No. (%)	59 (6.8%)	51 (5.6%)
Serious adverse events, No. (%)	10 (1.2%)	13 (1.4%)
Remote ischemic conditioning related adverse events, No. (%) [a]		
Pain in arms	0	NA
Redness or swelling in arms	3 (0.3%)	NA
Skin petechiae on arms	2 (0.2%)	NA
Palpitation	0	NA
Intracerebral hemorrhage	0	NA
Dizziness	1 (0.1%)	NA

Abbreviations: NA = not applicable.

[a] The adverse events were not present at the beginning of study, and whether the adverse events were associated with the remote ischemic conditioning will be further adjudicated by central principal investigator; the judgement criteria to evaluate association between adverse events and remote ischemic conditioning treatment were available in the Supplement 1; the final decision of remote ischemic conditioning related adverse events were made by the site principle investigator.

Appendix

Table of Contents

1. APPENDIX I: CONSORT CHECKLIST FOR ABSTRACT

Item	Description	Reported on line number
Title	Identification of the study as randomized	Page 5 Line 5
Authors *	Contact details for the corresponding author	Page 3 Line 5-11
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	Page 5 Line 5
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	Page 5 Line 10
Interventions	Interventions intended for each group	Page 5 Line 13-15
Objective	Specific objective or hypothesis	Page 5 Line 4
Outcome	Clearly defined primary outcome for this report	Page 5 Line 16-19
Randomization	How participants were allocated to interventions	Page 5 Line 13
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Page 5 Line 18-19
Results		
Numbers randomized	Number of participants randomized to each group	Page 5 Line 20-21
Recruitment	Trial status	Page 5 Line 10
Numbers analysed	Number of participants analysed in each group	Page 5 Line 21-22
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	Page 6 Line 1-3
Harms	Important adverse events or side effects	Page 6 Line 4-5
Conclusions	General interpretation of the results	Page 6 Line 6-7
Trial registration	Registration number and name of trial register	Page 6 Line 8
Funding	Source of funding	Page 13 Line 4-6

2. APPENDIX II: CONSORT CHECKLIST FOR HARMS

Table 2. **Checklist of Items To Include When Reporting Harms in Randomized, Controlled Trials***

Standard CONSORT Checklist: Paper Section and Topic	Standard CONSORT Checklist: Item Number	Descriptor	Reported on Page Number
Title and abstract	1	If the study collected data on harms and benefits, the title or abstract should so state.	1, 5-6
Introduction			
Background	2	If the trial addresses both harms and benefits, the introduction should so state.	7
Methods			
Participants	3		8
Interventions	4		9
Objectives	5		8
Outcomes	6	List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions). Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).	10
Sample size	7		11
Randomization			9
Sequence generation	8		9
Allocation concealment	9		9
Implementation	10		9
Blinding (masking)	11		11
Statistical methods	12	Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).	
Results			
Participant flow	13	Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment.	13
Recruitment	14		13
Baseline data	15		13
Numbers analyzed	16	Provide the denominators for analyses on harms.	14
Outcomes and estimation	17	Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent.†	14
Ancillary analyses	18	Describe any subgroup analyses and exploratory analyses for harms.†	15
Adverse events	19		
Discussion			18
Interpretation	20	Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms.‡	15
Generalizability	21		
Overall evidence	22		16-18

* This proposed extension for harms includes 10 recommendations that correspond to the original CONSORT checklist.
† Descriptors refer to items 17, 18, and 19.
‡ Descriptor refers to items 20, 21, and 22.

3. APPENDIX III: COMMITTEE MEMBERS

Steering Committee

- Xun-Ming Ji (Chair, Xuanwu Hospital, Capital Medical University, Beijing, China)
- Hui-Sheng Chen (Chief Investigator, General Hospital of Northern Theater Command, Shenyang, China)
- Yu-Tong Ma (Co-Principal Investigator, Beipiao Central Hospital, Beipiao, China)
- Yong Zhao (Co-Principal Investigator, Haicheng Chinese Medicine Hospital, Haicheng, China)
- Zhuo Li (Co-Principal Investigator, Panjin Central Hospital, Panjin, China)
- Wei-Zhong Wang (Co-Principal Investigator, Dandong Central Hospital, Dandong, China)
- Li-Hua Wang (Co-Principal Investigator, Second Affiliated Hospital of Harbin Medical University, Harbin, China)
- Duo-Lao Wang (Senior Medical Statistician, Liverpool School of Tropical Medicine, Liverpool, UK)
- Xin-Hong Wang (Senior Trials Manager, General Hospital of Northern Theater Command, Shenyang, China)
- Xiao-Qiu Li (Senior Trials Manager, General Hospital of Northern Theater Command, Shenyang, China)
- Dan Wang (Trials Manager, General Hospital of Northern Theater Command, Shenyang, China)
- Yu Cui (Medical Statistician, Shenyang Pharmaceutical University, Shenyang, China)

Data Monitoring Committee

- Yi-Long Wang (Chair, Tiantan Hospital, Capital Medical University, Beijing, China)
- Xiao-Wen Hou (Epidemiology, Shenyang Medical College, Shenyang, China)
- Yi Yang (Neurology, First Hospital of Jilin University, Changchun, China)
- Yu-Song Pan (Medical Statistics, Tiantan Hospital, Capital Medical University, Beijing, China)

Institution Human Research Ethics Committee

- Bao-Jun Liu (Chair, General Hospital of Northern Theater Command, Shenyang, China)
- Ping Chen (Associate-chair, General Hospital of Northern Theater Command, Shenyang, China)
- Xiao-Zhong Guo (General Hospital of Northern Theater Command, Shenyang, China)
- Long Liu (General Hospital of Northern Theater Command, Shenyang, China)
- Xiao-Zeng Wang (General Hospital of Northern Theater Command, Shenyang, China)
- Zhen-Dong Zheng (General Hospital of Northern Theater Command, Shenyang, China)
- Rong-Wu Xiang (Shenyang Pharmaceutical University, Shenyang, China)
- Dong Jiang (Liaoning Hehao Law Office, Shenyang, China)
- Bin Lin (Shenyang Sport University, Shenyang, China)

Quality Control Staff and Support

- Qiu-Shuang Wang (Cerebrovascular Disease Collaboration Innovation Alliance Office [CDCIA], Shenyang, China)
- Meng-Yao Ge (Cerebrovascular Disease Collaboration Innovation Alliance Office [CDCIA], Shenyang, China)
- Lin Tao (General Hospital of Northern Theater Command, Shenyang, China)

4. APPENDIX IV: LIST OF INVESTIGATORS IN RICAMIS TRIAL

Department of Neurology, Beipiao Central Hospital, Beipiao, China

- Yu-Tong Ma
- Wei Kang
- Ran Zhu
- Li-Gang Feng
- Zheng-Kui Wang
- Fei Jiang
- Xu Chen
- Jian Xu
- Ying-Jie Li
- Shi-Mei Geng
- Dan Zhang
- Yan-Li Wang
- Shu-Nan Bao
- Hong Gao

Department of Neurology, Haicheng Chinese Medicine Hospital, Haicheng, China

- Yong Zhao
- Yu Yang
- Ya-Nan Xia
- Fang-Ru Zhou
- Wan-Yu Zhu
- Song-Lin Zhang
- Xia Wu
- Yang Sheng
- Qiu-Ye Han
- Shang Gao
- Qiu-Xia Zhu

Department of Neurology, Panjin Central Hospital, Panjin, China

- Jing Han
- Ya-li Wang
- Yong-Hao Wang
- Li-Wei Wang
- Wei Du
- Yi-Zhuo Song
- Chun-Bin Zhang
- Jian-Guo Wang
- Ying Wang
- Zhuo Li
- Na Qian
- Ying-Li Zhang
- Yi Wang
- Jia-Jun Liu
- Ci Shen

Department of Neurology, Dandong Central Hospital, Dandong, China

- Chang-Qing Deng
- Ying-Xia Hu
- Dong-Ming Gao
- Yu-Qing Bi
- Li-Jie Zhang
- Zhen-Zhou Nie
- Cheng Bi
- Li-Xin Chen
- Ping Zheng
- Hui-Ting Song
- Cheng-Rong Xu
- Jing Shi
- Gui-An Liu
- Ni Sun
- Hao Deng
- Ming Sun
- Yong-Ning Jiang
- Hong-Liang Hui

Department of Neurology, China Railway 19th Bureau Group Central Hospital, Liaoyang, China

- Mei Hong
- Yang Yang
- Dan Wang
- Li-Ping Pan

Department of Neurology, Fuxin Second People's Hospital, Fuxin, China

- Ying Bao
- Ning Wang
- Cheng Yang
- Hai-Peng Tang
- Hai-Tao Jiang
- Xiao-Lu Sun
- Xiao-Feng Qiu

Department of Neurology, Dandong People's Hospital, Dandong, China

- Li-Hong Zhao
- Qian-Chao Zhang
- Xiao-Tong Yang
- Dan Wang
- Guo-Cheng Bi
- Chun-Yan Jiang

Department of Neurology, Wafangdian Third Hospital, Dalian, China

- Ren-Lin Zou
- Jing Guo
- Bing Xue
- Xing-Guo Jiang

- Jun-Chao Fu
- Wen-Long Ge
- Yue Li

Department of Neurology, Chaoyang Central Hospital, Chaoyang, China

- Ting-Guang Yan
- Xiao-Qian Jin
- Jin-Ying Wu
- Gang Liu

Department of Neurology, Chinese People's Liberation Army 230 Hospital, Dandong, China

- Hui Wang
- Yan Chen
- Yu-Jiao Hu
- Peng-Fei Li
- Lu Qu

Department of Neurology, General Hospital of Northern Theater Command, Shenyang, China

- Hui-Sheng Chen
- Xin-Hong Wang
- Dan Gao
- Jin-Di Yang
- Shuang Bao
- Chao He
- Zhao-Xia Fei
- Yu-Hang Dong
- Ze-Yang Yu
- Xian-Hui Sun
- Ji-Jie Wang
- Yan-Ni Du
- Zhi-Lin Jiang
- Juan Hua
- Ling-Yun Cui
- Fan-Qi Ding
- Lu Wang

Department of Neurology, Dandong First Hospital, Dandong, China

- Li-Shu Wan
- Yu-Hong Zhou
- Xue Dong
- Qi Tian
- Jie-Sheng Sun
- Ting-Ting Zhang
- Xiao-Feng Pan
- Xin-Fang Zhang

Department of Neurology, Suizhong County Hospital, Huludao, China

- Li Zhang
- Shui Hu

Department of Neurology, Liaoyang County Stroke Hospital, Liaoyang, China

- Lian-Qiang Wang
- Tao Yu
- Pan Wang

Department of Neurology, Fushun Second Hospital, Fushun, China

- Li-Yan Guo
- Yang-Jun Song
- Dan Li
- Wei Zhao
- Peng-Fei Song

Department of Neurology, Huanren Manchu Autonomous County People's Hospital, Benxi, China

- Ming-Nan Li
- Dan-Yu Jiao
- Xiao-Yu Tong

Department of Neurology, Panjin People's Hospital, Panjin, China

- Dong-Qing Wang
- Xiang Lu
- Yun-Long Ci
- Xue Zhang
- Jing Zhang

Department of Neurology, Sujiatun Stroke Hospital, Shenyang, China

- Da-Wei Chang
- Jun-Jie Tan

Department of Neurology, Taian County Chinese Medicine Hospital, Anshan, China

- Hong-Li Zhang
- Yun-Zhu Fan
- Xiu Liang
- Dong Liu
- Kai-Yu Men
- Yu-Jie Zhang
- Xing Meng
- Lu-Lu Zhang

Department of Neurology, Anshan Hospital, The First Affiliated Hospital of China Medical University, Anshan, China

- Jing Sun
- Yu-Xi Sun
- Xiao-Jun Wu
- Gui-Zhen Liu

Department of Neurology, Liaoyang County Central Hospital, Liaoyang, China

- Chong Meng
- Li-Jun Su

Department of Neurology, Xiuyan County Central Hospital, Anshan, China

- Zai-Hui Zhang
- Guang-Ping Li

- Chun-Ze Xie
- Yuan-Hang Sun

Department of Neurology, Tieling County Central Hospital, Tieling, China

- Li-Ying Shen
- Zhi-Qiang Huang
- Jian-Jiang Huang
- Shu-Jiao Liu
- Li Liu

Department of Neurology, The Affiliated Central Hospital of Shenyang Medical College, Shenyang, China

- Li Ma
- Yi Yan
- Run-Hui Li
- Tian-Ming Cao
- Chang Liu

Department of Neurology, Changtu County Central Hospital, Tieling, China

- Gui-Chun Wang
- Xiao-Ying Zhang
- Hong-Chi Liu
- Yue Tan
- Fang-Xue Li
- Yu-Ting Zhao
- Meng-Long Niu
- Chang-Li Li

Department of Neurology, Dengta Central Hospital, Dengta, China

- Ling Zhang
- Bing-Yan Shan

Department of Neurology, Donggang Central Hospital, Donggang, China

- Jing Li
- Jing Ma
- Xiao-Yun Ma
- Shi-Xiu Xun

Department of Neurology, Liaoning Jinqiu Hospital, Shenyang, China

- Fu-Sheng Bai
- Hong-Yan Lei
- Rui-Ping Wang
- Fang-Yuan Mou
- Xiao-Ying Hu

Department of Neurology, Huludao Central Hospital, Huludao, China

- Xiao-Hui Gong
- Yuan-Yuan Hao

Department of Neurology, Liaoyang Petrochemical General Hospital, Liaoyang, China

- Li-Yun Wang
- Xing-Yun Zuo

Department of Neurology, The Affiliated Xinhua Hospital of Dalian University, Dalian, China

- Ying Bai
- Ping Lin

Department of Neurology, Chinese People's Liberation Army 463 Hospital, Shenyang, China

- Yan-Song Li
- Si-Heng Li
- Jia Ding
- Guo-Qing Zhao
- Yong-Hong You

Department of Neurology, Huludao Second People's Hospital, Huludao, China

- Ye-Fang Feng
- Dong-Yang Zhao
- Jia-Qi Sun
- Zhuo-Ran Xu
- Wen-Huan Wang

Department of Stroke, Dashiqiao Central Hospital, Dalian, China

- Chong Ha
- Jie Yang
- Nuo Luan
- Wei-Xu Wang

Department of Neurology, Lvshun Chinese Medicine Hospital, Dalian, China

- Chang-Hao Jiang
- Qi Zhao
- Shan-Hao Zhao
- Yang Sun
- Na Liu
- Peng Wang

Department of Neurology, Zhangwu County People's Hospital, Jinzhou, China

- Jin-Hua Zhai
- Ruo-Nan Wang
- Fei Li
- Dan Zhu
- Xu-Dong Wang
- Song Jiang
- Ming-Xia Wu

Department of Neurology, Lvshunkou Distinct People's Hospital, Dalian, China

- Bing Han
- Mei-Hua Yi

Department of Neurology, Yingkou Central Hospital, Yingkou, China

- Ye Wang
- Xiao-Ning Wu

Department of Neurology, Jinzhou Central Hospital, Jinzhou, China

- Dong-Yu Wang
- Hai-Yan Yu

- Yan Li
- Xin Li
- Jin-Li Zhu

Department of Neurology, Liaoyang Second People's Hospital, Liaoyang, China

- Kui-Hua Yang
- Xiao Ma

Department of Neurology, Chinese People's Liberation Army 967 Hospital, Dalian, China

- Jing-Yu Li
- Feng-Gang Sun
- Qin Ma
- Xia Li

Department of Neurology, Lingyuan Central Hospital, Chaoyang, China

- Zhao-Min Meng
- Tie-Bin Si

Department of Neurology, Fuxin Central Hospital, Fuxin, China

- Xiu-Kun Yu
- Hai-Yan Yu

Department of Neurology, Chinese People's Liberation Army 321 Hospital, Baicheng, China

- Shao-Yuan Chen
- Xiao-Jing Wang
- Dan Yu

Department of Neurology, Benxi County First People's Hospital, Benxi, China

- Xiao-Hong Song
- F-Xia Sun

Department of Neurology, Liaoyang Third People's Hospital, Liaoyang, China

- Jun Xu
- Jia-Xu Tong

Department of Neurology, Fushun Central Hospital, Fushun, China

- Jing-Yang Chen
- Qiang Zhang
- Bin Xu

Department of Neurology, Dalian Liaoyu Hospital, Dalian, China

- Li Li
- Xin Zhang

Department of Neurology, Anshan Central Hospital, Anshan, China

- Zhen Jiao
- Shi-Hui Li
- Xu Yan
- Chun Nie
- Yang Wang
- Hong-Bo Xiao
- Xin Wang

Department of Neurology, Fushun Petrochemical General Hospital, Fushun, China

- Xiang-Wen Zheng

- Lian-Rui Guo

Department of Neurology, Dalian Youyi Hospital, Dalian, China

- Wen-Xu Zheng
- Li-Yan Tan

Department of Neurology, Pulandian Central Hospital, Dalian, China

- Ya-Jun Liu
- Lian Ning

Fushun Third Hospital, Fushun, China

- Xiao-Ling Wang
- Xiao-Jie Wang

Department of Neurology, Dalian Third People's Hospital, Dalian, China

- Min Yu
- Wei Lou

Department of Neurology, The Second Affiliated Hospital of China Medical University, Shenyang, China

- Juan Feng
- Yan Gao

5. APPENDIX V: RECRUITMENT BY SITE IN RICAMIS TRAIL

Inclusion site	Number of patients recruited
Department of Neurology, Beipiao Central Hospital	285
Department of Neurology, Panjin Central Hospital	213
Haicheng Chinese Medicine Hospital	199
Department of Neurology, Dandong Central Hospital	152
Department of Neurology, Fuxin Second People's Hospital	98
China Railway 19th Bureau Group Central Hospital	90
Dandong People's Hospital	84
Wafangdian Third Hospital	71
Chaoyang Central Hospital	65
General Hospital of Northern Theater Command	51
Chinese People's Liberation Army 230 Hospital	45
Dandong First Hospital	39
Suizhong County Hospital	36
Liaoyang County Stroke Hospital	34
Department of Neurology, The Affiliated Central Hospital of Shenyang Medical College	34
Department of Neurology, Taian County Chinese Medicine Hospital	33
Fushun Central Hospital	32
Fushun Second Hospital	30
Huanren Manchu Autonomous County People's Hospital	30
Panjin People's Hospital	29
Sujiatun Stroke Hospital	25
Anshan Hospital, The First Affiliated Hospital of China Medical University	23
Liaoyang County Central Hospital	22
Xiuyan County Central Hospital	21
Tieling County Central Hospital	20
Department of Neurology, Changtu County Central Hospital	19
Department of Neurology, Liaoning Jinqiu Hospital	16
Dengta Central Hospital	14
Donggang Central Hospital	14
Chemical Industry Branch, Huludao Central Hospital	13
Liaoyang Petrochemical General Hospital	12
The Affiliated Xinhua Hospital of Dalian University	12
Chinese People's Liberation Army 463 Hospital	11
Huludao Second People's Hospital	10
Department of Stroke, Dashiqiao Central Hospital	10
Lvshun Chinese Medicine Hospital	10
Zhangwu County People's Hospital	10
Lvshunkou Distinct People's Hospital	9
Department of Neurology, Yingkou Central Hospital	8
Jinzhou Central Hospital	8

Liaoyang Second People’s Hospital	7
Department of Neurology, Fuxin Central Hospital	7
Department of Neurology, Anshan Central Hospital	7
Chinese People’s Liberation Army 967 Hospital	7
Lingyuan Central Hospital	6
Chinese People’s Liberation Army 321 Hospital	5
Benxi County First People’s Hospital	4
Liaoyang Third People’s Hospital	4
Dalian Liaoyu Hospital	3
Fushun Third Hospital	3
Fushun Petrochemical General Hospital	3
Dalian Youyi Hospital	2
Pulandian Central Hospital	2
Dalian Third People’s Hospital	1
The Second Affiliated Hospital of China Medical University	1

6. APPENDIX VI: SUPPLEMENTAL METHODS

Structure interview for telephone assessment: we used a structured telephone interview and interview algorithm is as reported in a previous study.[1]

Central adjudication of outcomes: to enhance accuracy and masking of the efficacy outcome and safety outcome assessment, the 90-day modified Rankin Score was independently performed by two different assessors: a local assessors who performed the mRS interview in person or telephone, and another off-site central assessor who performed the mRS interview in telephone or through viewing a videotape of the mRS interview. If there was disagreement between local and the central assessors, a consensus was achieved by discussion. The local evaluator retained control of the final mRS score, following any discussion.

Definition of early neurological deterioration: early neurological deterioration is defined as an increase of two or more NIHSS compared to baseline after stroke within 7 days.[2]

Definition of stroke-associated pneumonia: stroke-associated pneumonia is defined according to the recommendation from the pneumonia in stroke consensus group.[3]

Definition of stroke: stroke was defined as an acute focal central neurological deficit lasting >24 hours that resulted in irreversible brain damage or body impairment by a vascular cause.[4]

Definition of other vascular events: other vascular events include pulmonary embolism, peripheral vessel incident, and cardiovascular incident.

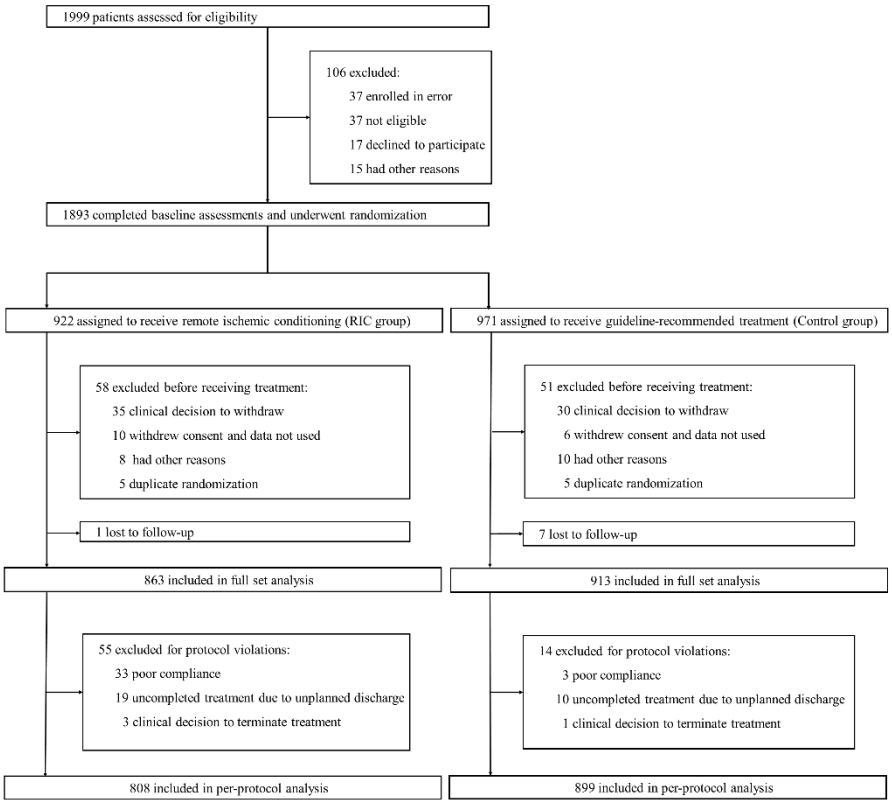
Clinicaltrials.gov registration

The RICAMIS trial is a prospective, random, open-label, blinded endpoint and multi-center study, which is registered at clinicaltrials.gov on 14th Nov 2018 (NCT03740971). The trial was initially set-up on 31st Oct 2018 and recruited their first patient on 26th Dec 2018.

1. Wilson JT, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. Stroke. 2002; **33:** 2243-6.
2. Kwon HM, Lee YS, Bae HJ, Kang DW. Homocysteine as a predictor of early neurological deterioration in acute ischemic stroke. *Stroke*. 2014; **45:** 871-3.
3. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. *Stroke*. 2015; **46:** 2335-40.
4. Campbell BCV, Khatri P. Stroke. *Lancet*. 2020; **396:** 129-42.

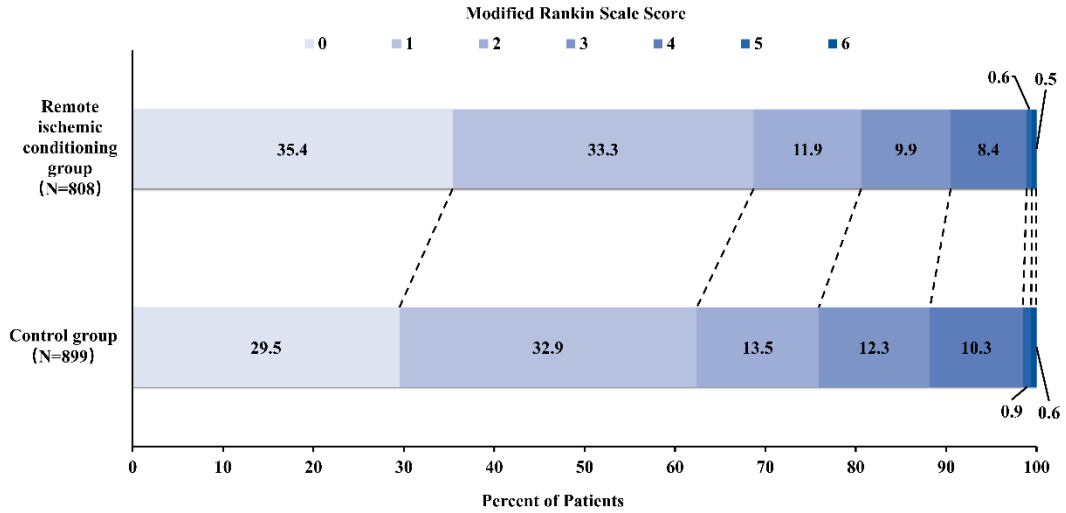
7. APPENDIX VII: SUPPLEMENTAL FIGURES

eFigure 1 Trial profile



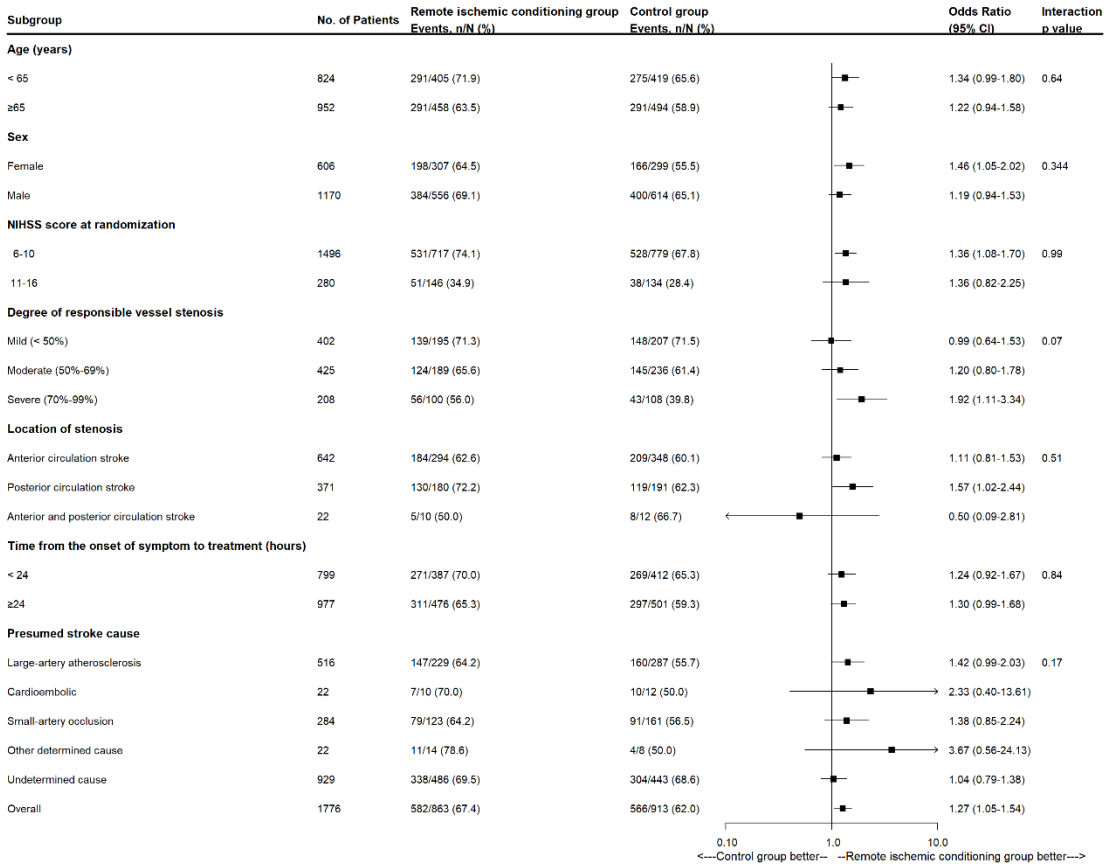
This figure shows overall patient flow in the trial, including in the full set analysis and per-protocol analysis. RIC=remote ischemic conditioning.

eFigure 2 Distribution of modified Rankin Scale Scores at 90 Days in the Per-Protocol Analysis



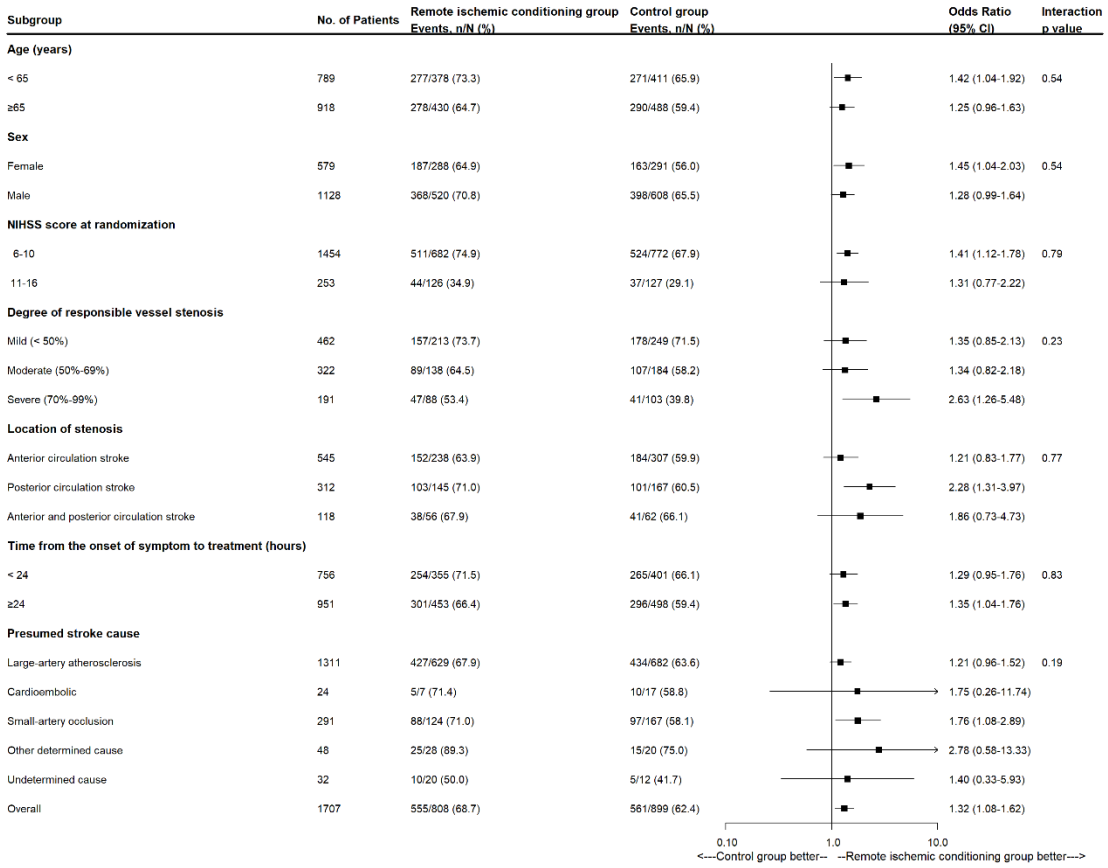
Raw distribution of scores is shown. Scores range from 0 to 6: 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death.

eFigure 3 Primary Outcome by Prespecified Subgroups in the Full Set Analysis



The primary outcome was the modified Rankin scale score 0 to 1 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CI. Scores on the NIHSS range from 6 to 16, with higher scores indicating more severe neurological deficits. For NIHSS score, subgroups were dichotomized by median value. Patients who underwent vessel imaging examinations were included in the subgroup analysis of degree of responsible vessel stenosis and location of stenosis. NIHSS = National Institute of Health Stroke Scale.

eFigure 4 Primary Outcome by Prespecified Subgroups in the Per-Protocol Analysis



The primary outcome was proportion of modified Rankin scale score 0-1 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CI. Scores on the NIHSS range from 6 to 16, with higher scores indicating more severe neurological deficits. For NIHSS score, subgroups were dichotomized by median value. Patients who underwent vessel imaging examinations were included in the subgroup analysis of degree of responsible vessel stenosis and location of stenosis. NIHSS = National Institute of Health Stroke Scale.

8. APPENDIX VIII: SUPPLEMENTAL TABLES

eTable 1. Baseline Characteristics and Procedural Details in the Per-Protocol Analysis

	Remote ischemic conditioning group (n=808)	Control group (n=899)
Baseline characteristics		
Age, mean (SD), years	65.2 (10.5)	65.3 (10.1)
Sex		
Male, No. (%)	520/808 (64.4%)	608/899 (67.6%)
Female, No. (%)	288/808 (35.6%)	291/889 (32.4%)
Body-mass index, mean (SD), kg/m^2	24.3 (3.0)	24.3 (2.9)
Current smoker, No. (%)	231/784 (29.5%)	244/864 (28.2%)
Current drinker, No. (%) [a]	119/793 (15.0%)	103/873 (11.8%)
Comorbidities, No. (%)		
Hypertension	496/797 (62.2%)	542/887 (61.1%)
Previous ischemic or hemorrhagic stroke	263/803 (32.8%)	287/893 (32.1%)
Diabetes	191/807 (23.7%)	215/894 (24.0%)
Hyperlipidemia	10/791 (1.3%)	9/884 (1.0%)
Previous TIA	8/806 (1.0%)	10/897 (1.1%)
Time from the onset of symptom to treatment, mean (SD), hours	25.2 (13.1)	25.1 (13.7)
Time to hospital discharge, mean (SD), days	11.7 (2.1)	11.6 (1.8)
Blood pressure at randomization, mean (SD), mm Hg		
Systolic	151.8 (18.8)	151.8 (18.6)
No. of patients	537	601
Diastolic	88.5 (11.0)	89.1 (11.3)
No. of patients	448	520
Blood glucose, mean (SD), mmol/L	7.3 (3.1)	7.5 (3.3)
No. of patients	348	422
NIHSS score at randomization, mean (SD) [b]	7 (6-9)	7 (6-9)
Estimated premorbid function (mRS), No. (%)		
No symptoms (score 0)	602/808 (74.5%)	671/899 (74.6%)
Symptoms without any disability (score 1)	206/808 (25.5%)	228/899 (25.4%)
Location of responsible vessel stenosis, No. (%) [c]		
Anterior circulation stroke	266/444 (59.9%)	343/542 (63.3%)
Posterior circulation stroke	169/444 (38.1%)	187/542 (34.5%)
Anterior and posterior circulation stroke	9/444 (2.0%)	12/542 (2.2%)
Degree of responsible vessel stenosis, No. (%) [c]		
Mild (< 50%)	183/444 (41.2%)	206/542 (38.0%)
Moderate (50%-69%)	172/444 (38.7%)	232/542 (42.8%)
Severe (70%-99%)	89/444 (20.1%)	104/542 (19.2%)
Presumed stroke cause, No. (%) [c]		
Undetermined cause	461/808 (57.1%)	436/897 (48.6%)

	Remote ischemic conditioning group (n=808)	Control group (n=899)
Large-artery atherosclerosis	212/808 (26.2%)	280/897 (31.2%)
Intracranial atherosclerosis	185/808 (22.9%)	248/897 (27.6%)
Small-artery occlusion	114/808 (14.1%)	161/897 (17.9%)
Other determined cause	14/808 (1.7%)	8/897 (1.0%)
Cardioembolic	7/808 (0.9%)	12/897 (1.3%)
Procedural details Procedural details		
Days of complete cycles of Remote ischemic conditioning, No. (%) [d]		
8	9/808 (1.1%)	NA
9	124/808 (15.3%)	NA
10	212/808 (26.3%)	NA
11	190/808 (23.5%)	NA
12	135/808 (16.7%)	NA
13	87/808 (10.8%)	NA
14	49/808 (6.1%)	NA
15	1/808 (0.1%)	NA
16	1/808 (0.1%)	NA

Abbreviations: IQR = inter-quartile range. NA = not applicable. NIHSS = National Institute of Health Stroke Scale. mRS = modified Rankin scale. SD = standard deviation.

[a] Current drinker means consuming alcohol at least once a week within one year before onset of the disease, and consuming alcohol continuously for more than one year.

[b] Patients with NIHSS scores 6 to 16 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[c] Diagnosis according to the clinician's interpretation of clinical features and results of investigators at the time of discharge from hospital; the presumed stroke cause was classified according to the "Trial of Org 10172 in Acute Stroke Treatment (TOAST)" classification system.

[d] The complete cycles was defined as that patients continually finished remote ischemic conditioning treatment twice daily.

eTable 2. Sensitive Analysis for Missing Primary Outcome in Dropout Subjects

Methods	**Without primary outcome imputation**				**With primary outcome imputation**				
	Remote ischemic conditioning group (863)	Control group (913)	Odds ratio (95% CI)	P value	Remote ischemic conditioning group (922)	Control group (971)	Odds ratio (95% CI)	P value	Imputation methods
mRS score 0-1 within 90 days, No. (%)	582/863 (67.4%)	566/913 (62.0%)	1.27 (1.05-1.54)	0.02	590/922 (64.0%)	577/971 (59.4%)	1.21 (1.01-1.46)	0.04	last observation carried forward
					582/922 (63.1%)	566/971 (58.3%)	1.23 (1.02-1.47)	0.03	Worst-case scenario
					641/922 (69.5%)	624/971 (64.3%)	1.27 (1.05-1.54)	0.02	Best-case scenario

eTable 3. Primary and Secondary Outcomes in the Per-Protocol Analysis Set.

	Remote ischemic conditioning group (n=863)	Control group (n=913)	Treatment metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	p value	Treatment Difference (95% CI)	p value
Primary outcome							
mRS [b] score 0-1 within 90 days, No. (%)	555/808 (68.7%)	561/899 (62.4%)	OR	1.32 (1.08-1.62)	0.007	1.45 (1.17-1.81)	0.001
			RR [c]	1.20 (1.05-1.37)	0.007	1.25 (1.10-1.41)	0.001
			RD [c]	6.3% (1.8%-10.8%)	0.006	6.6% (2.3%-11.0%)	0.003
Secondary outcomes							
mRS [b] score 0-2 within 90 days, No. (%)	652/808 (80.7%)	682/899 (75.9%)	OR	1.33 (1.05-1.68)	0.02	1.47 (1.14-1.88)	0.003
			RR [c]	1.25 (1.04-1.50)	0.02	1.30 (1.09-1.55)	0.004
			RD [c]	4.8% (0.9%-8.7%)	0.02	4.9% (1.2%-8.5%)	0.009
Early neurological deterioration within 7 days, No. (%) [d]	63/808 (7.8%)	58/899 (6.5%)	OR	1.23 (0.85-1.78)	0.28	1.21 (0.84-1.76)	0.31
			RR [c]	1.21 (0.86-1.70)	0.28	1.20 (0.85-1.69)	0.30
			RD [c]	1.3% (-1.1%-3.8%)	0.28	1.2% (-1.3%-3.6%)	0.35
Stroke-associated pneumonia within 12 days, No. (%) [e]	25/808 (3.1%)	19/899 (2.1%)	OR	1.48 (0.81-2.71)	0.20	1.48 (0.80-2.73)	0.21
			RR [c]	1.46 (0.81-2.64)	0.21	1.47 (0.82-2.66)	0.20
			RD [c]	1.0% (-0.5%-2.5%)	0.21	1.0% (-0.6%-2.5%)	0.22
Change in NIHSS f score at day 12 from baseline, median (IQR) [g]	4 (2-6)	4 (2-5)	Mean difference	1.30 (0.95-1.79)	0.10	1.32 (0.96-1.81)	0.09
Stroke or other vascular events within 90 days, No. (%) [h]	5/808 (0.6%)	6/899 (0.7%)	HR	0.89 (0.24-3.32)	0.86	0.86 (0.23-3.22)	0.83
Death within 90 days, No. (%) [h]	4/808 (0.5%)	5/899 (0.6%)	HR	0.89 (0.24-3.31)	0.86	0.85 (0.23-3.18)	0.81

Treatment effect is presented as OR or RR or RD or HR or mean difference (95% CI) of Remote ischemic conditioning versus control group, analyzed by unadjusted and adjusted binary logistic regression.

Abbreviations: OR = odds ratio. RR = risk ratio. RD = risk difference. HR= hazard ratio. CI = confidence interval. mRS = modified Rankin scale. NIHSS = National Institute of Health Stroke Scale. IQR = inter-quartile range.

[a] Adjusted for key prognostic covariates (age; sex; premorbid function [mRS score 0 or 1]; NIHSS score at randomization; history of stroke or TIA; and time from the onset of symptom to Remote ischemic conditioning time).

[b] mRS scores range from 0 to 6: 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death.

[c] Calculated with generalized linear model.

[d] Early neurological deterioration was defined as an increase between baseline and 7 days of ≥ 2 on the NIHSS score, but not result of cerebral hemorrhage (Supplement 3 p 15).

[e] Stroke-associated pneumonia was defined according to the recommendation from the pneumonia in stroke consensus group (Supplement 3 p 15).

[f] NIHSS scores range 0–42, with higher scores indicating greater stroke severity.

[g] Calculated with general linear model.

[h] Calculated with Cox regression model.

eTable 4. Adverse Events in the Full Analysis Set.

	Remote ischemic conditioning group (n=808)	**Control group (n=899)**
All the adverse events, No. (%)	49 (6.1%)	46 (5.1%)
Serious adverse events, No. (%)	6 (0.7%)	8 (0.9%)
Remote ischemic conditioning related adverse events, No. (%) [a]		
Pain in arms	0	NA
Redness or swelling in arms	1 (0.1%)	NA
Skin petechiae on arms	2 (0.2%)	NA
Palpitation	0	NA
Intracerebral hemorrhage	0	NA
Dizziness	0	NA

Abbreviations: NA = not applicable.

[a] The adverse events were not present at the beginning of study, and whether the adverse events were associated with the remote ischemic conditioning will be further adjudicated by central principal investigator; the judgement criteria to evaluate association between adverse events and remote ischemic conditioning treatment were available in the Supplement 1; the final decision of remote ischemic conditioning related adverse events were made by the site principal investigator.