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

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IMPORTANCE Preclinical and clinical studies have suggested a neuroprotective effect of remote ischemic conditioning (RIC), which involves repeated occlusion/release cycles on bilateral upper limb arteries; however, robust evidence in patients with ischemic stroke is lacking.

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

DESIGN, SETTING, AND PARTICIPANTS This multicenter, open-label, blinded-end point, randomized clinical trial including 1893 patients with acute moderate ischemic stroke was conducted at 55 hospitals in China from December 26, 2018, through January 19, 2021, and the date of final follow-up was April 19, 2021.

INTERVENTIONS Eligible patients were randomly assigned within 48 hours after symptom onset to receive treatment with RIC (using a pneumatic electronic device and consisting of 5 cycles of cuff inflation for 5 minutes and deflation for 5 minutes to the bilateral upper limbs to 200 mm Hg) for 10 to 14 days as an adjunct to guideline-based treatment (n = 922) or guideline-based treatment alone (n = 971).

MAIN OUTCOMES AND MEASURES The primary end point was excellent functional outcome at 90 days, defined as a modified Rankin Scale score of 0 to 1. All end points had blinded assessment and were analyzed on a full analysis set.

RESULTS Among 1893 eligible patients with acute moderate ischemic stroke who were randomized (mean [SD] age, 65 [10.3] years; 606 women [34.1%]), 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 (risk difference, 5.4% [95% CI, 1.0%-9.9%]; odds ratio, 1.27 [95% CI, 1.05-1.54]; *P* = .02). 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 Among adults with acute moderate ischemic stroke, treatment with remote ischemic conditioning compared with usual care significantly increased the likelihood of excellent neurologic function at 90 days. However, these findings require replication in another trial before concluding efficacy for this intervention.

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Visual Abstract

Editorial page 623

Multimedia

Supplemental content

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Group Information: The list of RICAMIS Investigators appears in Supplement 4.

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

The phenomenon of myocardial ischemic preconditioning[6] attracted much attention in the field of preclinical and clinical research.[7] Increasing evidence has demonstrated the neuroprotective action of remote ischemic conditioning (RIC) in preclinical studies by reducing brain infarction and improving neurologic outcomes.[7,8] Several clinical studies have supported the safety of RIC.[9-11] There has been a lack of robust evidence for the neuroprotective effect of RIC in patients with AIS due to small sample sizes, different RIC procedures, and heterogeneity of patients with varying extents of neurologic deficits.[12-15] In this context, a multicenter randomized clinical trial was designed to explore the efficacy of RIC for acute moderate ischemic stroke.

Key Points

Question Does remote ischemic conditioning, which involves repeated occlusion/release cycles on bilateral upper limb arteries, improve neurologic function in patients with acute moderate ischemic stroke?

Findings In this randomized clinical trial that included 1893 patients with acute moderate ischemic stroke, excellent neurologic 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 neurologic function in patients with acute moderate ischemic stroke, this trial requires replication before concluding efficacy for this intervention.

Methods

Study Design

The Remote Ischemic Conditioning for Acute Moderate Ischemic Stroke (RICAMIS) Study was a multicenter, open-label, blinded-end point, randomized clinical trial to assess the efficacy of 2 weeks of RIC in patients with acute moderate ischemic stroke within 48 hours from symptom onset. The study protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2. The trial took place at 55 medical sites in China (eAppendix 2 in Supplement 3). The trial protocol was approved by appropriate regulatory and ethical authorities at the ethics committee of General Hospital of Northern Theatre Command (formerly General Hospital of Shenyang Military Region) and other participating hospitals. An independent data monitoring committee monitored progress of the trial every 6 months. Signed informed consents were obtained from the patients or their legally authorized representative.

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, 6-16; range, 0-42, with higher scores indicating greater stroke severity), who had been functioning independently in the community before a stroke (modified Rankin Scale [mRS] scores, 0-1; range, 0 [no symptoms] to 6 [death]), 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 if a patient had received intravenous thrombolysis or other endovascular therapy; had uncontrolled severe hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg after agent treatment); had any contraindication for RIC (eg, upper limb with serious soft tissue injury, fracture, or vascular injury, distal upper limb with perivascular lesions); or had etiology of cardiogenic embolism (eg, atrial fibrillation) given the high risk of intracranial hemorrhage transformation. A full list of inclusion and exclusion criteria is in the study protocol (Supplement 1).

Randomization and Blinding

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 members were unblinded to the treatment allocation.

Procedures

The cuff of a pneumatic electronic autocontrol device (patent No: 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 mm Hg for 5 minutes) and deflation (for 5 minutes), for a total procedure time of 50 minutes, twice daily for 10 to 14 days.[12] 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 medication or statins).[1] All patients completed the RIC treatment in hospital. In the control group, patients received only guideline-recommended treatment. Patients in both groups received standard care at the discretion of the local investigator at each participating 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 criterion of RIC in the trial was defined as 80% to 120% completion of a 10- to 14-day RIC treatment program.

Neurologic 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 end point was whether there was excellent functional outcome at 90 days, defined as a score of 0 to 1 on the mRS for the evaluation of neurologic 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 (eMethods in Supplement 3).

The secondary end points were favorable 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 neurologic deterioration compared with baseline at 7 days, defined as more than 2 NIHSS score increases, but not as a result of cerebral hemorrhage (eMethods in Supplement 3); occurrence of stroke-associated pneumonia at 12 days (eMethods in Supplement 3); 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, palpitations, intracerebral hemorrhage, and dizziness not present at the beginning of the study. Whether the adverse event was associated with the RIC treatment was further adjudicated by the principal investigator (H.S.C.).

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 a trained and certified staff member in each center who was unaware of the randomized treatment assignment. To try to ensure validity and reproducibility of the evaluation, a training course was held for all investigators at each center. Central adjudication of clinical outcomes and adverse events were also done by assessors unaware of treatment allocation or clinical details; disagreement between the central adjudicator and site assessor was rare. If there was disagreement between local and central assessors, a consensus was achieved by discussion. The local evaluator retained control of the final mRS score, following any discussion.

Sample Size Calculation

Power calculations were based on the estimated treatment effects on a binary assessment of excellent functional outcome at 90 days. In the European Cooperative Acute Stroke Study III, alteplase administered 3.0 to 4.5 hours after the onset of stroke symptoms resulted in a 7.2% benefit in the primary end point (mRS score, 0-1) vs placebo[17]; therefore, 7% was chosen as the minimal detectable difference used to power the present 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 2-sided $\alpha = .05$) to detect the 7-percentage point greater excellent functional outcome in the RIC group. Assuming 10% lost to follow-up, the total sample size estimate was 1742. Therefore, this study planned to include 1800 participants (900 per group).

Statistical Analysis

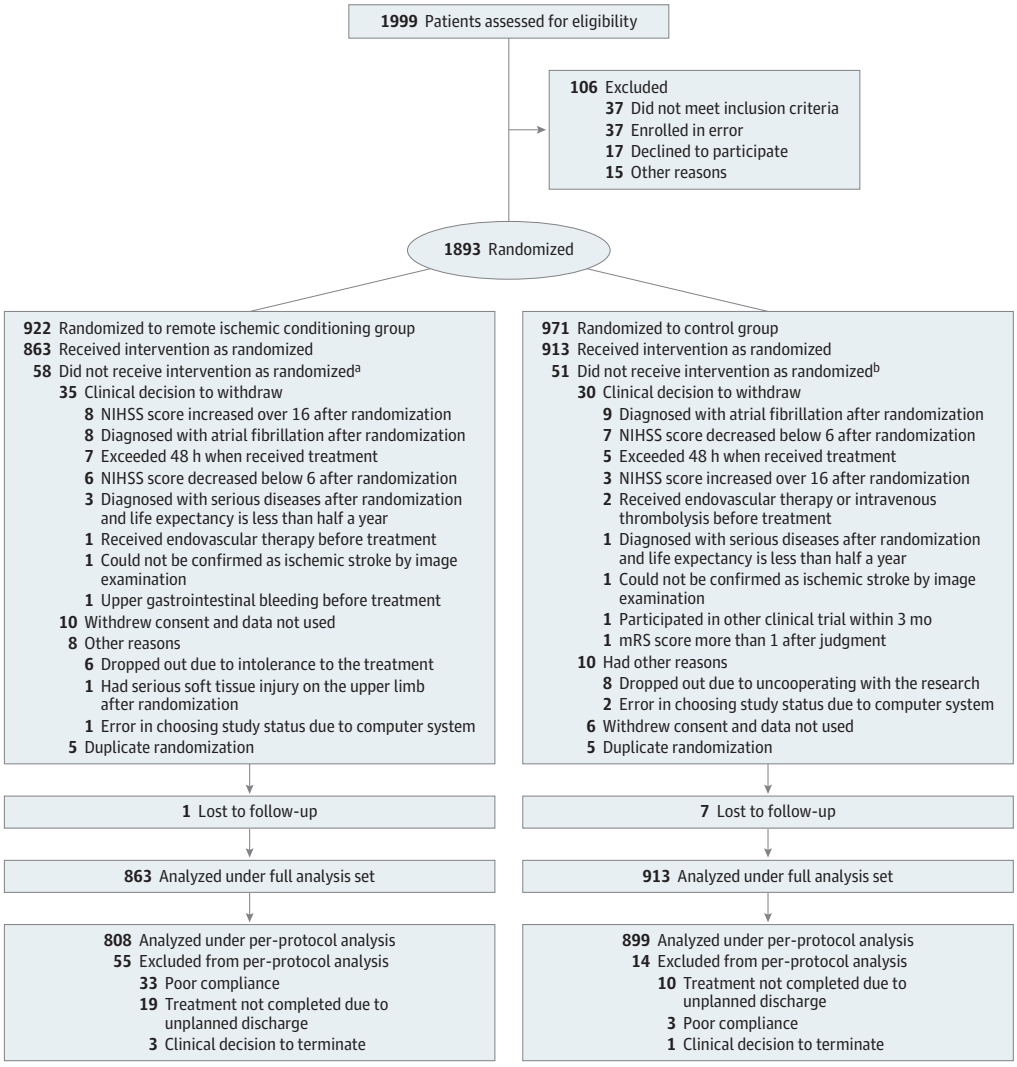
Primary analyses were performed on the full analysis set, which included all randomized participants with at least 1 postbaseline efficacy evaluation. Binary logistic regression analyses were performed for the primary outcome and secondary outcomes of favorable functional outcome at 90 days, occurrence of early neurologic deterioration, and stroke-associated pneumonia. The treatment effects for the above outcomes were presented as ORs with 95% CIs. In addition, risk ratios and risk differences with 95% CIs were calculated for the binary outcomes using a generalized linear model. Missing values in the primary outcome were imputed using the last observation carried forward method as well as worst-case scenario and best-case scenario approaches in sensitivity analyses. No interim analysis was performed in this study.

The mRS scores at 90 days were compared using ordinal logistic regression and ORs with 95% CIs were calculated. Change in log (NIHSS score) between admission and at 12 days was compared using a generalized linear model, and the geometric mean ratios between RIC and control groups with their 95% CIs were derived. Time-to-event outcomes of stroke, other vascular events, and death of any cause experienced by the 2 groups up to 90 days after randomization were compared using Cox regression models, and the corresponding treatment effects were presented as hazard ratios (HRs) with 95% CIs. The assumption of proportionality was tested by adding an interaction between time and treatment in the Cox model, and no interaction was found.

The primary analyses for primary and secondary outcomes were unadjusted. Covariate-adjusted analyses were also performed for all outcomes, adjusting for 6 prespecified prognostic factors: age, sex, premorbid function (mRS score, 0 or 1), NIHSS score at randomization, history of stroke or transient ischemic attack, 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 the primary outcome was performed on 7 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

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



Baseline characteristics and procedural details in patients missing primary outcome are shown in eTable 5 in Supplement 3. mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and RICAMIS, Remote Ischemic Conditioning for Acute Moderate Ischemic Stroke.

[a] Time from randomization to last contact of patients missing primary outcome in the remote ischemic conditioning group was a median of 5 days (IQR, 0-10).

[b] Time from randomization to last contact of patients missing primary outcome in the control group was a median of 7 days (IQR, 0-12).

(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 independent variables, and the *P* value presented for the interaction term.

In addition, per-protocol analyses were conducted for primary and secondary outcomes restricted to patients who received the complete intervention as specified in the protocol. A 2-sided *P* value of less than .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. SPSS software version 23 (IBM) and R software version 4.1.0 (R Foundation for Statistical Computing) were used for statistical analyses.

Results

Trial Population

Between December 26, 2018, and April 19, 2021, 1893 patients were enrolled and randomly assigned to the RIC group (922 patients) or control group (971 patients). A total of

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

	Group, No. (%)	
	Remote ischemic conditioning (n = 863)	Control (n = 913)
Baseline characteristics		
Age, mean (SD), y	65.3 (10.5)	65.3 (10.1)
Sex		
Male	556 (64.4)	614 (67.3)
Female	307 (35.6)	299 (32.7)
Body mass index, mean (SD)[a]	24.3 (3.0)	24.3 (2.9)
Current smoker, No./total (%)	259/839 (30.9)	246/878 (28.0)
Current drinker, No./total (%)[b]	137/848 (16.2)	103/887 (11.6)
Comorbidities, No./total (%)		
Hypertension	531/852 (62.3)	552/901 (61.3)
Diabetes	208/862 (24.1)	223/908 (24.6)
Previous silent ischemic or hemorrhagic stroke[c]	145/858 (16.9)	150/907 (16.5)
Previous symptomatic ischemic or hemorrhagic stroke	135/858 (15.7)	139/907 (15.3)
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), h	24.8 (13.2)	25.0 (13.7)
Time to hospital discharge, mean (SD), d	11.4 (2.4)	11.5 (1.9)
Blood pressure at randomization		
Systolic blood pressure, mean (SD), mm Hg	151.3 (18.7)	151.8 (18.8)
>140	569 (65.9)	610 (66.8)
Diastolic blood pressure, mean (SD), mm Hg	88.6 (11.2)	88.9 (11.4)
>90	478 (55.4)	524 (57.4)
Blood glucose, mean (SD), mg/dL	133.2 (55.8)	135 (59.4)
>126	372 (43.1)	433 (47.4)
NIHSS score at randomization, median (IQR)[d]	7 (6-9)	7 (6-9)
Estimated premorbid function (mRS)		
No symptoms (score, 0)	647 (75.0)	685 (75.0)
Symptoms without any disability (score, 1)	216 (25.0)	228 (25.0)
Location of responsible vessel stenosis[e]		
Circulation stroke, No./total (%)		
Anterior	294/484 (60.7)	348/551 (63.1)
Posterior	180/484 (37.2)	191/551 (34.7)
Anterior and posterior	10/484 (2.1)	12/551 (2.2)
Degree of responsible vessel stenosis, No./total (%)[e]		
Mild (<50%)	195/484 (40.3)	207/551 (37.6)
Moderate (50%-69%)	189/484 (39.0)	236/551 (42.8)
Severe (70%-99%)	100/484 (20.7)	108/551 (19.6)
Presumed stroke cause, No./total (%)[f]		
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)

(continued)

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

	Group, No. (%)	
	Remote ischemic conditioning (n = 863)	Control (n = 913)
Procedural details		
Days of complete cycles of remote ischemic conditioning[g]		
<8	55 (6.4)	NA
8	9 (1.0)	NA
9	124 (14.4)	NA
10	212 (24.6)	NA
11	190 (22.0)	NA
12	135 (15.6)	NA
13	87 (10.1)	NA
14	49 (5.7)	NA
15	1 (0.1)	NA
16	1 (0.1)	NA

Abbreviations: mRS, modified Rankin scale; NA, not applicable; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischemic attack.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Current drinker means consuming alcohol at least once a week within 1 year before onset of the disease and consuming alcohol continuously for more than 1 year.

[c] Reported in only patients who did not have prior symptomatic ischemic stroke.

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

[e] Definite conclusion based on vessel examinations and the diagnosis according to the clinician's interpretation of clinical features and results of investigators at the time of discharge from hospital. In the remote ischemic conditioning group, there were 19 patients who underwent vessel imaging and had visualized occlusion, 465 patients who underwent vessel imaging and did not have visualized occlusion, and 379 patients who did not undergo vessel imaging. In the control group, there were 21 patients who underwent vessel imaging and had visualized occlusion, 530 patients who underwent vessel imaging and did not have visualized occlusion, and 362 patients who did not undergo vessel imaging.

[f] The presumed stroke cause was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.

[g] A complete cycle was defined as patients who continually finished remote ischemic conditioning treatment twice daily.

117 patients (6.2%) 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 were lost to follow-up). Therefore, 1776 patients (863 in the RIC group and 913 in the control group) were included in the full analysis set (**Figure 1**; eFigure 1 in Supplement 3). The RIC procedure was completed according to protocol for 1707 patients (96.1%) (808 [93.6%] in the RIC group and 899 [98.5%] in the control group), who were included in the per-protocol analysis. Reasons for incomplete procedure are provided in Figure 1. The trial enrolled to completion in April 2021.

The treatment groups were well balanced with respect to patient baseline characteristics in the full analysis set (**Table 1**) and per-protocol analysis (eTable 1 in Supplement 3). 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 of the full analysis set, the proportion of patients with an mRS score of 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 an unadjusted OR of 1.27 (95% CI, 1.05-1.54; P = .02; **Table 2**, **Figure 2**), risk difference of 5.4% (95% CI, 1.0%-9.9%; P = .02), and a risk ratio of 1.17 (95% CI, 1.03-1.32; P = .02) (Table 2). Similar OR results were observed in the last observation carried forward, worst-case scenario, and best-case scenario sensitivity analyses (eTable 2 in Supplement 3). The OR remained significant after adjustment for the prespecified prognostic variables (OR, 1.41 [95% CI, 1.14-1.74]; P = .002). Similar results were also obtained in the per-protocol analysis (unadjusted OR, 1.32 [95% CI, 1.08-1.62]; P = .007; adjusted OR, 1.45 [95% CI, 1.17-1.81]; P = .001; eTable 3 in Supplement 3).

Secondary Outcomes

For the secondary outcomes of the full analysis set, there were significant differences in the odds of having an mRS score of 0 to 2 and mRS improvement at 90 days in both unadjusted and adjusted analyses (Table 2 and Figure 2). However, no significant differences were observed in the other secondary outcomes in both the unadjusted and adjusted full analysis sets, including early neurologic 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 an mRS score of 0 to 2 and mRS improvement within 90 days were also found between groups in both unadjusted and adjusted analyses, while no significant differences were evident in the other secondary outcomes in both unadjusted and adjusted analyses (eFigure 2 and eTable 3 in Supplement 3).

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

	Group, No. (%)			Unadjusted		Adjusted[b]	
	Remote ischemic conditioning (n = 863)	Control (n = 913)	Treatment effect metric[a]	Treatment difference (95% CI)	*P* value	Treatment difference (95% CI)	*P* value
Primary outcome							
mRS score of 0 to 1 within 90 d[c]	582 (67.4)	566 (62.0)	RR[d]	1.17 (1.03 to 1.32)	.02	1.18 (1.04 to 1.34)	.007
			RD, %[d]	5.4 (1.0 to 9.9)	.02	6.2 (2.0 to 10.4)	.004
Secondary outcomes							
mRS score of 0 to 2 within 90 d[c]	687 (79.6)	689 (75.5)	RR[d]	1.20 (1.01 to 1.43)	.04	1.22 (1.03 to 1.45)	.02
			RD, %[d]	4.1 (0.3 to 8.0)	.04	4.3 (0.9 to 7.8)	.01
Early neurologic deterioration within 7 d[e]	77 (8.9)	64 (7.0)	RR[d]	1.27 (0.93 to 1.75)	.14	1.26 (0.91 to 1.73)	.16
			RD, %[d]	1.9 (−0.6 to 4.4)	.14	1.8 (−0.8 to 4.3)	.17
Stroke-associated pneumonia within 12 d[f]	26 (3.0)	19 (2.1)	RR[d]	1.45 (0.81 to 2.60)	.21	1.48 (0.82 to 2.65)	.19
			RD, %[d]	0.9 (−0 to 2.4)	.21	1.0 (−0.4 to 2.5)	.17
Change in NIHSS score at day 12 from baseline, median (IQR)[g,d]	4 (2 to 6)	4 (2 to 5)	GMR	1.02 (0.99 to 1.05)	.32	1.02 (0.99 to 1.05)	.30
Stroke or other vascular events within 90 d[h]	7 (0.8)	6 (0.7)	HR	1.24 (0.42 to 3.68)	.70	1.21 (0.40 to 3.61)	.74
Death within 90 d[h]	7 (0.8)	10 (1.1)	HR	0.74 (0.28 to 1.94)	.54	0.63 (0.24 to 1.70)	.37

Abbreviations: GMR, geometric mean ratio; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; RD, risk difference; RR, risk ratio.

[a] Treatment effect is presented as RR, RD, GMR, HR, or mean difference (95% CI) of remote ischemic conditioning vs control group, analyzed by unadjusted and adjusted binary logistic regression.

[b] Adjusted for key prognostic covariates (age, sex, premorbid function [mRS score, 0 or 1], NIHSS score at randomization, history of stroke or transient ischemic attack, and time from the onset of symptom to remote ischemic conditioning).

[c] 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. There was 1 patient with disagreement over mRS (in the control group) between the central adjudicator and site assessor.

[d] Calculated using generalized linear model.

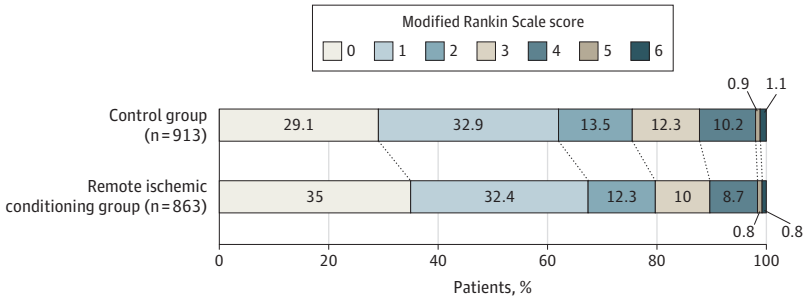
[e] Early neurologic deterioration was defined as an increase between baseline and 7 days of ≥2 on the NIHSS score, but not result of cerebral hemorrhage (eMethods in Supplement 3).

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

[g] NIHSS scores range from 0 to 42, with higher scores indicating greater stroke severity. Log(NIHSS+1) was analyzed using generalized linear model. There were 3 patients with disagreement over NIHSS (2 in the remote ischemic conditioning group and 1 in the control group) between the central adjudicator and site assessor.

[h] Calculated with Cox regression model.

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



The 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 was 1.29 (95% CI, 1.09-1.52), and the *P* value was .003; the adjusted odds ratio was 1.37 (95% CI, 1.16-1.63), and the adjusted *P* value was <.001.

Prespecified subgroup analysis showed no significant treatment heterogeneity 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 (eFigure 3 in Supplement 3). The results of the per-protocol analysis were similar to those of the full analysis set for the primary outcome (eFigure 4 in Supplement 3).

Adverse Events

Adverse events occurred in 59 of 863 patients (6.8%) in the RIC group and 51 of 913 patients (5.6%) in the control group, including 23 serious adverse events (10/863 [1.2%] in the RIC

Table 3. Adverse Events in the Full Analysis Set

	Group, No. (%)	
	Remote ischemic conditioning (n = 863)	Control (n = 913)
Adverse events		
All	59 (6.8)	51 (5.6)
Serious	10 (1.2)	13 (1.4)
Remote ischemic conditioning-related adverse events[a]		
Pain in arms[b]	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

Abbreviation: 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 was further adjudicated by the central principal investigator. The judgment criteria to evaluate association between adverse events and remote ischemic conditioning treatment are available in Supplement 1; the final decision of remote ischemic conditioning–related adverse events were made by the site principal investigator.

[b] We defined visual analog scale ≥1 as pain. Few cases of pain in arms were reported in the present study, which may be attributed to the following reasons: One possible reason may be due to patients being notified on the informed consent form that they could potentially feel uncomfortable but not be injured as part of the remote ischemic conditioning treatment, which may have resulted in some patients feeling slight pain (for example, visual analog scale = 1) but not reporting it. Another possible reason was that we missed the pain information of some patients who withdrew due to the intolerance to remote ischemic conditioning treatment when assigned to the remote ischemic conditioning group.

group and 13/913 [1.4%] in the control group) (**Table 3**). The results in the per-protocol analysis are shown in eTable 4 in Supplement 3. 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 the arms, 2 with skin petechiae on the arms, and 1 with dizziness.

Discussion

In this randomized clinical trial of patients with acute moderate ischemic stroke, treatment with RIC performed twice daily for 2 weeks as an adjunct to guideline-based treatment, compared with guideline-recommended treatment alone, resulted in a greater likelihood of excellent functional outcome at 90 days after symptom onset.

Although many studies have investigated the effect of RIC on ischemic stroke, previous studies have not provided strong evidence for the neuroprotective effect of RIC, in contrast to the present trial. There were several differences between this and previous studies. First, in this study, the target population had acute moderate ischemic stroke within 48 hours, whereas the specific population was less targeted in previous studies.[11,13,18,19] It is reasonable that targeted patients with stroke are most likely to benefit from neuroprotective therapy[5]; a neuroprotective effect could be underestimated in patients with mild neurologic deficit, while in patients with severe neurologic deficit stroke it is mostly due to large artery occlusion and would not be improved by neuroprotective treatment without reperfusion treatment. Second, previous studies had relatively small sample sizes, ranging from 20 to 188.[9-11,20-25] To our knowledge, the present study is the largest randomized clinical trial of RIC treatment in AIS. Third, treatment intensity in the current study (5 cycles of 5 minutes ischemic and 5 minutes reperfusion to bilateral upper limbs, twice daily for 2 weeks) was greater than in previous studies (eg, 4 cycles of 5 minutes ischemic and 5 minutes reperfusion during transportation to the hospital),[11] suggesting that longer duration of RIC may exert more neuroprotective effect. This is supported by 2 studies[12,18] in which RIC treatment twice daily for 2 weeks or until discharge with a mean duration of 11.2 days was found to be neuroprotective. Additionally, longer duration of RIC treatment (more than 300 days) may be effective for secondary stroke prevention.[13,26] Fourth, 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]

There was no significant effect of RIC on early neurologic improvement such as early neurologic deterioration at 7 days and change in NIHSS score at 12 days. The absence of significant effect on early outcome vs the positive effect on longer-term outcome of RIC may also explain negative results in previous studies, which mainly focused on early outcomes.[10,21,22]

There were 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. The mean time from onset to RIC treatment initiation (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 suggest that the mechanism of RIC may be more recovery effect than neuroprotection: 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 to chronic RIC-induced neurorestorative effect such as angioneurogenesis and neuroplasticity of periinfarct area.[27,28] This possibility is supported by one animal study with very delayed RIC (5 days after

stroke, repeated for 14 consecutive days) that did not yield reduction of infarct volume, but produced neurologic improvement at least for 3 months.[29] The underlying mechanism of RIC in this study warrants further investigation in the future. Research should examine additional biomarkers as intermediary outcomes to demonstrate the effect of early vs late RIC in stroke. In addition, the present study 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).

The RIC-related adverse events (such as redness and skin petechiae on arms) were consistent with those described in previous studies,[10,12,18,21,23,30] except for the absence of arm pain. It is possible that participants experienced such pain but did not report it or that participants who had pain were those who withdrew due to RIC intolerance.

Limitations

This study had several limitations. First, the open-label design did not allow blinding of the assigned treatment to participants and physicians. Blinded-end point assessments were performed to reduce observer bias, but assessment of the success of outcome blinding was not performed. Second, a structured interview was used to assess the mRS disability score, which may have affected the accuracy of assessors in distinguishing how much of an individual's disability was due to stroke vs nonstroke. Third, there may have been outcome measurement bias in the full analysis set and selection bias in the exclusions after randomization. The relatively large amount of dropout after randomization may have introduced attrition bias, although there was a similar proportion of dropout in the RIC vs control group. Fourth, data regarding physiotherapy and speech language therapy were not collected and could not be assessed for possible confounding. Fifth, confirmation of these findings is required, including in non-Chinese populations, given potential differences compared with other populations in body mass, comorbid factors, and patterns of cerebrovascular disease of patients with AIS.

Conclusions

Among adults with acute moderate ischemic stroke, treatment with remote ischemic conditioning compared with usual care significantly increased the likelihood of excellent neurologic function at 90 days. However, these findings require replication in another trial before concluding efficacy for this intervention.

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