



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Effect of Remote Ischemic Conditioning in Ischemic Stroke Subtypes: A Post Hoc Subgroup Analysis From the RESIST Trial

Blauenfeldt, Rolf Ankerlund; Mortensen, Janne Kaergaard; Hjort, Niels; Valentin, Jan Brink; Homburg, Anne-Mette; Modrau, Boris; Sandal, Birgitte Forsom; Gude, Martin Faurholdt; Berhndtz, Anne Brink; Johnsen, Søren Paaske; Hess, David C.; Simonsen, Claus Ziegler; Andersen, Grethe

Published in:
Stroke

DOI (link to publication from Publisher):
[10.1161/STROKEAHA.123.046144](https://doi.org/10.1161/STROKEAHA.123.046144)

Creative Commons License
CC BY 4.0

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Blauenfeldt, R. A., Mortensen, J. K., Hjort, N., Valentin, J. B., Homburg, A.-M., Modrau, B., Sandal, B. F., Gude, M. F., Berhndtz, A. B., Johnsen, S. P., Hess, D. C., Simonsen, C. Z., & Andersen, G. (2024). Effect of Remote Ischemic Conditioning in Ischemic Stroke Subtypes: A Post Hoc Subgroup Analysis From the RESIST Trial. *Stroke*, 55(4), 874-879. <https://doi.org/10.1161/STROKEAHA.123.046144>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

CLINICAL TRIALS



Effect of Remote Ischemic Conditioning in Ischemic Stroke Subtypes: A Post Hoc Subgroup Analysis From the RESIST Trial

Rolf Ankerlund Blauenfeldt, MD, PhD; Janne Kaergaard Mortensen¹, MD, PhD; Niels Hjort¹, MD, PhD; Jan Brink Valentin¹, MSc; Anne-Mette Homburg, MD; Boris Modrau¹, MD, PhD; Birgitte Forsom Sandal, MD; Martin Faurholdt Gude¹, MD, PhD; Anne Brink Berndtz¹, MD, PhD; Søren Paaske Johnsen¹, MD, PhD; David C. Hess¹, MD; Claus Ziegler Simonsen¹, MD, PhD; Grethe Andersen¹, MD, DMSc

BACKGROUND: Remote ischemic conditioning (RIC) is a simple and noninvasive procedure that has proved to be safe and feasible in numerous smaller clinical trials. Mixed results have been found in recent large randomized controlled trials. This is a post hoc subgroup analysis of the RESIST trial (Remote Ischemic Conditioning in Patients With Acute Stroke), investigating the effect of RIC in different acute ischemic stroke etiologies, and whether an effect was modified by treatment adherence.

METHODS: Eligible patients were adults (aged ≥ 18 years), independent in activities of daily living, who had prehospital stroke symptoms with a duration of less than 4 hours. They were randomized to RIC or sham. The RIC treatment protocol consisted of 5 cycles with 5 minutes of cuff inflation alternating with 5 minutes with a deflated cuff. Acceptable treatment adherence was defined as when at least 80% of planned RIC cycles were received. The analysis was performed using the entire range (shift analysis) of the modified Rankin Scale (ordinal logistic regression).

RESULTS: A total of 698 had acute ischemic stroke, 253 (36%) were women, and the median (interquartile range) age was 73 (63–80) years. Median (interquartile range) overall adherence to RIC/sham was 91% (68%–100%). In patients with a stroke due to cerebral small vessel disease, who were adherent to treatment, RIC was associated with improved functional outcome, and the odds ratio for a shift to a lower score on the modified Rankin Scale was 2.54 (1.03–6.25); $P=0.042$. The association remained significant after adjusting for potential confounders. No significant associations were found with other stroke etiologies, and the overall test for interaction was not statistically significant (χ^2 4.33, $P=0.23$).

CONCLUSIONS: In patients with acute ischemic stroke due to cerebral small vessel disease, who maintained good treatment adherence, RIC was associated with improved functional outcomes at 90 days. These results should only serve as a hypothesis-generating for future trials.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03481777.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: cerebral small vessel diseases ■ humans ■ ischemic stroke ■ neuroprotection ■ stroke

Remote ischemic conditioning (RIC) applied as transient cycles of limb ischemia and reperfusion by inflating and deflating a cuff on the upper extremity exerts

distant organ protection in preclinical and clinical studies.¹ RIC is a simple and noninvasive procedure that has proved to be safe and feasible in numerous smaller clinical

Correspondence to: Rolf Ankerlund Blauenfeldt, MD, PhD, Department of Neurology, Aarhus University Hospital, Palle Juul Jensens Blvd 165, Entrance J 518, 8200 Aarhus, Denmark. Email rolfblau@rm.dk

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.123.046144>.

For Sources of Funding and Disclosures, see page 879.

© 2024 The Authors. *Stroke* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
LAA	large artery atherosclerosis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
RESIST	Remote Ischemic Conditioning in Patients With Acute Stroke
RIC	remote ischemic conditioning
SVD	small vessel disease

trials.^{2–5} In the open-label randomized controlled RICAMIS trial (Remote Ischemic Conditioning for Acute Moderate Ischemic Stroke), RIC treatment initiated within 48 hours after stroke and continued for 2 weeks was associated with improved functional outcomes.⁶ This effect was most pronounced in patients with acute ischemic stroke (AIS) caused by large artery atherosclerosis (LAA).⁷ In the sham-controlled RICA trial (Chronic Remote Ischemic Conditioning in Patients With Symptomatic Intracranial Arterial Stenosis), daily RIC for 1 year was applied as a secondary preventive strategy, in patients with symptomatic intracranial stenosis. Chronic RIC significantly reduced the recurrent stroke rate in patients who were $\geq 50\%$ adherent to treatment, but the trial did not meet its primary efficacy end point.⁸ In the randomized, sham-controlled RESIST trial (Remote Ischemic Conditioning in Patients With Acute Stroke), RIC was applied in the prehospital phase within 4 hours from symptom onset and repeated at the hospital. Overall, RIC was not associated with a beneficial improvement in 90-day functional outcome, but whether there is heterogeneity in treatment effect according to stroke cause and adherence is unknown.⁹

[See related article, p 880](#)

Here, we present a post hoc analysis of the effect of per-protocol use of RIC in subgroups of AIS and its effect on functional outcome.

METHODS

Study Design

The RESIST was an investigator-initiated, multicenter, randomized, patient and outcome-assessor-blinded, sham-controlled clinical trial.^{9,10} The trial was approved by Danish regional research ethics committees (ID: 1–10-72–97-17), Data Protection Agency (ID: 1–16-02–16-18), and Danish Medicines Agency (ID: 2017114177; EUDAMED: CIV-17–11-022324) as an acute study, and consent was waived in the acute prehospital phase. Consent was obtained from all patients or relatives and trial guardians as soon as possible after arrival at the hospital. The trial was registered at <https://www.clinicaltrials.gov> (NCT03481777) and

followed the CONSORT (Consolidated Standards of Reporting Trials) reporting guideline. The data and analytical code that support the findings of this study are available from the corresponding author upon reasonable request. Individual participant data that underlie results in this article will be shared after deidentification. To gain access, data requestors will need to sign a data processing agreement. Eligible patients were adults (aged ≥ 18 years), who were independent in activities of daily living (modified Rankin Scale [mRS] score ≤ 2), with a prehospital putative stroke (evaluated by prehospital stroke score), presenting within 4 hours from symptom onset. Patients with diagnoses of AIS or intracerebral hemorrhage were defined as the target population. Patients were randomized 1:1 to RIC or sham. RIC devices and sham devices were programmed to perform 5 cycles, each with 5 minutes of cuff inflation and 5 minutes with a deflated cuff. For the RIC device, the minimum cuff pressure was 200 mm Hg; if the initial systolic blood pressure was above 175 mm Hg, the cuff would inflate to 35 mm Hg above the systolic blood pressure to ensure complete arterial occlusion (maximum cuff pressure, 285 mm Hg). The sham device would only inflate to a pressure of 20 mm Hg. At 6 hours after completion of the first RIC/sham protocol, an additional series of RIC/sham was performed (post-conditioning) for all patients with a target diagnosis. Treatment was started immediately after randomization in the ambulance or helicopter. In patients with a target diagnosis admitted to Aarhus University Hospital, ischemic postconditioning was continued twice daily for 7 days.

If the patient was discharged before the seventh day, he/she would administer the RIC/sham treatment at home and subsequently return the device. Data on compliance was stored on each device. The protocol has been described in detail elsewhere.^{9,10}

Adherence

Adherence data were electronically stored on each RIC and sham device and consisted of the number of cycles and time stamps for each completed cycle. Data were downloaded upon return of each device to the stroke center. Acceptable treatment adherence was defined as at least 80% of planned RIC cycles received. For patients planned to receive acute and 6-hour treatment, 8 of 10 cycles would be defined as acceptable treatment adherence and similar when 56 of 70 cycles were received in patients with planned RIC/sham for 7 days. In the analysis, adherent RIC patients are compared with sham-treated patients with the same level of adherence.¹¹

Outcomes Measures

The primary efficacy outcome measure was the mRS (ranging from 0 to 6: 0: no symptoms and 6: dead) at 90 days in patients with acceptable adherence in different AIS subgroups. The blinded assessments could be in-person or telephone-based assessments and were performed by at least 2 independent assessors. In the case of rater disagreement, a third assessor (in-person or telephone) would act as the final assessor. National Institutes of Health Stroke Scale (NIHSS) was performed at hospital arrival and after 24 hours in the target population. AIS subgroups were based on the clinical impression at discharge by the treating physician and were performed according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.¹² AIS subgroups were LAA disease (symptomatic precranial or intracranial stenosis; *International Classification of Diseases*,

Tenth Revision [ICD-10]: I63.2, I63.0, I63.1, and I63.5), small vessel disease (SVD; ICD-10: I63.3), cardioembolic (ICD-10: I63.4), unknown/multiple/rare (ICD-10: I63.8 and I63.9), or missing.

Statistical Analysis

The analysis was performed using the entire range (shift analysis) of the mRS (ordinal logistic regression), with a random effect on the stratification groups as previously described in the target population group.⁹ To investigate the effect of stroke cause and treatment effect on the primary end point, we used an ordinal logistic regression model, relating the odds of the primary outcome with the covariate of interest and the randomization group (RIC/sham) in patients with an acceptable treatment adherence of at least 80%.

Adjustments for reperfusion therapy (yes/no), age (continuous), women/men, prestroke mRS (categorical [mRS, 0, 1, 2]), and prehospital stroke severity (prehospital stroke score ranges from 1 to 6) were performed as a post hoc analysis to explore the effect of potential confounders. No correction for multiple testing has been made, as the analysis is only for hypothesis generation purposes. The overall test for interaction between treatment and stroke cause was performed using the χ^2 test. All analyses were performed with a 2-sided alpha level of 0.05. Statistical analyses were performed in STATA SE, version 18.0 (StataCorp, College Station, TX).

RESULTS

From March 16, 2018, to November 11, 2022, a total of 1611 patients underwent prehospital screening. Of these, 111 were screen failures. A total of 1500

patients were randomized; 67 patients were excluded mainly due to withdrawal of consent (Figure S1). A total of 902 patients were included in the target population group, and of these, 737 (82%) patients had AIS and 165 (18%) had ICH. In 39 patients with transient neurological symptoms and an acute lesion on MRI, there was no available information on stroke cause. In the remaining 698 patients with AIS, 147 (21%) had symptomatic precerebral or intracranial LAA disease, 93 (13%) had stroke due to SVD, 101 (15%) had cardioembolic, and 357 (51%) had multiple identified causes, rare causes, or undetermined causes. Baseline characteristics were well balanced between the 2 treatment arms. However, among patients with cardioembolic stroke, 37 (80%) in the RIC group had AF versus 33 (60%) in the sham group (Table S1; $P=0.027$). In 452 of 698 patients with AIS with an acceptable adherence, baseline characteristics are presented in Table 1.

Functional Outcome

In patients with a predefined acceptable treatment adherence ($\geq 80\%$), RIC was associated with improved functional outcomes in patients with AIS due to SVD (odds ratio, 2.54 [95% CI, 1.03–6.25]; $P=0.042$). The adjusted analysis did not change the association (adjusted odds ratio, 3.58 [95% CI, 1.30–9.88]; $P=0.013$).

There was no significant effect of adherence to RIC treatment and 90-day functional outcome in other

Table 1. Baseline Demographic, Clinical, and Treatment Characteristics Stratified by Stroke Cause in Patients With a Good Treatment Adherence

n	Total 452	LAA		SVD		Cardio		Multiple unknown	
		RIC 32	Sham 52	RIC 34	Sham 31	RIC 22	Sham 37	RIC 115	Sham 129
Age, y; median, IQR	71 (62–78)	74 (69–83)	71 (63–78)	69 (62–74)	67 (59–75)	71 (62–79)	72 (63–78)	69 (61–77)	72 (62–77)
Female, n (%)	148 (33%)	3 (9%)	14 (27%)	12 (35%)	11 (35%)	13 (59%)	14 (38%)	37 (32.2%)	44 (34.1%)
Hypertension, n (%)*	276 (61%)	25 (78%)	36 (69%)	24 (71%)	20 (65%)	10 (45%)	19 (51%)	69 (60.0%)	73 (56.6%)
Diabetes, n (%)*	61 (14%)	3 (9%)	4 (8%)	8 (24%)	6 (19%)	1 (5%)	3 (8%)	14 (12.2%)	22 (17.1%)
Atrial fibrillation, n (%)*	63 (14%)	3 (9%)	5 (10%)	1 (3%)	0 (0%)	16 (73%)	20 (54%)	11 (9.6%)	7 (5.4%)
Prior AIS, n (%)	77 (17%)	7 (22%)	11 (21%)	6 (18%)	5 (16%)	4 (18%)	8 (22%)	16 (13.9%)	20 (15.5%)
Prior TIA, n (%)	36 (8%)	2 (6%)	7 (13%)	4 (12%)	1 (3%)	1 (5%)	2 (5%)	10 (8.7%)	9 (7.0%)
Onset to randomization, min; median, IQR	58 (35–103)	54 (37–84)	61 (32–106)	68 (33–119)	54 (33–117)	40 (29–63)	48 (29–71)	67 (40–128)†	60 (36–94)†
PreSS, median (IQR)‡	2 (1–3)	3 (2–3)	3 (2–4)	2 (2–2)†	2 (2–3)†	3 (2–3)	2 (2–4)	2 (1–3)	2 (1–3)
Admission NIHSS score, median (IQR)§	4 (2–7)	4 (2–18)	6 (3–14)	3 (2–6)	5 (3–7)	4 (3–9)	4 (1–7)	3 (2–6)	4 (2–6)
Thrombectomy, n (%)	73 (16%)	11 (34%)	20 (38%)	0 (0%)	0 (0%)	6 (27%)	11 (30%)	13 (11%)	12 (9%)
Intravenous thrombolysis, n (%)	323 (72%)	28 (88%)	38 (73%)	24 (71%)	27 (87%)	13 (59%)	20 (54%)	85 (74%)	88 (68%)
Reperfusion therapy (IVT and EVT), n (%)	351 (78%)	29 (91%)	44 (85%)	24 (71%)	27 (87%)	15 (68%)	28 (76%)	89 (77%)	95 (74%)
Adherence, %; median, IQR	99 (91–101)	95 (88–100)	97 (89–100)	100 (93–101)	100 (93–101)	98 (94–100)	94 (89–100)	100 (94–103)	100 (91–105)

AIS indicates acute ischemic stroke; Cardio, cardioembolic stroke; EVT, endovascular therapy/thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PreSS, prehospital stroke score; RIC, remote ischemic conditioning; SVD, small vessel disease; and TIA, transient ischemic attack.

*Known or newly diagnosed.

†Denotes significant between groups differences.

‡Scores on the PreSS range from 0 to 6, with higher scores indicating a greater deficit.

§Scores on the NIHSS score range from 0 to 42, with higher scores indicating a greater deficit.

||Only intravenous thrombolysis with alteplase infusion was used during the study period.

Table 2. Odds for Improvement in Functional Outcome in Acute Ischemic Stroke Subtypes With Good Treatment Adherence

Acute ischemic stroke with good adherence (n=452)	Effect variable		P value
Large artery atherosclerosis (n=84)		OR (95% CI)	
Unadjusted	OR	0.95 (0.43–2.08)	0.902
Adjusted*	aOR	1.00 (0.43–2.33)	0.991
Small vessel disease (n=65)		Value (95% CI)	
Unadjusted	OR	2.54 (1.03–6.25)	0.042
Adjusted*	aOR	3.58 (1.30–9.88)	0.013
Cardioembolic (n=59)		Value (95% CI)	
Unadjusted	OR	0.64 (0.24–1.75)	0.388
Adjusted†	aOR	0.63 (0.21–1.83)	0.391
Multiple/unknown/rare (n=244)		Value (95% CI)	
Unadjusted	OR	1.06 (0.67–1.66)	0.805
Adjusted*	aOR	0.90 (0.57–1.43)	0.659

aOR indicates adjusted odds ratio; mRS, modified Rankin Scale; OR, odds ratio; and PreSS, prehospital stroke severity.

*Adjusted for reperfusion therapy (yes/no), age (continues), women/men, pre-stroke mRS (0, 1, or 2), and PreSS.

†Adjusted for reperfusion therapy (yes/no), age (continues), women/men, pre-stroke mRS (0, 1, or 2), atrial fibrillation (yes/no), and PreSS.

subgroups of AIS (Table 2). Between-group distribution of the 90-day mRS in all subgroups is presented in Figure S2.

Overall, a favorable functional outcome (mRS, 0–2) was found in 373 (83%) of 452 patients with AIS. RIC treatment was not associated with more patients achieving a favorable functional outcome in any of the subgroups (Table 3). No significant differences were found in early markers of neurological improvement or functional outcome (Table 3). The overall test for interaction between treatment and stroke cause was not significant (χ^2 , 4.33 [df, 3]; $P=0.23$).

The Figure shows a forest plot illustrating the odds ratio for a shift toward a better outcome stratified by treatment duration, RIC, and acceptable adherence in different AIS etiologies. In patients with SVD, receiving

80% of 7 days of RIC treatment was associated with a significant improvement in functional outcome but not in patients who planned to receive only the acute and 6-hour treatment. For other stroke etiologies, there was no significant benefit of receiving additional treatment for 7 days. The overall test of interaction between treatment and stroke cause was not statistically significant (acute and 6-hour treatment: χ^2 , 2.09 [df, 3]; $P=0.55$ and 7 days: χ^2 , 3.31 [df, 3]; $P=0.35$).

DISCUSSION

In this per-protocol subgroup analysis, we found evidence of treatment heterogeneity of RIC within stroke subgroups. In patients with AIS due to SVD and acceptable treatment adherence, RIC treatment compared with sham was associated with a significant improvement in mRS at 90 days. We found no association with other AIS etiologies. These results may guide future studies on RIC in stroke due to SVD but should be interpreted with caution.

The primary results of the RESIST trial did not show a treatment benefit of combined prehospital and in-hospital RIC for AIS. Two recent randomized trials applied RIC at later time points and demonstrated the possible efficacy of RIC. In the nonsham controlled trial RICAMIS (N=1893), bilateral upper extremity RIC was initiated within 48 hours of symptom onset in patients with moderate to severe AIS (NIHSS score, 6–16), who were not treated with reperfusion therapy. The majority of patients in RESIST received reperfusion therapies (75%). The median time from onset to RIC was 25 hours in RICAMIS compared with 56 minutes in RESIST. In the sham-controlled RICA trial (N=3033), bilateral upper extremity RIC was applied as a daily treatment for 1 year following a recent qualifying stroke/TIA. The primary end point of time to first recurrent ischemic stroke was not reached, but in patients who were adherent to treatment (defined as adhering >50% of days), daily RIC significantly reduced the risk of recurrent stroke.

Table 3. Early and Long-Term Neurological Outcomes in Subgroups of Acute Ischemic Stroke With Good Treatment Adherence

AIS	Total	LAA		SVD		Cardio		Multiple unknown	
		RIC	Sham	RIC	Sham	RIC	Sham	RIC	Sham
n	452	32	52	34	31	22	37	115	129
Favorable functional outcome (mRS, 0–2), n (%)	379 (83%)	25 (78%)	39 (75%)	31 (91%)	24 (78%)	18 (82%)	33 (89%)	97 (84%)	106 (82%)
24-h NIHSS score, median (IQR)	2 (0 to 4)	2 (0 to 4)	2 (0 to 6)	2 (1 to 3)	2 (0 to 5)	1 (0 to 4)	1 (0 to 2)	1 (0 to 3)*	2 (1 to 4)*
24-h NIHSS score drop ≥ 4 , n (%)	132 (29%)	14 (45%)	22 (42%)	9 (26%)	8 (26%)	8 (36%)	15 (41%)	28 (25%)	28 (22%)
24-h difference in NIHSS score, median (IQR)	–2 (–4 to 0)	–2 (–9 to –1)	–3 (–9 to –1)	–2 (–4 to 0)	–2 (–4 to 0)	–2 (–5 to 0)	–2 (–6 to 0)	–2 (–3 to 0)	–1 (–3 to 0)
90-d mortality, n (%)	13 (3%)	2 (6%)	2 (4%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	2 (2%)	6 (5%)

AIS indicates acute ischemic stroke; Cardio, cardioembolic stroke; IQR, interquartile range; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RIC, remote ischemic conditioning; and SVD, small vessel disease.

*Significant between groups differences.

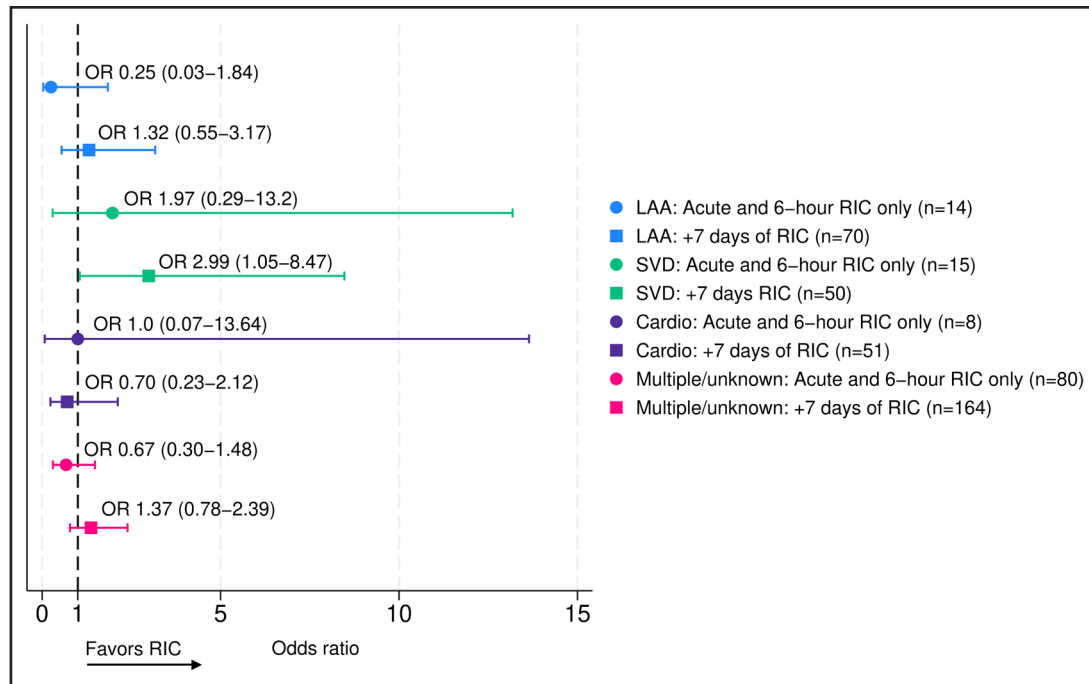


Figure. The effect of treatment duration on functional outcome in acute ischemic stroke subgroups.

ORs are unadjusted. Cardio indicates cardioembolic stroke; mRS, modified Rankin Scale; OR, odds ratio; LAA, large artery atherosclerosis; RIC, remote ischemic conditioning; and SVD, small vessel disease.

In RESIST, the unilateral dosing of RIC may be insufficient to elicit a response in a comorbid stroke population, and RIC may not provide enough protection in the hyperacute phases of stroke as the positive trials that have applied RIC in the subacute or chronic phases of stroke. On the other hand, a placebo response in the RICAMIS trial cannot be ruled out because the trial was not sham-controlled and the mRS is not an entirely objective measure.^{11,13}

Recently, the RICAMIS authors published a subgroup analysis demonstrating a higher treatment effect of RIC in patients with AIS due to LAA compared with non-LAA.⁷ It is unknown how many patients had a stroke due to SVD, which also may be limited by the inclusion criteria of stroke severity (NIHSS) of at least 6. Previous smaller trials have tested long-term RIC in patients with SVD or intracranial stenosis and found reduced growth in white matter hyperintensity volume compared with the control group and improved long-term cognitive function.^{14,15} The protective mechanisms may involve reduced inflammatory responses, enhanced recovery, and angiogenesis.^{1,16–20} Another study found beneficial effects on administering isosorbide mononitrate in patients with SVD.²¹ Interestingly, nitric oxide release is one of the proposed mechanisms of RIC and may explain some of the observed differences.¹ It is currently unknown whether these molecular pathways and the effects of RIC are differentially expressed in stroke subtypes.

In the present study, adherent patients with AIS caused by SVD had significantly improved outcomes when treated with RIC. The associations remained significant and strengthened after adjusting for potential confounders. In the stratified analysis according to the planned duration of RIC (acute and 6 hours versus additional 7 days), the direction of the estimates both favored RIC, but only the 7-day RIC treatment was associated with increased odds for functional improvement. The effect of RIC may be more pronounced if given for a longer duration or when applied after the acute phase of stroke, which would be in line with the results from the RICA and RICAMIS trials. The study has several limitations. The classification of stroke etiologies was based on the clinical impression of the discharging physician and was not centrally adjudicated. The sample size was small, the stroke severities at baseline were mild to moderate (NIHSS score, 4), and many received reperfusion therapies (75%), factors that risk introducing a ceiling effect to any potential treatment benefit of RIC. This may also limit the sensitivity secondary end points, such as a 24-hour drop in NIHSS of at least 4 points.

The current results should be interpreted with caution, as the primary trial result was neutral, and the subgroup of patients with SVD (n=93) was small. Furthermore, no correction for multiple comparisons has been made in this post hoc analysis, and the results should only serve as hypothesis-generating and guide future trials on RIC treatment in patients with AIS.

CONCLUSIONS

In this post hoc subgroup analysis, we found that in adherent patients with AIS due to SVD, RIC was associated with a significant improvement in mRS at 90 days. We found no significant association between other etiologies of AIS and functional outcomes.

ARTICLE INFORMATION

Received December 8, 2023; final revision received January 17, 2024; accepted January 19, 2024.

Presented in part at the International Stroke Conference, Phoenix, AZ, February 7–9, 2024.

Affiliations

Department of Neurology, Aarhus University Hospital, Denmark (R.A.B., J.K.M., N.H., C.Z.S., G.A.). Department of Clinical Medicine, Aarhus University, Denmark (R.A.B., J.K.M., N.H., M.F.G., C.Z.S., G.A.). Department of Clinical Medicine, Danish Center for Health Services Research, Aalborg University, Denmark (J.B.V., S.P.J.). Department of Neurology, Research Unit for Neurology, Odense University Hospital, Denmark (A.-M.H.). Department of Neurology, Aalborg University Hospital, Denmark (B.M.). Department of Neurology, Regional Hospital Gødstrup, Denmark (B.F.S., A.B.B.). Department of Research and Development, Prehospital Emergency Medical Services, Central Denmark Region, Aarhus, Denmark (M.F.G.). Department of Neurology, Medical College of Georgia, Augusta University, GA (D.C.H.).

Acknowledgments

The data that support the findings of this study are available from the corresponding author upon reasonable request. Individual participant data that underlie results in this article will be shared after deidentification. Proposals should be directed to rolfbblau@rm.dk. To gain access, data requestors will need to sign a data processing agreement. Dr Blauenfeldt and J.B. Valentin had full access to all the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis.

Sources of Funding

The trial received funding from TrykFonden (120636), the National Institute of Health (1R01NS112511-01A1), the Novo Nordisk Foundation (NNF00052924 and NNF0060998) the Manufacturer Vilhelm Pedersen and Wife's Foundation (NNF16OC0023474), and the Aase and Ejnar Danielsen Foundation (10-002120). 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 article; and decision to submit the article for publication.

Disclosures

Dr Blauenfeldt received lecture fees from Bayer, Pfizer, and Novo Nordisk, unrelated to the submitted work. Dr Hess was supported by a research grant from the National Institutes of Health. Dr Simonsen was supported by research grants from the Health Research Foundation of the Central Denmark Region. The other authors report no conflicts.

Supplemental Material

Figures S1–S2

Table S1

CONSORT Checklist and Protocols

REFERENCES

- Hess DC, Blauenfeldt RA, Andersen G, Hougaard KD, Hoda MN, Ding Y, Ji X. Remote ischaemic conditioning—a new paradigm of self-protection in the brain. *Nat Rev Neurol*. 2015;11:698–710. doi: 10.1038/nrneuro.2015.223
- Pico F, Lapergue B, Ferrigno M, Rosso C, Meseguer E, Chadenat ML, Bourdain F, Obadia M, Hirel C, Duong DL, et al. Effect of in-hospital remote ischemic preconditioning on brain infarction growth and clinical outcomes in patients with acute ischemic stroke: the RESCUE BRAIN randomized clinical trial. *JAMA Neurol*. 2020;77:11. doi: 10.1001/jamaneuro.2020.0326
- Hougaard KD, Hjort N, Zeidler D, Sørensen L, Nørgaard A, Hansen TM, von Weitzel-Mudersbach P, Simonsen CZ, Damgaard D, Gottrup H, et al. Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke*. 2014;45:159–167. doi: 10.1161/STROKEAHA.113.001346
- England TJ, Hedstrom A, O'Sullivan SE, Woodhouse L, Jackson B, Sprigg N, Bath PM. Remote ischemic conditioning after stroke trial 2: a phase IIb randomized controlled trial in hyperacute stroke. *J Am Heart Assoc*. 2019;8:e013572. doi: 10.1161/JAHA.119.013572
- England TJ, Hedstrom A, O'Sullivan S, Donnelly R, Barrett DA, Sarmad S, Sprigg N, Bath PM. RECAST (Remote Ischemic Conditioning after Stroke Trial): a pilot randomized placebo controlled phase II trial in acute ischemic stroke. *Stroke*. 2017;48:1412–1415. doi: 10.1161/STROKEAHA.116.016420
- Chen HS, Cui Y, Li XQ, Wang XH, Ma YT, Zhao Y, Han J, Deng CQ, Hong M, Bao Y, et al; RICAMIS Investigators. Effect of remote ischemic conditioning vs usual care on neurologic function in patients with acute moderate ischemic stroke: the RICAMIS randomized clinical trial. *JAMA*. 2022;328:627–636. doi: 10.1001/jama.2022.13123
- Cui Y, Yuan ZM, Liu QY, Wang YJ, Chen HS. Remote ischemic conditioning and outcomes in acute ischemic stroke with versus without large artery atherosclerosis. *Stroke*. 2023;54:3165. doi: 10.1161/STROKEAHA.123.045040
- Hou C, Lan J, Lin Y, Song H, Wang Y, Zhao W, Li S, Meng R, Hao J, Ding Y, et al. Chronic remote ischaemic conditioning in patients with symptomatic intracranial atherosclerotic stenosis (the RICA trial): a multicentre, randomised, double-blind sham-controlled trial in China. *Lancet Neurol*. 2022;21:1089. doi: 10.1016/S1474-4422(22)00335-0
- Blauenfeldt RA, Hjort N, Valentin JB, Homburg AM, Modrau B, Sandal BF, Gude MF, Hougaard KD, Damgaard D, Poulsen M, et al. Remote ischemic conditioning for acute stroke: the RESIST randomized clinical trial. *JAMA*. 2023;330:1236–1246. doi: 10.1001/jama.2023.16893
- Blauenfeldt RA, Hjort N, Gude MF, Behrmdtz AB, Fisher M, Valentin JB, Kirkegaard H, Johnsen SP, Hess DC, Andersen G. A multicentre, randomised, sham-controlled trial on REremote iSchemic conditioning in patients with acute Stroke (RESIST) – rationale and study design. *Eur Stroke J*. 2020;5:94–101. doi: 10.1177/2396987319884408
- Blauenfeldt RA, Simonsen CZ, Valentin JB, Johnsen SP, Hjort N, Andersen G. Outcomes following adherence to a randomized stroke trial protocol. *JAMA Netw Open*. 2024;7:e2349730. doi: 10.1001/jamanetworkopen.2023.49730
- Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993;24:35–41. doi: 10.1161/01.str.24.1.35
- Broderick JP, Adeoye O, Elm J. The evolution of the modified Rankin scale and its use in future stroke trials. *Stroke*. 2017;48:2007–2012. doi: 10.1161/STROKEAHA.117.017866
- Amorim S, Felício AC, Aagaard P, Suetta C, Blauenfeldt RA, Andersen G. Effects of remote ischemic conditioning on cognitive performance: a systematic review. *Physiol Behav*. 2022;254:113893. doi: 10.1016/j.physbeh.2022.113893
- Wang Y, Meng R, Song H, Liu G, Hua Y, Cui D, Zheng L, Feng W, Liebeskind DS, Fisher M, et al. Remote ischemic conditioning may improve outcomes of patients with cerebral small-vessel disease. *Stroke*. 2017;48:3064–3072. doi: 10.1161/STROKEAHA.117.017691
- Zhou D, Ding J, Ya J, Pan L, Wang Y, Ji X, Meng R. Remote ischemic conditioning: a promising therapeutic intervention for multi-organ protection. *Aging (Milano)*. 2018;10:1825–1855. doi: 10.18632/aging.101527
- Ramagiri S, Taliyan R. Remote limb ischemic post conditioning during early reperfusion alleviates cerebral ischemic reperfusion injury via GSK-3 β /CREB/BDNF pathway. *Eur J Pharmacol*. 2017;803:84–93. doi: 10.1016/j.ejphar.2017.03.028
- Li X, Ren C, Li S, Han R, Gao J, Huang Q, Jin K, Luo Y, Ji X. Limb remote ischemic conditioning promotes myelination by upregulating PTEN/Akt/mTOR signaling activities after chronic cerebral hypoperfusion. *Aging Dis*. 2017;8:392–401. doi: 10.14336/AD.2016.1227
- Xu R, He Q, Wang Y, Yang Y, Guo ZN. Therapeutic potential of remote ischemic conditioning in vascular cognitive impairment. *Front Cell Neurosci*. 2021;15:706759. doi: 10.3389/fncel.2021.706759
- Yu W, Ren C, Ji X. A review of remote ischemic conditioning as a potential strategy for neural repair poststroke. *CNS Neurosci Ther*. 2022;29:516–524. doi: 10.1111/cns.14064
- Wardlaw JM, Woodhouse LJ, Mhlanga II, Oatey K, Heye AK, Bamford J, Cvorovic V, Doubal FN, England T, Hassan A, et al; Lacunar Intervention Trial-2 (LACI-2) Investigator Group. Isosorbide mononitrate and cilostazol treatment in patients with symptomatic cerebral small vessel disease: the lacunar intervention trial-2 (LACI-2) randomized clinical trial. *JAMA Neurol*. 2023;80:682–692. doi: 10.1001/jamaneuro.2023.1526