Cochrane
Library

Cochrane Database of Systematic Reviews

Remote ischaemic conditioning for preventing and treating ischaemic stroke (Review)

Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X

Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X.
Remote ischaemic conditioning for preventing and treating ischaemic stroke.
Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012503.
DOI: [10.1002/14651858.CD012503.pub2](https://doi.org/10.1002/14651858.CD012503.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	8
OBJECTIVES	9
METHODS	9
RESULTS	11
Figure 1.	12
Figure 2.	14
Figure 3.	15
DISCUSSION	18
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	20
REFERENCES	21
CHARACTERISTICS OF STUDIES	24
DATA AND ANALYSES	51
Analysis 1.1. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 1 Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up.	52
Analysis 1.2. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 2 Death or dependency at completion of follow-up.	52
Analysis 1.3. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 3 Stroke severity.	53
Analysis 1.6. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 6 Cardiovascular events.	53
Analysis 1.8. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 8 Adverse events associated with RIC treatment.	54
Analysis 2.2. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 2 Death or dependency at the completion of follow up.	55
Analysis 2.3. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 3 Stroke severity.	55
Analysis 2.5. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 5 Improvement in psychological and cognitive impairment at completion of follow-up.	56
APPENDICES	56
WHAT'S NEW	59
CONTRIBUTIONS OF AUTHORS	59
DECLARATIONS OF INTEREST	59
SOURCES OF SUPPORT	59
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	59
INDEX TERMS	60

[Intervention Review]

Remote ischaemic conditioning for preventing and treating ischaemic stroke

Wenbo Zhao¹, Jing Zhang¹, Mordechai G Sadowsky², Ran Meng¹, Yuchuan Ding², Xunming Ji³

¹Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China. ²Department of Neurological Surgery, Wayne State University School of Medicine, Detroit, Michigan, USA. ³Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Contact: Xunming Ji, Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, 100053, China.
jixm@ccmu.edu.cn.

Editorial group: Cochrane Stroke Group.

Publication status and date: Edited (no change to conclusions), published in Issue 9, 2019.

Citation: Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X. Remote ischaemic conditioning for preventing and treating ischaemic stroke. *Cochrane Database of Systematic Reviews* 2018, Issue 7. Art. No.: CD012503. DOI: [10.1002/14651858.CD012503.pub2](https://doi.org/10.1002/14651858.CD012503.pub2).

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Remote ischaemic conditioning (RIC) has been developed as a neuroprotective strategy to prevent and treat ischaemic stroke. It usually involves restricting blood flow to limbs and then releasing the ischaemic blood to promote a neuroprotective effect. Preclinical studies have suggested that RIC may have beneficial effects in ischaemic stroke patients and those at risk of ischaemic stroke. However, existing evidence is insufficient to demonstrate the efficacy and safety of RIC in preventing and treating ischaemic stroke.

Objectives

To assess the benefits and harms of RIC for preventing ischaemic stroke and for treating people with ischaemic stroke and those at risk for ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (16 January 2018), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12) in the *Cochrane Library* (January 2018), MEDLINE Ovid (1946 to January 2018), Embase Ovid (1974 to January 2018), Web of Science Core Collection (1950 to January 2018) and three Chinese databases (January 2018). We also searched four ongoing trials registers, reference lists, and conference proceedings.

Selection criteria

We included randomised controlled trials (RCTs) comparing RIC with sham RIC or medical management in people with ischaemic stroke or at risk of ischaemic stroke.

Data collection and analysis

Two review authors independently selected studies, assessed trial quality and risk of bias, and extracted data. We used the GRADE approach to assess the quality of the evidence.

Main results

We included seven trials, involving 735 participants, in this review. We analysed the effects of RIC on preventing and treating ischaemic stroke respectively.

We evaluated risk of bias and judged it to be low for generation of allocation sequence in six studies and unclear in one study; unclear for allocation concealment in four studies and low in three studies; high for incomplete outcome data (attrition bias) in five studies and low in two studies; high for blinding in three studies and low in four studies; low for selective reporting; and high for other sources of bias in six studies and low in one study.

We included three trials (involving 371 participants) in the analysis of the effects of RIC on ischaemic stroke prevention. In people with symptomatic intracerebral artery stenosis, recurrent stroke was significantly reduced by RIC (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.12 to 0.83; 2 trials, 182 participants, low-quality evidence). In people with carotid stenosis undergoing carotid stenting, there was no significant difference in the incidence of ischaemic stroke between participants treated with RIC and non-RIC (RR 0.22, 95% CI 0.01 to 4.03; 1 trial, 189 participants, low-quality evidence); however the stroke severity (assessed by infarct volume) was significantly lower in participants treated with RIC (mean difference (MD) -0.17 mL, 95% CI -0.23 to -0.11; 1 trial, 189 participants, low-quality evidence). Adverse events associated with RIC were significantly higher in participants treated with RIC (RR 10.91; 95% CI 2.01 to 59.28; 3 trials, 371 participants, low-quality evidence), but no severe adverse event was attributable to RIC treatment. No participants experienced death or cardiovascular events during the period of the studies; and no trial reported haemorrhagic stroke or improvement in neurological, psychological or cognitive impairment.

We included four trials (involving 364 participants) in the analysis of the effects of RIC on ischaemic stroke treatment. In acute ischaemic stroke, for people receiving intravenous thrombolysis, the rate of death or dependency was significantly increased by RIC treatment compared with non-RIC treatment (RR 2.34; 95% CI 1.19 to 4.61; 1 trial, 285 participants, low-quality evidence). In people with acute ischaemic stroke, there was no significant difference between RIC and non-RIC for reducing stroke severity as assessed by the National Institutes of Health Stroke Scale score and the final infarct volume (standardised mean difference (SMD) -0.24 mL, 95% CI -1.02 to 0.54; 2 trials, 175 participants, very low quality evidence). There was no significant difference between RIC and non-RIC for improving the psychological impairment (SMD -0.37 points, 95% CI -1.15 to 0.41; 1 trial, 26 participants, very low quality evidence) and the cognitive impairment (SMD -0.26 points; 95% CI -0.72 to 0.21; 3 trials, 79 participants, low-quality evidence) in people with acute ischaemic stroke and cerebral small vessel disease. No trial reported ischaemic stroke, recurrent ischaemic stroke, improvement in neurological impairment, hemorrhagic stroke, cardiovascular events, and RIC associated adverse events.

Authors' conclusions

We found low-quality evidence that RIC may reduce the risk of recurrent stroke in participants with intracerebral artery stenosis and reduce stroke severity in participants undergoing carotid stenting, but it may increase death or dependence in participants with acute ischaemic stroke who are undergoing intravenous thrombolysis. However, there is considerable uncertainty about these conclusions because of the small number of studies and low quality of the evidence.

PLAIN LANGUAGE SUMMARY

Remote ischaemic conditioning for preventing and treating stroke caused by low blood flow

Review question

What are the benefits of using remote ischaemic conditioning (a noninvasive physical therapy that involves inflating blood pressure cuffs to reduce blood flow in arms and legs, and then releasing the affected blood around the body) in people with stroke or those at risk of stroke caused by low blood flow?

Background

Stroke is the leading cause of adult disability globally, and ischaemic stroke (caused by reduced blood flow) accounts for most strokes. Nearly a quarter of individuals with ischaemic stroke will experience further events (recurrent stroke). Remote ischaemic conditioning (RIC) is a strategy to protect and prevent damage to brain tissue by improving its ability to tolerate reduced blood flow. Studies have suggested that RIC may have beneficial effects for preventing and treating ischaemic stroke.

Study characteristics

This review included seven studies (specifically randomised controlled trials), involving 735 people. The studies compared RIC with sham RIC or medical management in people with ischaemic stroke or at risk of ischaemic stroke. Three trials (involving 371 people) were eligible for our analysis of RIC for preventing ischaemic stroke, and another four trials (involving 364 people) were eligible for our analysis of RIC for treating ischaemic stroke. The included trials were carried out in China, Denmark, and the UK.

Key results

The results of this review are current up to January 2018. In people with narrowing of arteries in the brain, RIC may reduce the risk of recurrent stroke. In people being treated with stenting (the insertion of a metal or plastic tube) for narrowed arteries in the neck, RIC may reduce the size of new brain injuries caused by reduced blood flow. However, its effect on clinical outcomes (stroke and death) was unclear. Adverse events were significantly more common in the RIC group but were not reported to be severe.

Among people with acute ischaemic stroke (where it had only been several hours from symptom onset) who received clot-dissolving medicines, we found that RIC may increase the risk of death or dependency (needing help from others). We found no significant differences in the size of the final stroke. In people with acute ischaemic stroke and chronic blood vessel disease of the brain, RIC did not affect measures of nerve function, mood, or thinking ability.

Quality of evidence

There is low-quality evidence which suggests that RIC may help prevent recurrent stroke in people with narrowed arteries in the brain, and may increase death or dependency in people with acute ischaemic stroke who received clot dissolving medication. The evidence is less clear for reducing the volume of the stroke (size of brain lesion caused by low blood flow). Further research is likely to have an important impact on our confidence in these findings.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. RIC versus non-RIC for preventing ischaemic stroke

RIC versus non-RIC for preventing ischaemic stroke

Patient or population: people at risk for ischaemic stroke

Setting: clinic and inpatient

Intervention: RIC

Comparison: non-RIC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-RIC for preventing ischaemic stroke	Risk with RIC				
Ischaemic stroke or recurrent ischaemic stroke	Symptomatic intracerebral artery stenosis or carotid stenting		RR 0.31 (0.12 to 0.76)	371 (3 RCTs)	⊕⊕⊕⊕ LOW 12	
	92 per 1000	29 per 1000 (11 to 70)				
Death or dependency	Symptomatic intracerebral artery stenosis or carotid stenting		not estimable	292 (2 RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Improvement in neurological impairment - not reported	-	-	-	-	-	
Improvement in psychological and cognitive impairment - not measured	-	-	-	-	-	
Cardiovascular events - not reported	-	-	-	-	-	
Adverse events associated with RIC treatment	Symptomatic intracerebral artery stenosis or carotid stenting		RR 10.91 (2.01 to 59.28)	371 (3 RCTs)	⊕⊕⊕⊕ LOW 13	
	0 per 1000	0 per 1000				

	(0 to 0)			
Stroke severity	-	MD 0.17 lower (0.23 lower to 0.11 lower)	-	189 (1 study) LOW ^{4 5}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **RIC:** remote ischaemic conditioning; **RCT:** randomised controlled trial;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgrade by two levels because of very serious risk of bias and serious imprecision. Very serious risk of bias resulted from: participants were not blinded to the treatment protocol in [Meng 2012](#) and [Zhao 2017](#); [Meng 2012](#) and [Meng 2015](#) used per-protocol analysis methods; the corresponding author was one of the inventor of the RIC devices used in the studies; and there was large number of participants lost to follow up during the study period.

² Serious imprecision. Incidence of ischaemic stroke was very lower in [Zhao 2017](#), and the CI for ischaemic stroke was wide.

³ Serious imprecision. Incidence of RIC-associated adverse events were very lower, and the CI for this outcome was very wide.

⁴ Downgrade by two levels because of serious risk of bias and serious indirectness. Very serious risk of bias results from: participants were not blinded to the treatment protocol; the corresponding author was one of the inventor of the RIC devices used; and there was large number of participants lost to follow up during the study period in [Zhao 2017](#).

⁵ Serious indirectness. The infarct volume was used as a surrogate endpoint to assess stroke severity in [Zhao 2017](#).

Summary of findings 2. RIC versus non-RIC treating ischaemic stroke

RIC versus non-RIC for treating ischaemic stroke

Patient or population: people with ischaemic stroke

Setting: emergency, clinic and inpatient

Intervention: RIC

Comparison: non-RIC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-RIC treating ischaemic stroke	Risk with RIC				

Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up - not measured	-	-	-	-	-
Death or dependency	Acute ischaemic stroke treated with intravenous thrombolysis		RR 2.34 (1.19 to 4.61)	285 (1 RCT)	⊕⊕○○ LOW ^{1 2}
	80 per 1000	187 per 1000 (95 to 369)			
Improvement in neurological impairment - not measured	-	-	-	-	-
Improvement in psychological and cognitive impairment at completion of follow-up	The mean psychological function was 55.4 points and the mean cognitive function was 27.08 points.	SMD 0.29 lower (0.68 lower to 0.11 higher)	-	105 (3 RCTs)	⊕⊕○○ LOW ^{3 4}
Cardiovascular events - not reported	-	-	-	-	-
Adverse events associated with RIC treatment - not reported	-	-	-	-	-
Stroke severity	-	SMD 0.24 lower (1.02 lower to 0.54 higher)	-	175 (2 study)	⊕○○○ VERY LOW ^{4 5 6}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **RIC:** remote ischaemic conditioning; **SMD:** standardised mean difference; **RCT:** randomised controlled trial;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgrade two levels by very serious risk of bias and serious imprecision. High risk of bias resulted from the unclear of allocation concealment, the unblinded treatment protocol to the participants, and large number of participants lost to follow up during the study period in [Hougaard 2014](#).

² Serious imprecision. There was a large number of participants excluded from the study after randomising in [Hougaard 2014](#).

- ³ Downgrade two levels by very serious risk of bias and serious inconsistency. Very serious risk of bias resulted from the unclear of allocation concealment and high risk of other bias in [Mi 2016](#) and [Wang 2017](#), only a small number of participant were included for this outcome, and the corresponding author was one of the inventors of the RIC devices used in [Mi 2016](#) and [Wang 2017](#).
- ⁴ Serious inconsistency. We detected high level of the heterogeneity for the cognitive impairment.
- ⁵ Downgrade two levels by very serious risk of bias, serious inconsistency and serious indirectness. High risk of bias resulted from the unclear of allocation concealment, the unblinded treatment protocol to the participants, and large number of participants lost to follow up during the study period in [Hougaard 2014](#); and the small number of participants in [England 2016](#).
- ⁶ Serious indirectness. The infarct volume was used as a surrogate endpoint to assess stroke severity in [Hougaard 2014](#).

BACKGROUND

Description of the condition

Stroke is the leading cause of adult disability globally, and its disease burden continues to increase (Feigin 2015; Roth 2015). Ischaemic stroke, which is due to blockage of a brain blood vessel, accounts for nearly 90% of all strokes; and nearly a quarter of individuals who have an ischaemic stroke will have recurrent strokes (Writing Group 2016). In 2013, more than 70% of stroke survivors and more than 50% of deaths from stroke were attributed to ischaemic stroke (Feigin 2015).

Fortunately, most ischaemic strokes are preventable. Prevention and screening of stroke not only reduces the incidence of ischaemic stroke and subsequent disability but may have beneficial effects on cognitive decline and other neuropsychological diseases. Key strategies for preventing ischaemic stroke include control of risk factors, anti-clotting therapy, intervention for vascular obstruction and lifestyle change (Steiger 2016). Although these strategies play important roles in clinical practice, some are not cost effective and others may result in severe adverse events.

Timely intervention to open the occluded artery and return blood flow to salvageable cerebral tissue via clot-treating therapies (including systemic and local administration of drugs to break up clots and use of various intra-arterial minimally-invasive devices to manually remove clots) are the most effective methods for salvaging brain tissue that had interrupted blood flow but is not already dead. The exact window of time for maximally effective treatment is unknown, but strong evidence shows that systemic administration of a drug to break up clots is only beneficial within 4.5 hours of symptom onset, while minimally-invasive management with second-generation mechanical clot-removal devices is beneficial for patients with specific type of stroke within 24 hours of symptom onset (Powers 2018; Nogueira 2018). Unfortunately, these treatments are expensive and are available only at select comprehensive stroke centres. Furthermore, injury to surviving brain tissue after reestablishment of blood flow (a phenomenon known as ischaemia/reperfusion injury) is a major source of morbidity and mortality (Bai 2015). These disadvantages severely influence the prognosis of ischaemic stroke worldwide, especially in countries with low to medium levels of resources, such as China.

Description of the intervention

Ischaemic conditioning is a strategy by which one or more cycles of a brief period of interruption of blood flow to an organ or tissue followed by resumption of flow confer protection against subsequent, more severe ischaemic events (Hausenloy 2016). This far-reaching phenomenon was first demonstrated by Murry and colleagues (Murry 1986). Since that time, ischaemic conditioning has been widely studied. However, a major disadvantage of attempting to condition a specific organ is that it requires application of an intervention directly to the target, which is not always feasible in clinical practice. A strategy by which the protective conditioning cycles are applied to an organ or tissue remote from the target organs may offer a far more attractive clinical application. Przyklenk and colleagues introduced a new method of carrying out ischaemic conditioning, in which the conditioning cycles of ischaemia were applied to a separate region (Przyklenk 1993). Later on, this strategy was named 'remote

ischaemic conditioning' (RIC). Investigators have evaluated many tissues and organs such as kidney, liver, limbs, and the mesenteric artery as remote conditioning sites in animals. RIC performed on limbs, generally with blood pressure cuffs inflated to a pressure that blocks blood flow in one or both directions, is now considered the most convenient and feasible method that can be used in clinical settings (Hausenloy 2016; Pan 2016). RIC can be divided into three types on the basis of initiation of conditioning: preconditioning (RIC applied before ischaemia), perconditioning (RIC applied after ischaemia onset and before reperfusion), and postconditioning (RIC applied during reperfusion) (Pan 2016).

Many research studies have shown RIC to be a well tolerated and effective strategy for protecting the brain from ischaemia or reperfusion injury (Hahn 2011; Hoda 2012; Hougaard 2014; Pan 2016; Ren 2015). It has been determined that RIC could increase brain tolerance to injury caused by ischaemia, reduce the risk of cerebral infarction, improve blood flow to the brain, and promote the formation of alternately-routed blood vessels to the brain (Hougaard 2014; Meng 2012; Pan 2016). Several randomised controlled trials (RCTs) have reported that RIC might confer neuroprotection against damage from acute ischaemic stroke and chronic cerebral ischaemia (Hougaard 2014; Meng 2012; Meng 2015). Although evidence suggests potential benefit of RIC for people with ischaemic stroke, many questions remain unanswered. The underlying protective mechanisms of RIC still need to be elucidated, and the optimal duration and number of ischaemia/reperfusion cycles have not been established. Additionally, the potential for complications related to pressure cuffs is regarded as low, and other adverse effects associated with RIC remain unknown. Finally, criteria are needed that can be used to identify ideal candidate people for RIC.

How the intervention might work

Characterisation of the mechanism by which RIC provides protection for the brain is currently incomplete, and most evidence has been provided by studies on cardiac preconditioning and postconditioning. Underlying mechanisms include two windows of protection: the early phase (action immediately after a stimulus that might play a role through affecting critical proteins) and the delayed phase (action days or weeks after a stimulus that might play a role in gene regulation and new protein synthesis) (Hahn 2011). Research findings indicate that protective signals may be transmitted from the conditioned organ to the brain through three routes: humoral, neuronal, and immunological pathways (Weber 2010).

Substances or humoral factors generated by the conditioned site may be circulated to the brain through the blood upon re-establishment of blood flow of the conditioned site and may exert protective effects through signal pathways. A neuronal pathway at conditioned sites might be stimulated by local production of factors such as adenosine, bradykinin or other neuropeptides, which then stimulate nerve signals to the brain, thus inducing neuroprotection. RIC may derive its protective effects via alteration of gene and small molecule expression within the immune system, which then activates immune cells and alters inflammatory responses (Lim 2012; Pan 2016). Therefore, although the three protective signal pathways are distinct, both neuronal and immunological pathways are linked to the humoral pathway.

Why it is important to do this review

RIC appears to be a well tolerated, cost-effective, easily implemented strategy that has the potential to provide specialised care for any user (e.g. patients, caregivers, physicians) in any circumstance (e.g. home, ambulance, hospital). Previous Cochrane review authors have evaluated RIC in vascular and endovascular surgical procedures ([Desai 2011](#)), and RIC has also been evaluated in coronary artery bypass grafting and kidney ischaemia-reperfusion injury in the *Cochrane Database of Systematic Reviews* ([Menting 2017](#); [Benstoem 2017](#)). RIC is developing as a neuroprotective strategy for ischaemic stroke prevention and treatment, and its implementation in clinical settings is increasing in many parts of the world. Several clinical trials have shown that RIC might reduce stroke recurrence and improve stroke outcomes, and that it is well tolerated without associated severe adverse events ([Hougaard 2014](#); [Meng 2012](#); [Meng 2015](#)). However, existing evidence is insufficient to demonstrate the efficacy and safety of RIC.

OBJECTIVES

To assess the benefits and harms of RIC for preventing ischaemic stroke and for treating people with ischaemic stroke and those at risk for ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included all identified randomised controlled trials (RCTs) comparing remote ischaemic conditioning (RIC) versus non-RIC (sham RIC or standard medical management alone) in people with ischaemic cerebrovascular diseases. We excluded uncontrolled trials as well as quasi-RCTs where allocation to treatment or control was not concealed (e.g. allocation by alteration, open random number list, date of birth, day of the week, or hospital number).

Types of participants

We included participants with any of the following: (1) acute ischaemic stroke diagnosed on the basis of the a combination of clinical examination findings and diagnostic test results or according to definitions for acute ischaemic stroke used by researchers to enrol patients in their RCTs; (2) chronic cerebral ischaemia (i.e. 14 days after symptom onset) or gradual-onset cerebral ischaemia (e.g. small vessel disease); (3) a definitive diagnosis of intracranial or extracranial cerebrovascular moderate and severe stenosis (i.e. > 50%) or occlusion confirmed by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). We excluded studies of participants undergoing cardiovascular intervention therapies, coronary artery bypass grafting, any other type of cardiac surgery, and people undergoing other surgeries, as the complication risk of ischaemic stroke was low in these patients.

Types of interventions

The RIC protocol consisted of remote ischaemic preconditioning, remote ischaemic perconditioning and remote ischaemic postconditioning, which were the same procedure but divided based on the order of its initiation and the occurrence of ischaemia. A remote stimulus was applied to any organ (e.g. upper and lower limbs). This stimulus consisted of one or more

cycles of brief ischaemia and reperfusion of varying duration. The control condition consisted of no intervention or standard medical management and sham RIC, which required application of a blood pressure cuff, tourniquet or other occlusive device without full interruption of blood flow.

Types of outcome measures

Primary outcomes

- Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up
- Death or dependency (e.g. Barthel Index (BI) score ≤ 60 , modified Rankin Scale (mRS) grade 3 to 6, defined by the trial author) at completion of follow-up

Secondary outcomes

- Stroke severity as measured by infarct volume, the National Institutes of Health Stroke Scale (NIHSS), the Canadian Neurological Scale (CNS), the Scandinavian Stroke Scale, the European Stroke Scale, the modified Rankin Scale (mRS) or other scales reported by trial authors
- Improvement in neurological impairment (e.g. NIHSS, mRS, CNS, other scales defined by trial authors) at completion of follow-up
- Improvement in psychological and cognitive impairment (e.g. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Wechsler Memory Scale (WMS), Wechsler Memory Scale-Revised (WMS-R), Luria-Nebraska Neuropsychological Battery (LNNB) Memory Scale, other scales defined by trial authors) at completion of follow-up
- Cardiovascular events (e.g. acute myocardial infarction, angina)
- Haemorrhagic stroke (e.g. intracerebral haemorrhage, subarachnoid haemorrhage)
- Adverse events associated with RIC treatment (e.g. soft tissue injury, venous thrombosis, artery dissection, events reported by trial authors)

Search methods for identification of studies

See the 'Specialised register' section in the [Cochrane Stroke Group](#) module. We attempted to identify all relevant RCTs without restriction on language or publication status, and arranged translation of relevant papers where necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (16 January 2018), and the following electronic bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12) in the *Cochrane Library* (searched 16 January 2018) ([Appendix 1](#))
- MEDLINE Ovid (from 1946 to 16 January 2018) ([Appendix 2](#))
- Embase Ovid (from 1974 to 16 January 2018) ([Appendix 3](#))
- Science Citation Index Expanded (SCI-EXPANDED) (Web of Science; 1950 to 10 January 2018) ([Appendix 4](#))
- Conference Proceedings Citation Index- Science (CPCI-S) (Web of Science; 1950 to 10 January 2018) ([Appendix 4](#))
- China Biological Medicine Database (CBM; www.sinomed.ac.cn/) (from 1978 to 10 January 2018) ([Appendix 5](#))

- China Doctoral Dissertations Full-text Database (CDFD) (CNKI; from 1984 to 10 January 2018) ([Appendix 6](#))
- China Academic Journal Network Publishing Database (CAJD) (CNKI; from 1915 to 10 January 2018) ([Appendix 7](#))

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist and adapted it for the other databases ([Appendix 2](#)).

We also conducted a search of the following research registers to identify ongoing matched trials (10 January 2018).

- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch) ([Appendix 8](#))
- ClinicalTrials.gov (www.clinicaltrials.gov/) ([Appendix 9](#))
- Stroke Trials Registry (www.strokecenter.org/trials/) ([Appendix 10](#))
- ISRCTN Registry (www.isrctn.com) ([Appendix 11](#))

Searching other resources

In an effort to identify other published, unpublished, and ongoing studies, we searched reference lists of relevant trials, and relevant journals (*Brain Circulation* and *Conditioning Medicine*) and conference proceedings (European Stroke Conference, International Stroke Conference, and Neuroscience Conferences). We also searched for and contacted trialists and researchers in the field where necessary.

Data collection and analysis

Selection of studies

Two review authors (WBZ and JZ) independently screened titles and abstracts of records identified through literature search activities and excluded those that were obviously irrelevant and duplicated. We retrieved the full text of remaining articles, and the same two review authors (WBZ and JZ) independently screened full-text articles to identify studies for inclusion or exclusion on the basis of our predetermined [Criteria for considering studies for this review](#). The two authors resolved any disagreements through discussion or by consulting a third author (RM).

Data extraction and management

Two review authors (WBZ and JZ) independently extracted and recorded study details on a data extraction form. We extracted the following data: methods, characteristics of participants, interventions, treatment duration, primary and secondary outcomes and time points reported. The same two authors cross-checked all extracted data and resolved any differences in the extracted data by referring to the original articles and through discussion. We extracted data to allow an intention-to-treat (ITT) analysis (including all participants in the groups to which they were originally randomly allocated).

For continuous outcomes, we used means and standard deviations for each group. If median and interquartile ranges were used in the original article, we translated them to means and standard deviations ([Wan 2014](#)). For binary outcomes, we extracted the number of participants with the event in each group.

Assessment of risk of bias in included studies

Two review authors (WBZ and JZ) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved disagreements by discussion or by consultation with a third review author (RM) where necessary. We assessed risk of bias according to the following domains: selection bias; performance bias; detection bias; attrition bias; reporting bias and other possible bias.

For each domain, we categorised each study as presenting 'low risk', 'high risk', or 'unclear risk' of bias and provided information from the study report, together with a justification for our judgement, in the 'Risk of bias' tables.

Measures of treatment effect

We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data (e.g., ischaemic stroke, recurrent ischaemic stroke, death, dependency, haemorrhagic stroke, cardiovascular events). For continuous data (e.g. scores from scales), we used mean differences (MDs) with 95% CIs for data measured in the same way between trials, and standardised mean differences (SMDs) with 95% CIs to combine data when different scales were used for measurement. We narratively described skewed data reported as medians and interquartile ranges.

Unit of analysis issues

In most studies, the unit of analysis was the individual participant and a single measurement for each outcome was collected and analysed. However, for cross-over trials, the unit of analysis included only the first phase in the analysis. For cluster-randomised trials, the unit of analysis was the cluster.

Dealing with missing data

We carried out analyses according to the ITT principle: we used the number of initially randomised individuals as the denominator. If data were missing, we contacted the corresponding author or co-authors through the address or email given in the publication. When this was not possible, we calculated best- and worst-case scenarios for dichotomous data: the best-case scenario would mean participants with missing data were alive or achieved dependence or did not experience stroke, and the worst-case scenario would mean that participants with missing data were dead or experienced stroke or did not achieve dependence.

Assessment of heterogeneity

We assessed heterogeneity between study results using the I^2 statistic. We defined a value greater than 50% as indicating substantial heterogeneity.

Assessment of reporting biases

We had intended to use funnel plots to assess the potential existence of reporting bias if more than 10 studies were included in this review. However, because we only seven included studies, we assessed reporting bias qualitatively on the basis of the study characteristics.

Data synthesis

We conducted a meta-analysis using Review Manager 5 ([Review Manager 2014](#)). We used RR as a measure of effect for binary outcomes and MD or SMD as a measure of effect for continuous outcomes. We used a random-effects model to better estimate the effect size of different studies, regardless of whether heterogeneity was significant.

GRADE and 'Summary of findings' table

We summarised the evidence by creating 'Summary of findings' tables using GRADEproGDT (<https://gradepro.org/>), in which we imported data from Review Manager 5. We used the GRADE approach to assess the quality of evidence as high, moderate, low, or very low, based on the following five considerations: study limitations, imprecision, consistency of effect, indirectness and publication bias ([Higgins 2011](#)). The table presents results and our assessments of the quality of evidence for the main outcomes.

Subgroup analysis and investigation of heterogeneity

We had intended to performed subgroup analysis to investigate heterogeneity by analysing differences in the number of RIC cycles and their length, the position of RIC (upper versus lower limb, unilateral versus bilateral), and length of RIC treatment (fractionated versus continuous). However, in this review only seven trials were eligible for analysis: three studies for the analysis of RIC for preventing ischaemic stroke, and another four studies for the analysis of RIC for treating ischaemic stroke. Given the limited number of included studies, there were not enough data for subgroup analysis.

Sensitivity analysis

We had intended to perform sensitivity analyses if the results were substantially heterogeneous, by 1) excluding studies with inadequate allocation concealment; 2) excluding studies that did not use blinding; 3) excluding studies in which loss to follow-up was not reported or was greater than 10%; 4) excluding unpublished studies; 5) excluding studies that did not use sham as a comparison; and 6) excluding long studies, large studies or those using imputed data to determine their influence on study results. However, we did not perform any sensitivity analyses because of the limited number of included studies, and no substantial heterogeneity was found in this review.

RESULTS

Description of studies

A detailed description of all studies can be found in [Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of ongoing studies](#).

Results of the search

We identified a total of 8765 records from database searching in January 2018. After removing 1668 duplicates, 7097 records remained, which we screened and excluded 7066 records. We retrieved 31 full-text articles and abstracts and assessed them for eligibility. Finally, we identified seven trials and assessed them for eligibility as per protocol with refined inclusion criteria. We excluded 16 studies with reasons (see [Characteristics of excluded studies](#)), and identified eight ongoing studies. We present details of the seven included trials in [Characteristics of included studies](#). For an illustration of these results, please see the study flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

Seven trials met our inclusion criteria. The first trial was a single-centre trial conducted in the UK ([England 2016](#)). The trial compared remote ischaemic conditioning (RIC) with sham RIC in 26 participants (13 in each group) with acute ischaemic stroke. RIC and sham RIC were started within 24 hours of stroke onset and performed manually using a standard upper arm blood pressure cuff in the nonparetic arm. RIC consisted of four cycles of five minutes' inflation (20 mmHg above systolic blood pressure) and five minutes' deflation; and sham RIC consisted of four cycles of five minutes' inflation (30 mmHg) and five minutes' deflation. The primary outcome was tolerability and feasibility of RIC after acute ischaemic stroke, and the duration of follow-up was 90 days.

The second trial was a single-centre trial conducted in Denmark ([Hougaard 2014](#)). The trial compared intravenous thrombolysis plus RIC with intravenous thrombolysis alone in 285 participants with acute ischaemic stroke. Because of the imbalanced randomisation and large number of participants excluded from the analysis after randomisation, there were unbalanced numbers of participants between the two groups (160 in the intervention group, and 125 in the control group). RIC was started in the ambulance and induced by four inflations of a standard upper limb blood pressure cuff to either 200 mmHg or 25 mmHg above the systolic blood pressure, each lasting five minutes and separated by five minutes of cuff deflation. The primary outcome was the penumbra salvage, and the duration of follow-up was 90 days.

The third trial was conducted in two centres in China ([Meng 2012](#)). The trial compared standard medical treatment plus RIC and standard medical treatment alone in 103 participants (51 in the intervention group and 52 in the control group) with symptomatic intracranial artery stenosis. RIC, consisting of five cycles of bilateral arms ischaemia (induced by inflating tourniquets to 200 mmHg) for five minutes followed by reperfusion for another five minutes, was performed twice daily for a total of 300 consecutive days. Standard medical treatment including antiplatelet agents, lipid control agents, and antidiabetic agents (if necessary). The primary outcome was time point of the first stroke recurrence event, and the duration of follow up was 300 days.

The fourth trial was a single-centre trial conducted in China ([Meng 2015](#)). The trial compared RIC and sham RIC in 79 octogenarian and nonagenarian participants (40 in the intervention group and 39 in the control group) with symptomatic intracerebral artery stenosis. RIC consisted of five cycles of simultaneous bilateral arms ischaemia (induced by inflating tourniquets to 200 mmHg) for five minutes followed by reperfusion for another five minutes. Sham RIC consisted of five cycles of bilateral arms ischaemia (induced by inflating tourniquets to 30 mmHg) for five minutes, followed by reperfusion for another five minutes. Both RIC and sham RIC were performed for 180 consecutive days. Medical management included either clopidogrel 75 mg/day in combination with atorvastatin 20 mg/day or aspirin 100 mg/day and clopidogrel 75 mg/day in combination with atorvastatin 20 mg/day. The duration of follow-up was 180 days.

The fifth trial was a single-centre trial conducted in China ([Mi 2016](#)). The trial compared RIC and sham RIC in 17 participants (nine in the intervention group and eight in the control group) with cerebral small vessel disease. Both RIC and sham RIC were achieved using an automated cuff inflator placed on bilateral arms that were inflated

to 200 mmHg and 50 mmHg respectively. Both RIC and sham RIC consisted of five cycles of five minutes' ischaemia follow by five minutes' reperfusion. All participants were required to receive RIC or sham RIC treatment twice daily for one year. The primary outcome was changes in brain lesions, evaluated by the number of lacunar infarctions and white matter lesions volume, and the duration of follow-up was one year.

The sixth trial was a single-centre trial conducted in China ([Wang 2017](#)). The trial compared RIC and sham RIC in 36 participants (18 in the intervention group and 18 in the control group) with cerebral small vessel disease-related mild cognitive impairment. Both RIC and sham RIC were achieved using an automated cuff inflator placed on bilateral arms that were inflated to 200 mmHg and 50 mmHg respectively. Both RIC and sham RIC consisted of five cycles of five minutes' ischaemia follow by five minutes' reperfusion. All participants were required to receive RIC or sham RIC treatment twice daily for one year. The primary outcome was the change of brain lesions, and the follow-up duration was one year.

The seventh trial was a single-centre trial conducted in China ([Zhao 2017](#)). The trial compared RIC plus standard medical treatment, sham RIC plus standard medical treatment and standard medical treatment alone in 189 participants (63 in each group) with severe carotid artery stenosis. RIC and sham RIC consisted of five cycles of bilateral arms ischaemia for five minutes, followed by reperfusion for another five minutes, and they were performed twice daily for two weeks before carotid stenting. Both RIC and sham RIC procedures were performed by using an electric autocontrol device with cuffs that inflated to a pressure of 200 mmHg and 60 mmHg respectively during the ischaemic period. The primary outcomes were the presence of one or more new brain lesions on diffusion weighted imaging (DWI) within 48 hours after carotid artery stenting, and the incidence of clinical events (i.e. ischaemic stroke, transient ischaemic attack (TIA), acute myocardial infarction, haemorrhagic stroke, hyperperfusion syndrome, and death) within six months after stenting. The duration of follow-up was six months.

Excluded studies

We excluded 16 studies from this review. The [Characteristics of excluded studies](#) table provides summary details.

We excluded seven studies because the participants underwent percutaneous coronary intervention or cardiac surgery ([Cho 2017](#); [Coverdale 2017](#); [Davies 2013](#); [Hoole 2009](#); [Hudetz 2014](#); [Sloth 2014](#); [Zhong 2013](#)). We excluded one study because the included participants underwent transfemoral transcatheter aortic valve implantation ([Kahlert 2017](#)). One study randomised participants treated with major vascular surgery, including carotid endarterectomy; we excluded it because we did not obtain the data on participants treated with carotid endarterectomy after emailing the author ([Healy 2015](#)). We excluded four studies because they did not assess ischaemic stroke in their outcome assessment ([Jing 2011](#); [Meng 2017](#); [Sales 2017](#); [Walsh 2010](#)). Another study was not a randomised controlled trial ([Joseph 2015](#)), and another study has passed the completion date but the status has not been verified after more than two years, and no paper or results have been published to date ([NCT01672515](#)). We excluded one study because the comparison was between healthy people and patients ([Hyngstrom 2016](#)).

Risk of bias in included studies

The 'Risk of bias' assessments for all included studies are summarised in [Figure 2](#) and [Figure 3](#).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
England 2016	+	+	+	+	+	+	+
Hougaard 2014	+	?	-	+	-	+	-
Meng 2012	+	?	-	+	-	+	-
Meng 2015	+	+	+	+	-	+	-
Mi 2016	+	?	+	+	+	+	-
Wang 2017	?	?	+	+	-	+	-
Zhao 2017	+	+	-	+	-	+	-

Allocation

The method of randomisation was described and considered adequate with low risk of bias in six included studies (England 2016; Hougaard 2014; Meng 2012; Meng 2015; Mi 2016; Zhao 2017). Four studies reported that the random sequence was generated by using computer-generated random number sequence (Meng 2012; Meng 2015; Mi 2016; Zhao 2017). One study reported

that the randomisation was performed by drawing from a large number of sealed opaque envelopes (Hougaard 2014). One study reported that the randomisation was generated by minimisation (England 2016). Another study only reported that randomisation was performed by an independent statistician; the details were not reported, therefore we judged the risk of bias as unclear (Wang 2017).

Allocation concealment was adequate with low risk of bias in three studies, one of which used a web-based randomisation method (England 2016), and two of which used sequentially numbered, opaque, sealed envelopes (Meng 2015; Zhao 2017). Allocation concealment was unclear for three trials which only reported that the assignments were sealed, but not whether the assignment was sequentially numbered (Hougaard 2014; Mi 2016; Wang 2017). One study did not report the details of allocation (Meng 2012).

Blinding

Because of the nature of RIC treatment, if no sham RIC treatment was used, it was impossible to blind the participants. Therefore, we judged two studies as being at high risk of bias (Hougaard 2014; Meng 2012), and four as being at low risk of bias (Meng 2015; England 2016; Mi 2016; Wang 2017). One study was comprised of three groups (RIC group, sham RIC group, and control group); although sham RIC was included in the study, it was also impossible to blind the participants (Zhao 2017). Therefore, we also judged this trial as having high risk of performance bias.

One study was an outcome-blinded, placebo-controlled trial (England 2016). All other studies reported that the outcome assessors were blinded to the treatment protocol (Hougaard 2014; Meng 2012; Meng 2015; Mi 2016; Wang 2017; Zhao 2017). We therefore judged all the trials as having low risk of detection bias.

Incomplete outcome data

We judged two studies as having low risk of attrition bias as there were no participants lost to follow-up during the study period (England 2016; Mi 2016). We judged three trials as having high risk of attrition bias because of the following losses to follow-up: 35 out of 103 (34.0%) participants (Meng 2012); 21 out of 79 (26.6%) participants (Meng 2015); and 6 out of 36 (16.7%) participants (Wang 2017). We judged the two remaining studies as having high risk of attrition bias because 158 out of 443 (35.7%) participants were excluded in the as-treated analyses (Hougaard 2014); and 27 out of 189 (14.3%) participants were lost to the analyses of imaging and 42 out of 189 (22.2%) participants were lost to the analyses of clinical events (Zhao 2017).

Selective reporting

All included studies registered their study protocols in one of the clinical trial registration websites, and all predefined study outcomes were published. Therefore, we judged all included studies as low risk of reporting bias (England 2016; Hougaard 2014; Meng 2012; Meng 2015; Mi 2016; Wang 2017; Zhao 2017).

Other potential sources of bias

We judged five trials performed in the same centre in China to be high risk of other bias because these trials had the same principle investigator, who was one of the inventors of the electric autocontrol RIC device used in these studies (Meng 2012; Meng 2015; Mi 2016; Wang 2017; Zhao 2017). We judged one other study to be at high risk of other bias because two authors were shareholders in the company where the devices used in the study were made (Hougaard 2014). We judged the remaining study to be at low risk of other potential bias as we identified no other bias (England 2016).

Effects of interventions

See: [Summary of findings for the main comparison RIC versus non-RIC for preventing ischaemic stroke](#); [Summary of findings 2 RIC versus non-RIC treating ischaemic stroke](#)

See: [Summary of findings for the main comparison](#) and [Summary of findings 2](#).

Three studies focused on remote ischaemic conditioning (RIC) for preventing ischaemic stroke (Meng 2012; Meng 2015; Zhao 2017), while the other four studies focused on RIC for treating ischaemic stroke (England 2016; Hougaard 2014; Mi 2016; Wang 2017). The outcomes used in these two categories of studies were different. Therefore, we analysed RIC for preventing and treating ischaemic stroke separately. Although multiple relative risks were used for outcomes analyses, caution should be taken when using these results as the presented data were extracted from only one or two studies with small sample sizes and low quality of evidence.

RIC versus non-RIC for preventing ischaemic stroke

Three studies focused on RIC for preventing ischaemic stroke (Meng 2015; Meng 2012; Zhao 2017). The total number of participants was 371.

Primary outcomes

1.1. Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up

Ischaemic stroke was reported in Zhao 2017 and recurrent ischaemic stroke was reported in Meng 2012 and Meng 2015.

1.1.1 Ischaemic stroke

One study (Zhao 2017), involving 189 participants (50.9% of the total number of participants included in this part of review) presented data on ischaemic stroke. There was no significant difference in the incidence of ischaemic stroke between those allocated to RIC versus those allocated to non-RIC (risk ratio (RR) 0.22, 95% confidence interval (CI) 0.01 to 4.03; $P = 0.31$) (Analysis 1.1).

1.1.2 Recurrent ischaemic stroke

Two studies (Meng 2012; Meng 2015), involving 182 participants (49.1% of the total number of participants included in this part of review), presented data on recurrent ischaemic stroke. The incidence of recurrent ischaemic stroke was significantly reduced by RIC treatment (RR 0.32, 95% CI 0.12 to 0.83; $P = 0.02$) (Analysis 1.1).

1.2. Death or dependency at completion of follow-up

Death was not reported in Meng 2015. The other two studies (Meng 2012; Zhao 2017) reported that no participant died during the study period, so analysis was not applicable to the outcome of death. None of the trials (Meng 2012; Meng 2015; Zhao 2017) reported any forms of dependency that enabled us to include them for analysis.

Secondary outcomes

1.3. Stroke severity

This outcome was assessed by infarct volume in Zhao 2017, which involving 189 participants (50.9% of the total number of participants included in this part of review). Infarct volume

was calculated using magnetic resonance imaging (MRI) scans. In participants with multiple lesions, the total infarct volume was added up. The infarct volume was significantly smaller in participant treated with RIC compared with those not treated with RIC (MD -0.17 mL, 95% CI -0.23 to -0.11; $P < 0.01$; $I^2 = 3\%$) ([Analysis 1.3](#)).

1.4. Improvement in neurological impairment at completion of follow-up

None of the three trials reported this outcome in a form that enabled us to include them for this analysis.

1.5. Improvement in psychological and cognitive impairment at completion of follow-up

None of the three trials reported this outcome in a form that enabled us to include them for this analysis.

1.6. Cardiovascular events

This outcome was not reported in [Meng 2015](#). The other two studies ([Meng 2012](#); [Zhao 2017](#)) reported that no participant experienced cardiovascular events during the study period, so analysis was not applicable to this outcome.

1.7. Haemorrhagic stroke

None of the three trials reported this outcome in a form that enabled us to include them for this analysis.

1.8. Adverse events associated with RIC treatment

All studies (371 participants; 100% of the total number of participants included in this part of review) reported data on adverse events associated with RIC treatment. One study reported that no participant experienced any adverse events associated with RIC treatment ([Meng 2012](#)). One study reported that 6/63 participants experienced arm skin petechiae from repeated pressure cuff applications ([Zhao 2017](#)), and the other study reported that sporadic petechiae in 3/40 participants were observed ([Meng 2015](#)). The adverse events associated with RIC treatment were significantly higher in participants treated with RIC (RR 10.91; 95% CI 2.01 to 59.28; $P = 0.006$; $I^2 = 0\%$). No participant experienced severe adverse events associated with RIC treatment.

RIC versus non-RIC for treating ischaemic stroke

Four studies focused on RIC for treating ischaemic stroke ([England 2016](#); [Hougaard 2014](#); [Mi 2016](#); [Wang 2017](#)). The total number of participants was 364.

Primary outcomes

2.1. Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up

None of the four trials reported these outcomes in any forms that enabled us to include them for this analysis.

2.2. Death or dependency at completion of follow-up

Both death and dependency were reported by one study including 285 participants (78.3% of the total number of participants included in this part of review) ([Hougaard 2014](#)). Dependency, assessed by the mean and median of the modified Ranks Scale score and the Barthel Index, was reported in one study

([England 2016](#)); we tried to contact the study authors to get the incidence of dependency, but failed to receive any response. Two other studies did not report any of the outcomes ([Mi 2016](#); [Wang 2017](#)). Therefore we only included [Hougaard 2014](#) in this analysis. The rate of death or dependency was significantly increased by RIC treatment compared with non-RIC treatment (RR 2.34; 95% CI 1.19 to 4.61; $P = 0.01$) ([Analysis 2.2](#)).

Secondary outcomes

2.3. Stroke severity

This outcome was assessed by the infarct volume in [Hougaard 2014](#) and the NIHSS scores in [England 2016](#).

2.3.1. Final infarct volume

This outcome was assessed by the final infarct volume in one study with 149 participants (40.9% of the total number of participants included in this part of review) ([Hougaard 2014](#)). No significant difference was detected between participants allocated to RIC treatment and those allocated to non-RIC treatment (SMD 0.08 mL; 95% CI -0.24 to 0.41; $P = 0.61$) ([Analysis 2.3](#)).

2.3.2. NIHSS scores

Scores on the NIHSS at three-month follow-up were reported in [England 2016](#), which included 26 participants (9.1% of the total number of participants included in this part of review). There was no significant difference between participants allocated to RIC treatment and those allocated to non-RIC treatment (SMD -0.73 points; 95% CI -1.53 to 0.07; $P = 0.07$) ([Analysis 2.3](#)).

2.4. Improvement in neurological impairment at completion of follow-up

None of the four trials reported this outcome in a form that enabled us to include them for this analysis.

2.5. Improvement in psychological and cognitive impairment at completion of follow-up

The psychological function was reported in [England 2016](#) and the cognitive function was reported in three studies ([England 2016](#); [Mi 2016](#); [Wang 2017](#)).

2.5.1 Psychological impairment

Psychological impairment was only reported in [England 2016](#), which included 26 participants (9.1% of the total number of participants included in this part of review). The Zung Depression Score was used for the assessment. There was no significant difference between participants allocated to RIC treatment and those allocated to non-RIC treatment (SMD -0.37 points; 95% CI -1.15 to 0.41; $P = 0.35$) ([Analysis 2.5](#)).

2.5.2 Cognitive impairment

Three studies reported results of the Mini-Mental State Examination (MMSE) ([England 2016](#); [Mi 2016](#); [Wang 2017](#)). Seventy-nine participants (21.7% of the total number of participants included in this part of review) were included in this analysis. There was no significant difference in cognitive function between participants allocated to RIC treatment and those allocated to non-RIC treatment (SMD -0.26 points; 95% CI -0.72 to 0.21; $P = 0.28$) ([Analysis 2.5](#)).

2.6. Cardiovascular events

None of the trials reported this outcome in a form that enabled us to include them for this analysis.

2.7. Haemorrhagic stroke

None of the trials reported this outcome in a form that enabled us to include them for this analysis.

2.8. Adverse events associated with RIC treatment

None of the trials reported this outcome in a form that enabled us to include them for this analysis.

Subgroup analyses

Given the limited number of included studies, we did not perform subgroup analyses. If we include more studies in future updates of this review, we will explore differences in the results by creating subgroups according to the number of RIC cycles or their length, position of RIC treatment, and length of treatment.

Sensitivity analyses

We did not perform sensitivity analyses because of the limited number of included studies.

Funnel plots

We could not use funnel plots because only seven studies were included in this review, and three focused on RIC for preventing ischaemic stroke and the other four focused on RIC for treating ischaemic stroke.

DISCUSSION

In this Cochrane Review, we have assessed the benefits and harms of remote ischaemic conditioning (RIC) for either preventing or treating ischaemic stroke.

Summary of main results

RIC for preventing ischaemic stroke

Due to the low incidence of death and cardiovascular events in the study population, these analyses were not applicable. Two studies assessed effects of RIC in preventing recurrent ischaemic stroke in participants with symptomatic intracerebral artery stenosis (Meng 2012; Meng 2015), and one study assessed the effects of RIC in preventing ischaemic stroke after carotid stenting in participants with severe carotid stenosis (Zhao 2017). Based on the included studies, we found that RIC might prevent recurrent ischaemic stroke in people with symptomatic intracerebral artery stenosis, and reduce post-stenting infarct volumes in people undergoing carotid stenting.

Two studies reported adverse events associated with repeated RIC treatment, such as sporadic petechiae in local arm skin (Meng 2015; Zhao 2017). Although the adverse events associated with RIC treatment were significantly higher in participants treated with RIC, no severe adverse events (such as venous thrombosis, arterial dissection, or death) were reported.

RIC for treating ischaemic stroke

Two studies assessed the effects of RIC in treating acute ischaemic stroke (Hougaard 2014; England 2016), and another two studies

assessed effects of RIC in treating cerebral small vessel disease (Mi 2016; Wang 2017). Based on the included studies, we found that RIC did not significantly reduce the final infarct volume in people with acute ischaemic stroke who received intravenous thrombolysis, but it might increase the death or dependency of these people. We also found that neurological impairment, assessed by the National Institutes of Health Stroke Scale (NIHSS) score, and psychological impairment were not significantly improved by RIC in this patient population. However, it should be noted that the sample size of one included trial was rather small ($n = 26$), and the number of participants lost to follow-up in another included study was rather high.

One study compared cognitive function between acute ischaemic stroke participants treated with RIC and non-RIC (England 2016), while two studies compared cognitive function between cerebral small vessel disease participants treated with RIC and non-RIC (Mi 2016; Wang 2017). There was no significant difference in cognitive function between the groups; however, it should be noted that the sample size of the three included trials was rather small ($n = 79$).

Overall completeness and applicability of evidence

In this review, we widened the protocol inclusion criteria to allow various RIC treatment protocols, and included all trials that recruited people with ischaemic cerebrovascular disease.

The three studies focused on preventing ischaemic stroke were carried out in China, and intracerebral artery atherosclerosis was common in this patient population. This may indicate that the results of RIC for preventing ischaemic stroke are likely to be only applicable to the Chinese population, and possibly to Asians, among whom there is a high prevalence of intracerebral artery atherosclerosis. The three included studies tested the same RIC treatment protocol (bilateral arms, five cycles of five minutes' ischaemia/reperfusion, twice daily) with different treatment duration (two weeks, 180 days, and 300 days). We found low-quality evidence that RIC could prevent recurrent ischaemic stroke in participants with symptomatic intracerebral artery stenosis, and reduce post-stenting new infarct volumes in participants undergoing carotid stenting. RIC treatment for preventing recurrent ischaemic stroke and ischaemic stroke should be reviewed in light of this evidence. Due to the low incidence of death and cardiovascular diseases, and the relatively small sample sizes of the included studies, the current review found no evidence that RIC could prevent death and cardiovascular diseases in people with ischaemic cerebrovascular disease. The three included studies reported RIC-specific adverse events, such as sporadic localised petechiae in arm skin, but none of them reported any severe adverse events related to RIC treatment.

Four studies focused on RIC for treating ischaemic stroke. One recruited participants with acute ischaemic stroke within 24 hours of symptom onset in the UK (England 2016), one recruited ischaemic stroke candidates considered for intravenous thrombolysis within 4.5 hours in Denmark (Hougaard 2014), one recruited participants with cerebral small vessel disease in China (Mi 2016), and one recruited participants with cerebral small vessel disease-related mild cognitive impairment in China (Wang 2017). This may mean that the results of this review are likely to be applicable to people from these countries. The included studies tested two treatment protocols (four cycles of unilateral arm and five cycles of bilateral arms, five minutes' ischaemia/reperfusion),

and treatment duration of RIC varied from once to twice daily for 12 consecutive months. We found that RIC may increase death or dependency in people with acute ischaemic stroke who received intravenous thrombolysis, but we did not find any clear evidence that RIC had any effects on the final infarct volume, or psychological impairment in people with acute ischaemic stroke. Neither did we find any influence of RIC on the cognitive impairment in people with acute ischaemic stroke and cerebral small vessel disease. RIC for treating acute ischaemic stroke and cerebral small vessel disease should be reviewed in light of this evidence. Given the poor prognosis of acute ischaemic stroke, especially in those with large artery occlusion, further evidence relating to the use of RIC in this patient population or in combination with endovascular therapy or intravenous thrombolysis would be useful to better clarify the potential benefits and risks in this scenario.

Quality of the evidence

We assessed the quality of the evidence by using the GRADE approach (Guyatt 2008), and we presented the results in [Summary of findings for the main comparison](#) and [Summary of findings 2](#).

Four studies did not specify how allocation concealment was achieved, so we assessed them as having unclear risk of selection bias. Three studies were not blinded for participants, so we assessed them as having high risk of performance bias; and six studies had a high percentage of participants lost to follow-up, so we assessed them as having high risk of attrition bias. Overall, for each of the outcomes reported in our 'Summary of findings' tables, we graded the quality of evidence as low or very low.

From the three studies focused on RIC for preventing ischaemic stroke, there is low-quality evidence that RIC performed better than non-RIC in preventing recurrent ischaemic stroke in people with symptomatic intracerebral artery stenosis if treated for several consecutive months, and in reducing incidence of post-stenting new infarct volume in people undergoing carotid stenting if treated for two consecutive weeks before stenting. However, further research is likely to have a substantial impact on our confidence in the above estimations.

Four studies focused on RIC for treating ischaemic stroke. There is low-quality evidence that RIC might increase death or dependency in acute ischaemic stroke participants treated with intravenous thrombolysis. There is low-quality evidence that RIC performed no better or no worse than non-RIC in improving psychological impairment in people with acute ischaemic stroke if started within 24 hours of ictus, and there is low-quality evidence that RIC performed no better or no worse than non-RIC in improving cognitive impairment in people with acute ischaemic stroke and cerebral small vessel disease. There is very low quality evidence that RIC performed no better or no worse than non-RIC in reducing stroke severity (assessed by NIHSS score and infarct volume) in people with acute ischaemic stroke whether or not treated with intravenous thrombolysis. However, further research is likely to have an important impact on our confidence in the above estimations.

Potential biases in the review process

We carried out a comprehensive search across major databases, and we believe that we identified all relevant studies. In addition, we contacted the study authors for additional data when needed.

However, as less than 10 trials were included this review and all included studies had a small sample size, potential known and unknown biases cannot be excluded. In addition, this meta-analysis was slightly hampered by missing data because of studies reporting outcome data as medians and interquartile ranges. We were unable to obtain raw data for these studies, and this may cause biases to our analyses.

Agreements and disagreements with other studies or reviews

The findings of our review regarding RIC for preventing ischaemic stroke are different from other meta-analyses in the literature. Two Cochrane Reviews (one of which included 29 studies involving 5392 participants who underwent cardiovascular surgery, and the other four studies involving 232 participants who underwent vascular and endovascular surgery) and a non-Cochrane review (which included 23 studies involving a total of 2200 participants who underwent cardiovascular surgery) analysed the effectiveness of RIC on preventing stroke (Benstoem 2017; Desai 2011; Healy 2014). These three previous reviews concluded that RIC had no effect on stroke. This discrepancy may be attributable to the different study populations included in different reviews. In this review, we analysed the effects of RIC in preventing ischaemic stroke in people with symptomatic intracerebral artery stenosis or undergoing carotid stenting, and all these participants had a high possibility of recurrent stroke or new brain infarct. However, in people undergoing cardiovascular surgery, vascular surgery and endovascular surgery, the incidence of stroke is relatively very low, and many studies found no participants developing this complication.

There has been no previous systematic review of RIC versus non-RIC in treating ischaemic stroke. The evidence in this review that RIC should not be used routinely in treating ischaemic stroke disagrees with the conclusions of the authors of the four included studies. However, due to the flaws identified in the included studies, further studies on the efficacy of RIC for treating ischaemic stroke are welcomed.

AUTHORS' CONCLUSIONS

Implications for practice

We found low-quality evidence that remote ischaemic conditioning (RIC) may reduce the risk of recurrent stroke in participants with intracerebral artery stenosis, reduce infarct volume in participants undergoing carotid stenting, and increase dependence or death in participants with acute ischaemic stroke who are undergoing intravenous thrombolysis. However, based on the current low-quality evidence from several small trials, it is difficult to determine whether people with symptomatic intracerebral artery stenosis, acute ischaemic stroke, cerebral small vessel disease, or those undergoing carotid artery stenting will benefit from RIC. Routine use of RIC to prevent or treat ischaemic stroke cannot be supported by the current evidence. Although adverse events were more common with RIC caused by cuff inflation, serious adverse events were not reported.

Implications for research

Further large-scale trials may be worthwhile to determine the efficacy of RIC in treating acute ischaemic stroke, especially those treated with reperfusion therapy (e.g. intravenous thrombolysis

and endovascular therapy). Researchers are also encouraged to investigate RIC in other subtypes of cerebrovascular diseases (e.g. haemorrhagic stroke). Furthermore, the optimal dose and the treatment protocol for RIC treatment needs further investigation. The safety of RIC needs to be further determined in adequately-designed studies, and further studies should be conducted and reported according to the CONSORT Statement ([Schulz 2010](#)).

ACKNOWLEDGEMENTS

We thank Hazel Fraser (Managing Editor, Cochrane Stroke Group) and Joshua Cheyne (Information Specialist, Cochrane Stroke

Group) for their valuable help during the preparation and revision of this review. We thank Peter Langhorne, Paul Nederkoorn, Aryelly Rodriguez (the Cochrane Stroke Group editors), Jessica Sharp (the Copyeditor), and Dee Shneiderman (consumer reviewer for this review) for their expert advice, helpful comments and suggestions, and assistance with this review. We thank Jin Xu (Department of Library, Xuanwu Hospital, Capital Medical University) for her valuable assistance when preparing and revising the review.

REFERENCES

References to studies included in this review

England 2016 {published data only}

England T, Hedstrom A, O'Sullivan S, Donnelly R, Sprigg N, Bath P. Remote ischaemic conditioning after stroke trial (RECAST). *International Journal of Stroke* 2016;**11** Suppl 4:6.

Hougaard 2014 {published data only}

Hougaard KD, Hjort N, Zeidler D, Sorensen L, Norgaard A, Hansen TM, et al. Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke* 2014;**45**(159):67. [PUBMED: PMID: 24203849]

Meng 2012 {published data only}

Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* 2012;**79**(18):1853-61. [PUBMED: PMID: 23035060]

Meng 2015 {published data only}

Meng R, Ding Y, Asmaro K, Brogan D, Meng L, Sui M, et al. Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. *Neurotherapeutics* 2015;**12**(3):667-77. [PUBMED: PMID: 25956401]

Mi 2016 {published data only}

Mi T, Yu F, Ji X, Sun Y, Qu D. The interventional effect of remote ischemic preconditioning on cerebral small vessel disease: a pilot randomized clinical trial. *European Neurology* 2016;**76**(1-2):28-34. [PUBMED: PMID: 27351719]

Wang 2017 {published data only}

Wang Y, Meng R, Song H, Liu G, Hua Y, Cui D, et al. Remote ischemic conditioning may improve outcomes of patients with cerebral small-vessel disease. *Stroke* 2017;**48**(11):3064-72. [PUBMED: PMID: 29042490]

Zhao 2017 {published data only}

Zhao W, Meng R, Ma C, Hou B, Jiao L, Zhu F, 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):1325-35. [PUBMED: PMID: 28174194]

References to studies excluded from this review

Cho 2017 {published data only}

Cho YJ, Lee EH, Lee K, Kim TK, Hong DM, Chin JH, et al. Long-term clinical outcomes of remote ischemic preconditioning and postconditioning outcome (rispo) trial in patients undergoing cardiac surgery. *International Journal of Cardiology* 2017;**231**:84-9.

Coverdale 2017 {published data only}

Coverdale NS, Hamilton A, Petsikas D, McClure RS, Malik P, Milne B, et al. Remote ischemic preconditioning in high-risk cardiovascular surgery patients: a randomized-controlled

trial. [http://www.semthorcardiovascsurg.com/article/S1043-0679\(17\)30238-1/fulltext](http://www.semthorcardiovascsurg.com/article/S1043-0679(17)30238-1/fulltext) 2017.

Davies 2013 {published and unpublished data}

Davies WR, Brown AJ, Watson W, McCormick LM, West NEJ, Dutka DP, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up. *Circulation: Cardiovascular Interventions* 2013;**6**(3):246-51.

Healy 2015 {published data only (unpublished sought but not used)}

Healy DA, Boyle E, McCartan D, Bourke M, Medani M, Ferguson J, et al. A multicenter pilot randomized controlled trial of remote ischemic preconditioning in major vascular surgery. *Vascular and Endovascular Surgery* 2015;**49**(8):220-7.

Hoole 2009 {published data only}

Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, et al. Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: a prospective, randomized control trial. *Circulation* 2009;**119**(6):820-7.

Hudetz 2014 {published data only}

Hudetz J, Patterson K, Iqbal Z, Gandhi S, Pagel P. Remote ischemic preconditioning prevents deterioration of short-term postoperative cognitive function after cardiac surgery using cardiopulmonary bypass: results of a pilot investigation. *Journal of Cardiothoracic and Vascular Anesthesia* 2014;**29**(2):382-8.

Hyngstrom 2016 {published and unpublished data}

Hyngstrom A, Schmit BD, Gutterman DD, Durand MJ. Ischemic preconditioning as a method to improve motor function post stroke. *Archives of Physical Medicine and Rehabilitation* 2016;**97**(10):819 (Abst. 804).

Jing 2011 {published and unpublished data}

Jing G, Zheng L. Protective effects of remote ischemic preconditioning on cerebral injury in patients undergoing cardiac valve replacement with CPB. *Journal of Xian Jiaotong University* 2011;**32**(4):473-6.

Joseph 2015 {published data only}

Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Khalil M, Tang A, et al. Secondary brain injury in trauma patients: the effects of remote ischemic conditioning. *Journal of Trauma and Acute Care Surgery* 2015;**78**(4):698-705.

Kahlert 2017 {published data only}

Kahlert P, Hildebrandt HA, Patsalis PC, Al-Rashid F, Janosi RA, Nensa F, et al. No protection of heart, kidneys and brain by remote ischemic preconditioning before transfemoral transcatheter aortic valve implantation: interim-analysis of a randomized single-blinded, placebo-controlled, single-center trial. *International Journal of Cardiology* 2017;**231**(3):248-54.

Meng 2017 {published data only}

Meng R, Zhao W, Li S, Sui M, Zhou D, Wu W, et al. Long-term regular remote ischemic conditioning promotes arterial collateral opening and reconstruction in patients with intracranial atherosclerotic stenosis. *Stroke* 2017;**48**:A76-A76.

NCT01672515 {unpublished data only}

NCT01672515. Protective effects of remote limb ischemic preconditioning on acute cerebral infarction. <https://clinicaltrials.gov/ct2/show/NCT01672515> (accessed 10 January 2018).

Sales 2017 {published data only}

Sales AHA, Barz M, Bette S, Wiestler B, Ryang YM, Meyer B, et al. Impact of ischemic preconditioning on surgical treatment of brain tumors: a single-center, randomized, double-blind, controlled trial. *BMC Medicine* 2017;**15**(1):137.

Sloth 2014 {published data only}

Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *European Heart Journal* 2014;**35**(3):168-75.

Walsh 2010 {published data only}

Walsh SR, Nouraei SA, Tang TY, Sadat U, Carpenter RH, Gaunt ME. Remote ischemic preconditioning for cerebral and cardiac protection during carotid endarterectomy: results from a pilot randomized clinical trial. *Vascular and Endovascular Surgery* 2010;**44**(6):434-9.

Zhong 2013 {published data only}

Zhong H, Gao Z, Chen M, Zhao J, Wang F, Li L, et al. Cardioprotective effect of remote ischemic postconditioning on children undergoing cardiac surgery: a randomized controlled trial. *Paediatric Anaesthesia* 2013;**23**(8):726-33.

References to ongoing studies
NCT02169739 {unpublished data only}

NCT02169739. Remote preconditioning over time to empower cerebral tissue (REM-PROTECT) [Pilot, Randomized, Controlled, Staggered Start, Feasibility Trial of Ischemic Preconditioning, a Promising Novel Treatment for Stroke Prevention]. <https://clinicaltrials.gov/show/NCT02169739> (first received 23 June 2014).

NCT02189928 {unpublished data only}

NCT02189928. Remote iSchemic Conditioning in acUte BRAin Infarction Study (RESCUE-BRAIN) [Lower Limb Ischaemic Preconditioning in Acute Cerebral Infarction (<H6): Multicenter Randomized Study With Stratification on IV Thrombolysis and PROBE Design (Prospective Randomized Open Trial With Blinded End-Point)]. <https://clinicaltrials.gov/show/NCT02189928> (first received 15 July 2014).

NCT02323425 {unpublished data only}

NCT02323425. Effects of limb ischemic postconditioning in young sICAS (EPIC-sICAS) [Effects of Upper Limb Ischemic Postconditioning on Collateral Circulation in Young Symptomatic Intracranial Atherosclerosis]. <https://clinicaltrials.gov/show/NCT02323425> (first received 23 December 2014).

NCT02534545 {unpublished data only}

NCT02534545. Remote ischemic conditioning for avoiding recurrence of symptomatic intracranial atherosclerotic stenosis (sICAS) [Remote Ischemic Conditioning for Avoiding Recurrence of Ischemic Stroke in Patients With Symptomatic Intracranial Atherosclerotic Stenosis]. <https://clinicaltrials.gov/show/NCT02534545> (first received 27 August 2015).

NCT02779712 {unpublished data only}

NCT02779712. Remote ischaemic conditioning after stroke trial (ReCAST-2) [Remote Ischaemic Conditioning After Stroke Trial (ReCAST-2): A Pilot Randomised Controlled Phase II Trial Evaluating Remote Ischaemic Conditioning (RIC) After Hyperacute Stroke 2]. <https://clinicaltrials.gov/show/NCT02779712> (first received 20 May 2016).

NCT03105141 {unpublished data only}

NCT03105141. Optimized remote ischemic conditioning (RIC) treatment for patients with chronic cerebral ischemia [The Impact of Repeated Bilateral Limb Remote Ischemic Conditioning on Patients With Chronic Cerebral Ischemia: Establishment of Optimized Algorithm on the Basis of Feasibility, Safety and Efficacy]. <https://clinicaltrials.gov/show/NCT03105141> (first received 7 April 2017).

NCT03208166 {unpublished data only}

NCT03208166. Pilot study of pre-ischemic conditioning for intracranial atherosclerosis (PICASSO) [Pilot Study of Pre-Ischemic Conditioning for Intracranial Atherosclerosis]. <https://clinicaltrials.gov/show/NCT03208166> (first received 5 July 2017).

NCT03231384 {unpublished data only}

NCT03231384. rt-PA thrombolytic therapy in combination with remote ischemic conditioning for acute ischemic stroke [Safety and Feasibility of Rt-PA Thrombolytic Therapy in Combination With Remote Ischemic Conditioning for Acute Ischemic Stroke(rtPA-RIC1)]. <https://clinicaltrials.gov/show/NCT03231384> (first received 27 July 2017).

Additional references
Bai 2015

Bai J, Lyden PD. Revisiting cerebral postischemic reperfusion injury: new insights in understanding reperfusion failure, hemorrhage, and edema. *International Journal of Stroke* 2015;**10**(2):143-52.

Benstoem 2017

Benstoem C, Stoppe C, Liakopoulos OJ, Ney J, Hasenclever D, Meybohm P, et al. Remote ischaemic preconditioning for coronary artery bypass grafting (with or without valve surgery).

Cochrane Database of Systematic Reviews 2017, Issue 5. [DOI: [10.1002/14651858.CD011719.pub3](https://doi.org/10.1002/14651858.CD011719.pub3)]

Desai 2011

Desai M, Gurusamy KS, Ghanbari H, Hamilton G, Seifalian AM. Remote ischaemic preconditioning versus no remote ischaemic preconditioning for vascular and endovascular surgical procedures. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: [10.1002/14651858.CD008472.pub2](https://doi.org/10.1002/14651858.CD008472.pub2)]

Feigin 2015

Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 study. *Neuroepidemiology* 2015;**45**(3):161-76.

Guyatt 2008

Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6.

Hahn 2011

Hahn CD, Manlhiot C, Schmidt MR, Nielsen TT, Redington AN. Remote ischemic per-conditioning: a novel therapy for acute stroke?. *Stroke* 2011;**42**(10):2960-2.

Hausenloy 2016

Hausenloy DJ, Yellon DM. Ischaemic conditioning and reperfusion injury. *Nature Reviews Cardiology* 2016;**13**(4):193-209.

Healy 2014

Healy DA, Khan WA, Wong CS, Moloney MC, Grace PA, Coffey JC, et al. Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis. *International Journal of Cardiology* 2014;**176**(1):20-31.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Hoda 2012

Hoda MN, Siddiqui S, Herberg S, Periyasamy-Thandavan S, Bhatia K, Hafez SS, et al. Remote ischemic preconditioning is effective alone and in combination with intravenous tissue-type plasminogen activator in murine model of embolic stroke. *Stroke* 2012;**43**(10):2794-9.

Lim 2012

Lim SY, Hausenloy DJ. Remote ischemic conditioning: from bench to bedside. *Frontiers in Physiology* 2012;**3**:27.

Menting 2017

Menting TP, Wever KE, Ozdemir-van Brunschot DMD, Van der Vliet DJA, Rovers MM, Warle M. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury.

Cochrane Database of Systematic Reviews 2017, Issue 3. [DOI: [10.1002/14651858.CD010777.pub2](https://doi.org/10.1002/14651858.CD010777.pub2)]

Murry 1986

Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;**74**(5):1124-36.

Nogueira 2018

Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *New England Journal of Medicine* 2018;**378**(1):11-21.

Pan 2016

Pan J, Li X, Peng Y. Remote ischemic conditioning for acute ischemic stroke: dawn in the darkness. *Reviews in the Neurosciences* 2016;**27**(5):501-10.

Powers 2018

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;**49**(3):e46-e110.

Przyklenk 1993

Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993;**87**(3):893-9.

Ren 2015

Ren C, Wang P, Wang B, Li N, Li W, Zhang C, et al. Limb remote ischemic per-conditioning in combination with post-conditioning reduces brain damage and promotes neuroglobin expression in the rat brain after ischemic stroke. *Restorative Neurology and Neuroscience* 2015;**33**(3):369-79.

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roth 2015

Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *New England Journal of Medicine* 2015;**372**(14):1333-41.

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332.

Steiger 2016

Steiger N, Cifu AS. Primary prevention of stroke. *Journal of the American Medical Association* 2016;**316**(6):658-9.

Wan 2014

Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;**14**:135.

Weber 2010

Weber C. Far from the heart: receptor cross-talk in remote conditioning. *Nature Medicine* 2010;**16**(7):760-2.

Writing Group 2016

Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke

statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;**133**(4):e38-236.

References to other published versions of this review

Zhao 2017

Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X. Remote ischaemic conditioning for preventing and treating ischaemic stroke. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: [10.1002/14651858.CD012503](https://doi.org/10.1002/14651858.CD012503)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

England 2016

Methods	<p>Study design: RCT</p> <p>Generation of the allocation sequence: minimised on age, sex, NIHSS score, and systolic blood pressure</p> <p>Allocation concealment: web-based, 1:1 allocation</p> <p>Study grouping: parallel group</p> <p>Masking: triple-blinded (participants, investigator, outcome assessor)</p> <p>Analysis method: ITT analysis</p> <p>Total duration of study: 27 months, from March 2013 to July 2015</p>
Participants	<p>26 participants (intervention = 13; placebo control = 13)</p> <p>UK</p> <p>Single centre: Derby Teaching Hospitals NHS Foundation Trust</p> <p>Setting: inpatient</p> <p>Sex: both (65.4% men, 34.6% women)</p> <p>Mean age: 76.2 years old</p> <p>Inclusion criteria: adults with an ischaemic stroke in the past 24 hours causing arm or leg weakness</p> <p>Exclusion criteria: mRS score > 3, thrombolysis for index event, and significant comorbidity</p>
Interventions	<p>Participants were randomly assigned to either of 2 groups:</p> <p>Group 1: RIC group (n = 13), standard medical management plus RIC. RIC consisted of 4 cycles of intermittent limb ischaemia; alternating 5 minutes' inflation (20 mmHg above systolic blood pressure) and 5 minutes' deflation performed manually using a standard upper arm blood pressure cuff in the non-paretic arm.</p> <p>Group 2: placebo control group (n = 13), standard medical management plus sham RIC. Sham RIC consisted 4 cycles of intermittent limb ischaemia; alternating 5 minutes' inflation (30 mmHg) and 5 minutes' deflation performed manually using a standard upper arm blood pressure cuff in the nonparetic arm.</p> <p>Concomitant medications: single antiplatelets, blood pressure and cholesterol reduction treatment</p>

England 2016 (Continued)

Outcomes	<p>Primary outcome: tolerability and feasibility of RIC after acute ischaemic stroke</p> <p>Secondary outcomes: surrogate markers of efficacy (plasma S100-β, matrix metalloproteinase-9, troponin T), inflammation (C-reactive protein), and other putative biomarker (heat shock proteins and endocannabinoids). Transcranial Doppler was performed as a continuous beat-to-beat recording during the intervention; central pressures measured with Sphygmocor. Serious adverse events, mRS score, impairment (NIHSS score and motricity index), BI, extended activities of daily living, Zung Depression Scale, and cognition (MMSE) were measured at day 90.</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow-up: 100%</p> <p>Demographic: adequately reported and similar</p> <p>Principle investigator: Timothy J England, PhD, FRCP</p> <p>Funding: British Medical Association Vera Down Grant</p> <p>Notable authors' disclosures: no</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study minimised on age, sex, NIHSS score, and systolic blood pressure.
Allocation concealment (selection bias)	Low risk	Web-based, and 1:1 allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The intervention group received RIC procedure and the control group received sham procedure.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was a single-centre, randomised, outcome-blinded, placebo-controlled trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's prespecified outcomes had been reported in the pre-specified way.
Other bias	Low risk	No other bias identified

Hougaard 2014

Methods	<p>Study design: RCT</p> <p>Randomisation: drawing from a large number of sealed opaque envelopes</p> <p>Allocation concealment: sealed opaque envelopes</p> <p>Study grouping: parallel group</p>
---------	--

Hougaard 2014 (Continued)

Masking: single-blinded (outcome assessor)

Analysis method: PP analysis

Total duration of study: 19 months, from June 2009 to January 2011

Participants	<p>285 participants (intervention = 160; control = 125)</p> <p>Denmark</p> <p>Single centre: Aarhus University Hospital</p> <p>Setting: emergency</p> <p>Sex: both (57% men, 59% women)</p> <p>Mean age: 66.9 years old</p> <p>Inclusion criteria: eligible patients were ≥ 18 years of age with symptoms of acute stroke according to the prehospital services assessment, as per standardised national guidelines (modified Face, Arm, Speech Test (FAST) criteria).</p> <p>Exclusion criteria: contraindications to rtPA or MRI, known hypersensitivity to Gadovist or any of its ingredients, acute or chronic severe renal impairment, and people with a non-stroke diagnosis</p>
Interventions	<p>Participants were randomly assigned to either of 2 groups:</p> <p>Group 1: RIC group (n = 81), intravenous thrombolysis plus RIC. RIC was induced by 4 inflations of a standard upper limb blood pressure cuff to either 200 mmHg or 25 mmHg above the patient's systolic blood pressure, each lasting 5 minutes and separated by 5 minutes of cuff deflation</p> <p>Group 2: control group (n = 68), intravenous thrombolysis alone</p> <p>Concomitant medications: standard care according to national guidelines for the treatment of acute ischaemic stroke by intravenous thrombolysis</p>
Outcomes	<p>Primary outcome: the penumbra salvage</p> <p>Secondary outcomes: final infarct size, infarct growth, and clinical outcome at 3 months</p> <p>Other outcomes: risk of infarction in treated and untreated tissue according to the severity of the level of hypoperfusion at admission</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow-up: 52.3%</p> <p>Demographic: inadequately reported</p> <p>Principle investigator: Kristina Dupont Hougaard, MD</p> <p>Funding: the study was funded by grants from the Danish National Research Foundation, the Aase and Ejnar Danielsen Foundation, and the Tryg Foundation. Bayer AG supplied the contrast media for perfusion scans.</p> <p>Notable disclosures: 2 authors are shareholders in CellAegis Devices Inc, who made the RIC device in the study.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Hougaard 2014 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was performed by drawing from a large number of sealed opaque envelopes.
Allocation concealment (selection bias)	Unclear risk	Sealed opaque envelopes were used, but whether envelopes were sequentially numbered is unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were not blinded to the treatment protocol.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes assessors were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	"As-treated" analysis was done with substantial departure of the intervention received from that assigned at randomisation.
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's prespecified outcomes had been reported in the prespecified way.
Other bias	High risk	2 authors were shareholders in CellAegis Devices Inc where the devices used in this study were made.

Meng 2012

Methods	Study design: RCT Generation of the allocation sequence: random number Allocation concealment: unclear Study grouping: parallel group Masking: single-blinded (outcome assessor) Analysis method: PP analysis Total duration of study: unclear
Participants	103 participants (intervention = 51; control = 52) China 2 centres Setting: clinic and inpatient Sex: both (58.8% men, 41.2% women) Mean age: 60.6 years old Inclusion criteria: 1) intracranial artery stenosis (measured as 50% by angiography or 70% by ultrasound, CTA or MRA) patient with corresponding stroke and TIA within 30 days from the start of the study; 2) age range 18 to 80 years; 3) NIHSS score 0–15, and mRS score 2–4 (mRS 0–1 were excluded); 4) ABCD2 score 6–7; 5) stable vital signs, normal hepatic and renal functions; 6) no haemorrhagic tendency; 7) Trial of Org 10172 in Acute Stroke Treatment (TOAST) 1 subtype

Meng 2012 (Continued)

Interventions	<p>Participants were randomly assigned to one of 2 groups:</p> <p>Group 1: RIC group (n = 38), standard medical management plus RIC. RIC consisted of 5 cycles of bilateral upper limbs ischaemia (induced by inflating tourniquets to 200 mmHg) for 5 minutes followed by reperfusion for another 5 minutes, performed twice daily for a total of 300 consecutive days.</p> <p>Group 2: control group (n = 30), standard medical management alone</p> <p>Concomitant medications: antiplatelet agents, lipid control agents, and antidiabetic agents (if necessary)</p>
Outcomes	<p>Primary outcome: time point of the first stroke recurrence event</p> <p>Secondary outcome: time to which mRS recovers to 0–1</p> <p>Other outcomes: RIC treatment intolerance</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow-up: 66%</p> <p>Demographic: adequately reported and similar</p> <p>Principle investigator: Xunming Ji, MD, PhD</p> <p>Funding: this study was sponsored by the National Natural Science Foundation (30870854 and 30770741, China) and the Foundation of the Beijing High Level Health Systems Talented Technical Personnel Program (2009-03-02, China).</p> <p>Conflicts of interest of authors: the corresponding author is one of the inventors of the electric auto-control device used in the study.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants were randomly divided into 2 groups according to a random number.
Allocation concealment (selection bias)	Unclear risk	The method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Doctors and participants were unmasked to the treatment protocol and allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators responsible for evaluating the results of NIHSS, mRS scores, TCD, MRI, and SPECT, and the examiners who were responsible for testing plasma samples of the participants were masked to the treatment protocol and allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	35 (33.98%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Study authors published findings on all the predefined study outcomes.

Meng 2012 (Continued)

Other bias	High risk	The corresponding author is one of the inventors of the electric autocontrol RIC device used in the study.
------------	-----------	--

Meng 2015

Methods	<p>Study design: RCT</p> <p>Generation of the allocation sequence: computer-generated blocked randomisation technique</p> <p>Allocation concealment: numbered, opaque, sealed envelopes</p> <p>Study grouping: parallel group</p> <p>Masking: triple-blinded (participants, investigator, outcome assessor)</p> <p>Analysis method: PP analysis</p> <p>Total duration of study: from 2008 to 2012</p>
Participants	<p>79 participants (intervention = 40; control = 39)</p> <p>China</p> <p>Single centre: Xuanwu Hospital, Capital Medical University</p> <p>Setting: clinic and inpatient</p> <p>Sex: both (62.1% men, 37.9% women)</p> <p>Mean age: 83.8 years old</p> <p>Inclusion criteria: 1) intracranial arterial stenosis patients (at least 70% assessed by MRA or CTA) presented with ischaemic stroke or TIA within 7 days; 2) age 80–95 years; 3) NIHSS score of 0–15, and mRS score of 2–4; 4) ABCD2 score of 6–7; 5) stable vital signs, and normal hepatic and renal function; 6) no haemorrhagic tendency; 7) TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype 1 of stroke</p>
Interventions	<p>Participants were randomly assigned to either of 2 groups:</p> <p>Group 1: RIC group (n = 30), standard medical management plus RIC treatment. RIC treatment consisted of 5 cycles of simultaneous bilateral upper arm ischaemia for 5 minutes followed by reperfusion for another 5 minutes, performed twice daily for 180 consecutive days. The RIC procedure was performed using an electric autocontrol device with cuffs that inflated to a pressure of 200 mmHg during the ischaemic period.</p> <p>Group 2: control group (n = 28), standard medical management sham RIC treatment. Sham RIC treatment consisted of 5 cycles of bilateral upper arm ischaemia for 5 minutes followed by reperfusion for another 5 minutes, performed twice daily for 180 consecutive days. The sham procedure was performed using an electric autocontrol device with cuffs that inflated to a pressure of 30 mmHg during the ischaemic period.</p> <p>Concomitant medications: either clopidogrel 75 mg/day in combination with atorvastatin 20 mg/day or aspirin 100 mg/day and clopidogrel 75 mg/day in combination with atorvastatin 20 mg/day</p>
Outcomes	<p>Safety outcomes: 1) objective signs of tissue or neurovascular injury resulting from RIC treatment; 2) development of symptomatic or asymptomatic upper extremity deep vein thrombosis as detected by a vascular ultrasound; 3) elevation of plasma myoglobin levels beyond normal limits after RIC treatment; 4) symptomatic haemorrhagic transformation after cerebral infarction; 5) participants not tolerating RIC treatment</p>

Meng 2015 (Continued)

Clinical outcomes: 1) stroke and TIA recurrence during the 180 consecutive days of treatment were defined as primary outcome endpoints; 2) improvement of the NIHSS score (≥ 8 points or ≤ 1 point from the baseline) or a mRS of 0–2 were the secondary outcomes

Blood evaluation outcome: dynamic changes in plasma levels of hsCRP, leukocyte count, fibrinogen, D-dimer, PAI-1 TPA, and platelet aggregation rates in 30 days of RIC and sham RIC

Notes	<p>External blinded review of outcomes</p> <p>Follow up: 73.4%.</p> <p>Demographic: adequately reported and similar</p> <p>Principle investigator: Xunming Ji, MD, PhD</p> <p>Funding: this study was sponsored by the National Natural Science Foundation (81371289), China, The Foundation of the Beijing High Level Health Systems (Talented Technical Personnel Program 2009-03-02), China; and The National Key Department of Neurology funded by Chinese Health and Family Planning Committee</p> <p>Notable disclosures: the corresponding author is one of the inventors of the electric auto-control device used in the study.</p>
-------	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was generated by using a computer-generated blocked randomisation technique.
Allocation concealment (selection bias)	Low risk	The allocation sequence is computer generated and subsequently concealed in consecutively numbered, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham RIC was used as placebo control.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research assistants responsible for local skin status evaluations, blood pressure measurements, heart rate measurements, plasma sample assays, and neuroradiology interpretation were blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	21/79 (26.6%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Authors published findings on all the predefined study outcomes
Other bias	High risk	The corresponding author is one of the inventors of the electric autocontrol RIC device used in the study.

Mi 2016

Methods	<p>Study design: RCT</p> <p>Generation of the allocation sequence: computerised random number sequence</p> <p>Allocation concealment: unclear</p>
---------	---

Remote ischaemic conditioning for preventing and treating ischaemic stroke (Review)

Mi 2016 (Continued)

	<p>Study grouping: parallel group</p> <p>Masking: double-blinded (investigator, outcome assessor)</p> <p>Analysis method: ITT analysis</p> <p>Total duration of study: 14 months, from to August 2012 to October 2013</p>
Participants	<p>17 participants (intervention = 9; placebo control = 8)</p> <p>China</p> <p>Single centre: Xuanwu Hospital, Capital Medical University</p> <p>Setting: clinic and inpatient</p> <p>Sex: both (41.2% men, 58.8% women)</p> <p>Mean age: 63.5 years old</p> <p>Inclusion criteria: people diagnosed with small vessel disease</p> <p>Exclusion criteria: 1) history of intracranial haemorrhage; 2) significant bleeding in other parts of the body; 3) history of atrial fibrillation; 4) history of myocardial infarction within 6 months; 5) Moyamoya disease, hereditary small vessel disorders (e.g. CADASIL or Fabry) and mitochondrial encephalomyopathy; 6) significant bleeding coagulation dysfunction; 7) severe liver/kidney disease, cancer, or critical illness pertaining to internal medicine and surgery</p>
Interventions	<p>Participants were randomly assigned to either of 2 groups:</p> <p>Group 1: RIC group (n = 9), standard medical management plus RIC. RIC was achieved using an automated cuff inflator placed on bilateral arms that was inflated to 200 mmHg. The cuff remained inflated for 5 minutes, followed by 5 minutes of reperfusion. Each preconditioning session consisted of 5 cycles of ischaemia/reperfusion. All participants were required to receive RIC treatment twice daily for 1 year.</p> <p>Group 2: control group (n = 8), sham RIC was achieved using an automated cuff inflator placed on bilateral arms that was inflated to 50 mmHg. The cuff remained inflated for 5 minutes, followed by 5 minutes of reperfusion. Each conditioning session consisted of 5 cycles of ischaemia/reperfusion. All participants were required to receive RIC treatment twice daily for 1 year.</p> <p>Concomitant medications: unclear</p>
Outcomes	<p>Primary outcome: changes in brain lesions evaluated by the number of lacunar infarctions and white matter lesions volume</p> <p>Secondary outcomes: changes in cognitive functions, cerebral haemodynamics, and the Dizziness Handicap Inventory scores</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow up: 100%</p> <p>Demographic: inadequately reported</p> <p>Principle investigator: Xunming Ji, Yongxin Sun, MD, PhD</p> <p>Funding: Talent Cultivation Foundation, the High-Level Health Technology Talent Construction Program of the Beijing Municipal Health Bureau (008-0019); the Talent Cultivation Foundation, Beijing Outstanding Talents Cultivation Fund, Beijing Municipal Committee (2012D005018000007); and the Natural Science Foundation, Shanghai Jiao Tong University School of Medicine (YZ1006)</p> <p>Conflicts of interest of authors: the authors report no disclosure.</p>

Mi 2016 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was generated using a computerised random number sequence.
Allocation concealment (selection bias)	Unclear risk	"Participant assignments were sealed and handed to specialized staff", but it remains unclear whether the assignments were sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham RIC was used as placebo control.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes assessors were blinded to the treatment protocol and assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant was lost to follow-up.
Selective reporting (reporting bias)	Low risk	Authors published findings on all the predefined study outcomes.
Other bias	High risk	One author is one of the inventors of the electric autocontrol RIC device used in the study.

Wang 2017

Methods	Study design: RCT Generation of the allocation sequence: unclear Allocation concealment: unclear Study grouping: parallel group Masking: double-blinded (investigator, outcome assessor) Analysis method: PP analysis Total duration of study: 35 months, from to July 2012 to June 2015
Participants	36 participants (intervention = 18; placebo control = 18) China Single centre: Xuanwu Hospital, Capital Medical University Setting: clinic and inpatient Sex: both (50% men, 50% women) Mean age: 63.1 years old Inclusion criteria: 1) Han Chinese, aged from 45 to 80 years; 2) patient or caregiver report of cognitive decline with regard to memory or other cognitive domains lasting for at least 3 months; 3) neither nor-

Wang 2017 (Continued)

mal nor demented on the basis of the criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) with normal or slightly impaired activities of daily living, with MMSE score of ≥ 20 (primary school) or ≥ 24 (junior school or above) and MoCA score of ≤ 26 ; 4) the presence of lacunes or WMHs on MRI according to Standards for Reporting Vascular Changes on Neuroimaging criteria; 5) the absence of vascular narrowing $> 50\%$ luminal diameter that could cause haemodynamic changes (mean flow velocity > 90 cm/s for the intracranial internal carotid artery, 100 cm/s for the middle carotid artery, > 80 cm/s for basilar artery or vertebral artery) measured by TCD according to the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis criteria

Exclusion criteria: 1) history of intracranial haemorrhage or significant bleeding in other parts of the body; 2) history of atrial fibrillation or myocardial infarction within 6 months; 3) hereditary or inflammatory small-vessel disorders; 4) significant bleeding disorder; 5) history of brain tumours, psychoses, or acute stroke within 6 months of symptom onset; 6) severe renal or hepatic disease, cancer, or critical illness; 7) systolic blood pressure > 200 mmHg with medication; 8) any soft tissue or vascular injury and any disease of the extremities that would contraindicate RIC; 9) no informed consent; 10) failure to complete the entire treatment regimen (the participant's completion rate was $> 80\%$ of the RIC or sham-RIC treatments for 1 year or the participant was excluded from the final analysis)

Interventions	<p>Participants were randomly assigned to either of 2 groups:</p> <p>Group 1: RIC group ($n = 18$), standard medical management plus RIC. RIC was achieved using an automated cuff inflator placed on bilateral arms that was inflated to 200 mmHg. The cuff remained inflated for 5 minutes, followed by 5 minutes of reperfusion. Each preconditioning session consisted of 5 cycles of ischaemia/reperfusion. All participants were required to receive RIC treatment twice daily for 1 year.</p> <p>Group 2: control group ($n = 18$), sham RIC was achieved using an automated cuff inflator placed on bilateral arms that was inflated to 50 mmHg. The cuff remained inflated for 5 minutes, followed by 5 minutes of reperfusion. Each conditioning session consisted of 5 cycles of ischaemia/reperfusion. All participants were required to receive RIC treatment twice daily for 1 year.</p> <p>Concomitant medications: antiplatelet agents, statins, and vascular risk factors modification</p>
Outcomes	<p>Primary outcome: the change of brain lesions measured on MRI fluid-attenuated inversion recovery</p> <p>Secondary outcomes: changes of cognitive function measured by MMSE and MoCA, plasma biomarkers, cerebral haemodynamic parameters measured by TCD both at baseline and at the end of 1-year</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow up: 83.3%</p> <p>Demographic: adequately reported</p> <p>Principle investigator: Xunming Ji, MD, PhD</p> <p>Funding: National Science Foundation for Distinguished Young Scholars (81325007), Beijing Municipal Administration of Hospitals' Mission Plan (20150802), National Natural Science Foundation of China (81371289) and Scientific Research Project of Beijing Municipal Education Commission (KM20160025015)</p> <p>Conflicts of interest of authors: the authors report no disclosure.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed by an independent statistician, but the details were not reported.
Allocation concealment (selection bias)	Unclear risk	"Participant assignments were sealed and handed to specialized staff", but it remains unclear whether the assignments were sequentially numbered

Wang 2017 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham intervention was used and participants were blinded to the treatment protocol.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes assessors were blinded to the treatment protocol and assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximately 17% participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Authors published findings on all the predefined study outcomes.
Other bias	High risk	One author is one of the inventors of the electric autocontrol RIC device used in the study.

Zhao 2017

Methods	<p>Study design: RCT</p> <p>Generation of the allocation sequence: computer-generated list in randomly sequenced blocks of 6</p> <p>Allocation concealment: numbered, sealed, opaque envelopes</p> <p>Study grouping: parallel group</p> <p>Masking: single-blinded (outcome assessor)</p> <p>Analysis method: ITT and PP analysis</p> <p>Total duration of study: 29 months, from to 1 August 2012 to 20 December 2014</p>
Participants	<p>189 participants (intervention = 63; control = 63; sham intervention = 63)</p> <p>China</p> <p>Single centre: Xuanwu Hospital, Capital Medical University</p> <p>Setting: clinic and inpatient</p> <p>Sex: both (71.4% men, 28.6% women)</p> <p>Mean age: 66.6 years old</p> <p>Inclusion criteria: 1) ≥ 18 years of age; 2) tolerance to any of the necessary medications, including clopidogrel, aspirin, and statins; 3) ability to complete a brain MRI examination; 4) a negative pregnancy test within 7 days before randomisation for any woman with childbearing potential; 5) stable vital signs, and normal renal and hepatic functions; 6) participant or his or her legally authorised representative was able to provide an informed consent</p>
Interventions	<p>Participants were randomly assigned to one of 3 groups:</p> <p>Group 1: RIC group (n = 63), standard medical management plus RIC. RIC was performed twice daily for 2 weeks before carotid stenting. The RIC consisted of 5 cycles of simultaneous bilateral upper arm ischaemia for 5 minutes followed by reperfusion for another 5 minutes. The procedure was performed using an electric autocontrol device with cuffs that inflated to a pressure of 200 mmHg during the ischaemic period</p>

Zhao 2017 (Continued)

Group 2: control group (n = 63), standard medical management alone

Group 3: sham RIC group (n = 63), standard medical management plus sham RIC. Sham RIC procedure during which bilateral upper arm cuffs were inflated to a pressure of 60 mmHg for 5 minutes, followed by 5 minutes of relaxation of the cuffs, for a total of 5 cycles twice daily until the day before carotid stenting

Concomitant medications: antiplatelets and statins were mandatory. Administration of antihypertensive agents and antidiabetic agents were elective at discretion of the treating physician.

Outcomes	<p>Primary outcome: the presence of ≥ 1 new brain lesions on DWI within 48 hours after CAS and the incidence of clinical events (i.e. ischaemic stroke, TIA, acute myocardial infarction, haemorrhagic stroke, hyperperfusion syndrome, and death) within 6 months after CAS</p> <p>Secondary outcomes: the number and volume of new brain lesions on DWI within 48 hours; the changes in plasma hs-CRP levels, NSE levels, and S-100B levels; and adverse events within 6 months</p> <p>Other outcomes: 1) elevation of plasma NSE and S-100B levels beyond normal limits after RIC and sham RIC procedure; 2) inability to tolerate RIC or sham RIC procedure that leads to discontinuation from the study; 3) objective signs of tissue or neurovascular injury resulting from RIC and sham RIPC procedure</p>
Notes	<p>External blinded review of outcomes</p> <p>Follow up: 85.7% for the primary outcome</p> <p>Demographic: adequately reported and similar</p> <p>Principle investigator: Xunming Ji, MD, PhD</p> <p>Funding: this study was funded by The National Science Fund for Distinguished Young Scholars (No. 81325007), Chang Jiang Scholars Program (No. T2014251), and Beijing Municipal Science and Technology Commission (No. Z141107001514006).</p> <p>Conflicts of interest of authors: the corresponding author is one of the inventors of the electric auto-control device used in the study.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a computer-generated list in randomly sequenced blocks of 6.
Allocation concealment (selection bias)	Low risk	Participants were enrolled according to numbered, sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants and the treating physicians were not blinded to the treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors were blinded to the treatment protocol.
Incomplete outcome data (attrition bias) All outcomes	High risk	27 (14.3%) participants were lost for the analysis of primary outcomes.

Zhao 2017 (Continued)

Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes that are prespecified have been reported.
Other bias	High risk	The corresponding author is one of the inventors of the electric autocontrol RIC device used in the study.

CAS: carotid artery stenting
CTA: computed tomography angiography
DWI: diffusion weighted imaging
ITT: intention-to-treat
MoCA: Montreal Cognitive Assessment
MMSE: Mini Mental State Examination
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
PP: per protocol
RCT: randomised controlled trial
RIC: remote ischaemic conditioning
rtPA: recombinant tissue plasminogen activator
SPECT: single-photon emission computed tomography
TCD: transcranial Doppler
TIA: transient ischaemic attack
WMHs: white matter hyperintensities

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cho 2017	Study randomised people undergoing cardiac surgery
Coverdale 2017	Study randomised people undergoing cardiovascular surgery
Davies 2013	Study randomised acute coronary syndrome patients treated with percutaneous coronary intervention
Healy 2015	Study randomised people treated with major vascular surgery, including carotid endarterectomy. We contacted the study authors to ask if they could provide data on patients treated with carotid endarterectomy but we did not receive a response.
Hoole 2009	Study randomised acute coronary syndrome patients treated with percutaneous coronary intervention
Hudetz 2014	RIC was used in people undergoing cardiac surgery
Hyngstrom 2016	RIC was used in both healthy volunteers and people with ischaemic cerebrovascular disease but did not compare RIC with sham RIC or control.
Jing 2011	Laboratory tissue study. After emailing the authors, there was no determination of stroke.
Joseph 2015	Not an RCT
Kahlert 2017	Study randomised people treated with transfemoral transcatheter aortic valve implantation
Meng 2017	This RCT investigated the effects of RIC on cerebral collaterals and the underlying mechanisms in people with symptomatic intracranial atherosclerotic stenosis, instead of ischaemic stroke.

Study	Reason for exclusion
NCT01672515	The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than 2 years. No paper or results have been published.
Sales 2017	This study evaluated the effect of RIC for preventing new postoperative ischaemic lesions, but ischaemic stroke was not included in the outcome assessments.
Sloth 2014	Study randomised acute coronary syndrome patients treated with percutaneous coronary intervention
Walsh 2010	Ischaemic stroke was not included in the outcome assessment
Zhong 2013	Study randomised people treated with cardiac surgery

RCT: randomised controlled trial

RIC: remote ischaemic conditioning

Characteristics of ongoing studies *[ordered by study ID]*

[NCT02169739](#)

Trial name or title	Remote preconditioning over time to empower cerebral tissue (REM-PROTECT)
Methods	RCT (2 groups) Single-blind (outcomes assessor) Follow-up: 12 months, 24 months
Participants	60 participants Inclusion criteria 1. Clinical 1. Clinical lacunar stroke syndrome within the past 6 months 2. Absence of signs or symptoms of cortical dysfunction 3. No proximal large vessel atherosclerosis, intracranial atherosclerosis or cerebellar stroke 4. No major cardioembolic source requiring anticoagulation or other specific therapy 2. Imaging 1. MRI presence of a small subcortical ischaemic, any 1 or more of: DWI lesion < 2.0 cm in size at largest dimension and corresponding to the clinical syndrome. Well delineated focal hyperintensity < 2.0 cm in size at largest dimension (including rostro-caudal extent) on FLAIR or T2 and clearly corresponding to the clinical syndrome. If other focal hyperintensities are present, the case will be discussed with the principal investigator prior to randomisation. Multiple (at least 2) hypointense lesions of size 0.3-1.5 cm at largest dimension (including rostro-caudal extent) only in the cerebral hemispheres on FLAIR or T1 in people whose qualifying event is clinically hemispheric. Well delineated hypointense lesion < 1.5 cm in size at the largest dimension (including rostro-caudal extent) on FLAIR or T1 corresponding to the clinical syndrome. MRI must be done at least 1 month after the qualifying stroke 2. Absence of cortical stroke and large (> 1.5 cm) subcortical stroke, recent or remote 3. White matter hyperintensity score of 2 (moderate) or 3 (severe) on the European Scale of Age-Related White Matter Change 4. Absence of cerebral amyloid antipathy (CAA) as per Boston Criteria Exclusion criteria:

NCT02169739 (Continued)

1. Disabling stroke (Rankin Scale ≥ 4)
2. Previous intracranial haemorrhage (excluding traumatic) or hemorrhagic stroke
3. Age under 40 years
4. High risk of bleeding (e.g. recurrent GI or GU bleeding, active peptic ulcer disease, etc.)
5. Anticipated requirement for long term use of anticoagulants (e.g. recurrent deep venous thrombosis)
6. Prior cortical or retinal stroke (diagnosed either clinically or by neuroimaging), or other prior cortical or retinal TIA
7. Prior ipsilateral carotid endarterectomy
8. Impaired renal function: estimated GFR < 40
9. Intolerance or contraindications to aspirin or clopidogrel (including thrombocytopenia, prolonged INR)
10. Mini Mental Status Exam score < 24 (adjusted for age and education)
11. Medical contraindication to MRI
12. Pregnancy or women of child-bearing age who are not following an effective method of contraception
13. Pre-existing neurologic, psychiatric, or advanced systemic disease that would confound the neurological or functional outcome evaluations
14. SBP < 90 or > 200
15. Known history of limb vascular disease, limb vascular bypass surgery, or limb deep venous thrombosis
16. Prisoners
17. Homeless individuals
18. People unable to give informed consent and no available legally authorised representative to provide informed consent
19. People unlikely to be compliant with therapy/unwilling to return for follow-up visits
20. Concurrent participation in another study with investigational drug or device treatment
21. Other likely specific cause of stroke (e.g. dissection, vasculitis, prothrombotic diathesis, drug abuse)

Interventions	<ol style="list-style-type: none"> 1. RIC group: in combination with intensive standard medical secondary prevention stroke treatment, all participants will undergo RIC once or twice daily for up to four 5-minute cycles of bilateral upper extremity ischaemia separated by 5-minute periods of reperfusion 2. Control group: intensive standard medical secondary prevention stroke treatment alone
Outcomes	<p>Primary outcome</p> <ol style="list-style-type: none"> 1. Feasibility (time frame: 12 months): primary endpoints will be descriptive statistics describing the implementation of the RPreC procedure, including behavioral adherence to treatment, physiologic attainment of limb ischaemia, and patient self-reported comfort-discomfort during treatment <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Safety (time frame: 24 months): the lead safety endpoint will be all serious adverse events, and the secondary safety endpoints will be deep and superficial vein thrombosis and all cause mortality 2. Biomarker efficacy (time frame: 12 months): the lead efficacy endpoint will be volumetric progression of white matter ischaemic injury on magnetic resonance imaging (biomarker efficacy); and the primary MRI endpoint will be the proportion of people with increase in total white matter hyperintensity volume (as % of total brain volume) above 1.0%
Starting date	November 2015
Contact information	Latisha K Sharma, MD; Tel: 310-794-6379; email: lali@mednet.ucla.edu

NCT02169739 (Continued)

Notes	The study is currently recruiting participants. The estimated study completion date is June 2018. Results not yet published
-------	--

NCT02189928

Trial name or title	REmote iSchemic Conditioning in acUTE BRAin INfarction Study (RESCUE-BRAIN)
Methods	<p>A multicenter, randomised, controlled study (2 groups)</p> <p>Single-blind (outcomes assessor)</p> <p>Follow-up: 24 hours, 7 days, 3 months</p>
Participants	<p>200 participants</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Patients ≥ 18 years 2. Carotid ischaemic stroke 3. NIHSS score between 5 and 25 4. Brain MRI performed within 6 hours from symptoms onset 5. Obtaining a written informed consent of the patient or a third party (parent or close), or emergency inclusion process 6. Affiliated with a Medicare (or rightful beneficiary) <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Presence of a leg ulcer or a bad skin condition in the lower limbs 2. History of arterial occlusive disease of the lower limbs 3. Sickle cell disease known (risk of vaso-occlusive crisis) 4. History of phlebitis in the lower limbs 5. History of cerebral infarction older than 3 months 6. Participation in another interventional acute phase protocol 7. People under guardianship 8. Pathologies involving life-threatening within 6 months and making it impossible to evaluate to 3 months 9. People depending on others before the ischaemic stroke (Rankin Score previous > 2) 10. Pregnant women
Interventions	<ol style="list-style-type: none"> 1. RIC group: usual care (thrombolysis or not) with RIC. RIC is performed with lower limb tourniquet put on half thigh, the protocol includes 4 cycles (5 minutes each) of inflation cuff 110 mmHg above systolic blood pressure followed by 4 cycles (5 minutes each) of deflation in between 2. Control group: usual care (thrombolysis or not)
Outcomes	<p>Primary outcome</p> <ol style="list-style-type: none"> 1. Brain MRI changes of DWI brain infarction volume (cc) between baseline ($< H6$) and day 1 in the 2 groups of participants (time frame: 24 hours) <p>Secondary outcome</p> <ol style="list-style-type: none"> 1. Percentage of participants with mRS < 2 at 3 months in the 2 groups (time frame: 3 months) <p>Other outcomes</p>

NCT02189928 (Continued)

1. Safety of remote preconditioning ischaemic process (time frame: 7 days): rate of lower limb ischaemia and deep venous thrombosis in Per CID group
2. Safety of remote preconditioning ischaemic process (time frame: 7 days): rate of early neurological worsening (NIHSS score (d1- d0) > 4 points) in Per-CID and control group
3. Safety of remote preconditioning ischaemic process (time frame: 7 days): percentage of hemorrhagic transformation in case of IV thrombolysis in the 2 groups

Starting date	January 2015
Contact information	Amina Cattenoy, Project Manager; Tel: +33 1 39 23 97 77; email: acattenoy@ch-versailles.fr
Notes	The study is currently recruiting participants. The estimated study completion date is January 2019. Results not yet published

NCT02323425

Trial name or title	Effects of limb ischaemic postconditioning in young sICAS (EPIC-sICAS)
Methods	RCT (2 groups) Open label Follow-up: 14 days, 1 month, 6 months, and 1 year
Participants	100 participants Inclusion criteria <ol style="list-style-type: none"> 1. Age between 18 to 45 years old 2. Symptomatic intracranial atherosclerotic stenosis (sICAS): cranial CTA/MRA/TCD/DSA confirmed the diagnosis, participants with ischaemic stroke or TIA in the brain region supplied by the stenosis artery 3. NIHSS score 0-15 4. Written informed consent was signed Exclusion criteria <ol style="list-style-type: none"> 1. Cerebral haemorrhage and other parts of the active bleeding disease 2. Severe aphasia, unable to express himself 3. History of brain tumour, brain trauma, cerebral embolism or other brain lesions 4. Severe lesions of severe cardiac, liver or kidney disease, malignancy or other systemic organ dysfunction 5. Blood pressure < 90 mmHg/60 mmHg or > 200 mmHg/110 mmHg after treatment 6. Dementia or mental illness 7. Using angiotensin-converting enzyme inhibitors 8. History of major surgery or trauma 4 weeks prior to admission 9. Without informed consent Elimination criteria <ol style="list-style-type: none"> 1. People with poor compliance, refusal to take regular treatment and examination 2. Patient's condition became exacerbated, with NIHSS score elevated more than 4
Interventions	1. RIC group: standard medical management combined with RIC twice daily for 180 consecutive days. RIC procedure: bilateral upper arms ischaemia by inflation cuff to 180 mmHg for 3 x 5 minutes, interspersed with 5 minutes of no inflation and thus reperfusion

NCT02323425 (Continued)

	2. Control group: standard medical management for 180 consecutive days
Outcomes	<p>Primary outcome</p> <ol style="list-style-type: none"> 1. Mean change of collateral circulation within 6 months post treatment (time frame: baseline and 6 months after treatment): collateral circulation will be evaluated by Magnetic Resonance Angiography (MRA), Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), Arterial spin-labelled (ASL) perfusion magnetic resonance, transcranial cerebral Doppler (TCD), single photon emission computed tomography (SPECT). <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Mean change of symptomatic recovery (time frame: baseline and 14 days, 1 month, 6 months, and 1 year after treatment): neurological function will be assessed by the National Institute of Health stroke scale (NIHSS) scores and Activity of Daily Living Scale (ADL) 2. Mean change of serum vascular endothelial growth factor (VEGF) and basic Fibroblast Growth Factor (bFGF) within 10 days after treatment (time frame: baseline and 10 days after treatment)
Starting date	March 2015
Contact information	Guogang Luo, M.D, Ph.D; Tel: +8618991232449; email: lguogang@163.com
Notes	The study is currently recruiting participants. The estimated study completion date is March 2018. Results not yet published

NCT02534545

Trial name or title	Remote ischaemic conditioning for avoiding recurrence of symptomatic intracranial atherosclerotic stenosis
Methods	<p>A multicentre, randomised, placebo-controlled study (2 groups)</p> <p>Quadruple-blinded (participant, care provider, investigator, outcomes assessor)</p> <p>Follow-up: 1 year, 3 years</p>
Participants	<p>3000 participants</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Men or women age from 40 to 80 years old 2. People having an ischaemic stroke or a TIA prior to randomisation. People having an ischaemic stroke within 30 days with mRS score ≤ 4 at baseline. People having a TIA within 15 days with Oxfordshire Community Stroke Project on the basis of age, blood pressure (BP), clinical features, and duration of TIA symptoms (ABCD2) score ≥ 4 at baseline 3. The entry event is attributed to symptomatic atherosclerotic stenosis (50-99%) in an intracranial qualifying artery (carotid artery, middle cerebral artery (M1), vertebral artery, or basilar artery) that is documented by MRA or CTA 4. Informed consent obtained <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Thrombolytic therapy within 24 hours prior to enrolment 2. Progressive neurological signs within 24 hours prior to enrolment 3. Cerebral venous thrombosis/stenosis 4. Intracranial arterial stenosis due to arterial dissection, Moya Moya disease; any known vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with cerebrospinal fluid (CSF) pleocytosis

NCT02534545 (Continued)

	<p>sis; radiation induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; post-partum angiopathy; suspected vasospastic process, suspected recanalized embolus</p> <ol style="list-style-type: none"> Any of the following unequivocal cardiac source of embolism: rheumatic mitral and or aortic stenosis, prosthetic heart valves, atrial fibrillation, atrial flutter, sick sinus syndrome, left atrial myxoma, patent foramen ovale, left ventricular mural thrombus or valvular vegetation, congestive heart failure, bacterial endocarditis, or any other cardiovascular condition interfering with the participation Uncontrolled severe hypertension (sitting systolic blood pressure > 180 mmHg and/or sitting diastolic blood pressure > 110 mmHg after medication) People with abnormal laboratory parameters: aspartate transaminase (AST) and/or alanine transaminase (ALT) > 3 x upper limit of normal range; creatinine clearance < 0.6 ml/s and/or serum creatinine > 265 µmol/l (> 3.0 mg/dl); platelets < 100 x 10⁹/L Any intracranial haemorrhage (parenchymal, subarachnoid, subdural, epidural) within 90 days prior to enrolment Intracranial neoplasm, cerebral aneurysm or arteriovenous malformation Known retinal haemorrhage or visceral bleeding within 30 days prior to enrolment Severe haemostatic disorder or severe coagulation dysfunction Subclavian arterial stenosis ≥ 50% or subclavian steal syndrome Extracranial stenosis ≥ 50% Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, or plan to perform one of these procedures within 12 months after enrolment Major surgery (including open femoral, aortic, or carotid surgery, cardiac) within previous 30 days or scheduled in the 12 months after enrolment Contraindication for RIC: severe soft tissue injury, fracture, or peripheral vascular disease in the upper limbs Life expectancy < 3 years Pregnant or breastfeeding women Unwilling to be followed-up or poor compliance for treatment People being enrolled or having been enrolled in other clinical trial within 3 months prior to this clinical trial People unsuitable for enrolment in the clinical trial according to investigators decision making
Interventions	<ol style="list-style-type: none"> RIC group: participants will be treated with RIC once daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation Sham-RIC group: participants will be treated with sham-RIC once daily for 12 months. Sham-RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 60 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation
Outcomes	<p>Primary outcome</p> <ol style="list-style-type: none"> Time from randomisation to the first occurrence of fatal or non-fatal ischaemic stroke (time frame: during the first 12 months from randomisation) <p>Secondary outcomes</p> <ol style="list-style-type: none"> Time from randomisation to the first occurrence of a composite of fatal or non-fatal stroke (ischaemic and haemorrhagic), fatal or non-fatal myocardial infarction, and TIA (time frame: during the first 12 months from randomisation) Time from randomisation to the first occurrence of each component of the composite of fatal or non-fatal stroke (ischaemic and haemorrhagic), fatal or non-fatal myocardial infarction, and TIA (time frame: during the first 12 months from randomisation) Time to death from all causes from randomisation (time frame: during the first 12 months from randomisation)

NCT02534545 (Continued)

Other outcomes

1. Scores assessed by NIHSS (time frame: during the first 12 months from randomisation)
2. Scores assessed by mRS (time frame: during the first 12 months from randomisation)
3. Scores assessed by BI (time frame: during the first 12 months from randomisation)
4. Number of participants with abnormal laboratory values (time frame: 3 years)
5. Number of participants with adverse events that are related to treatment (time frame: 3 years)

Starting date	September 2015
Contact information	Xunming Ji, MD. PhD; Tel: 86-10-83198952; email: jixunming@vip.163.com
Notes	The study is currently recruiting participants. The estimated study completion date is September 2018. Results not yet published

NCT02779712

Trial name or title	Remote ischaemic conditioning after stroke trial (ReCAST-2)
Methods	RCT (2 groups) Double-blinded (participant, outcomes assessor) Follow-up: 1 day, 14 days, 90 days
Participants	60 participants Inclusion criteria <ol style="list-style-type: none"> 1. Suspected clinical stroke with 6 hours of onset of neurological symptoms 2. Age > 18 3. Written or witnessed oral consent, or relative/consulter advice Exclusion criteria <ol style="list-style-type: none"> 1. Pre-morbid dependency mRS > 3 2. Dementia 3. Coma (GCS < 8) 4. Malignancy or significant co-morbidity thought to limit life expectancy to < 6 months 5. Blood sugar < 3.5 mmol/L 6. Taking part in another clinical trial of an investigational medicinal product (CTIMP) 7. Pregnancy
Interventions	<ol style="list-style-type: none"> 1. RIC group: 4 cycles of intermittent limb ischaemia - alternating 5 minutes' inflation (20 mmHg above systolic BP) followed by 5 minutes' deflation of a standard upper arm blood pressure cuff. 1 dose (= 4 cycles) of intermittent upper limb ischaemia (1 cycle = 5 minutes' inflation to 20 mmHg above systolic BP, 5 minutes deflation). Dose escalation: a) recruits 1-20 receive this cycle once; b) recruits 21-40 receive a second dose of 4-cycles 1 hour after the first; c) recruits 41-60 receive further dosing, twice daily until day 4. 2. Sham-RIC group: 4 cycles of alternating 5 minutes' inflation (up to 30 mmHg) followed by 5 minutes' deflation of a standard upper arm blood pressure cuff. 4 cycles of intermittent sham procedure (1 cycle = 5 minutes' inflation to 30 mmHg, 5 minutes' deflation), matching the dose escalation described in the intervention
Outcomes	Primary outcome

NCT02779712 (Continued)

1. Trial feasibility (time frame: 90 days)

Secondary outcomes

1. Vascular event rate (time frame: day 1, day 4 $\pm$ 1, day 90 $\pm$ 7): number of participants with a vascular event (including limb ischaemia, recurrent stroke, myocardial infarction, venous thrombo-embolism)
2. Treatment-related serious adverse event rates (time frame: day 1, day 4 $\pm$ 1, day 90 $\pm$ 7)
3. Plasma biomarkers (time frame: immediately before RIC/sham at baseline; immediately after RIC/sham on day 1; day 4 $\pm$ 1): biomarkers include S100-beta protein, heat-shock proteins and cytokines
4. Impairment (time frame: day 4 $\pm$ 1, day 90 $\pm$ 7): assessed by the NIHSS
5. Dependency (time frame: day 90 $\pm$ 7): assessed by the mRS
6. Disability (time frame: day 90 $\pm$ 7): assessed by the BI
7. Mood (time frame: day 90 $\pm$ 7): assessed by Zung Depression Scale
8. Telephone cognition (time frame: day 90 $\pm$ 7): assessed by Modified Telephone Interview for Cognitive Status

Starting date	August 2016
Contact information	Nikola Sprigg, MD; email: nikola.sprigg@nottingham.ac.uk
Notes	The study is currently recruiting participants. The estimated study completion date is September 2018. Results not yet published

NCT03105141

Trial name or title	Optimized remote ischaemic conditioning (RIC) treatment for patients with chronic cerebral ischaemia
Methods	RCT Double-blinded (care provider, outcomes assessor) Follow-up: 1, 3, 6, and 12 months
Participants	600 participants Inclusion criteria <ol style="list-style-type: none">1. Age ranging from 45 to 80 years of age, both genders2. Patients diagnosed with an ischaemic stroke or TIA before admission and the following requirements should be satisfied as well: the occurrence of an ischaemic stroke within 30 days and with a baseline mRS score $\leq$ 4; the occurrence of a TIA within 15 days and with a baseline Oxfordshire Community Stroke Project on the basis of age, blood pressure, clinical features, and duration of TIA symptoms (ABCD2) score $\geq$ 43. Patients with symptomatic intracranial atherosclerotic stenosis that is attributed to at least 50% stenosis of the diameter of a major intracranial artery (carotid artery, or middle cerebral artery (M1)) verified by MRA or CTA4. Informed consent obtained from patients or health care proxy, as appropriate, able to cooperate and participate in follow-up visits Exclusion criteria <ol style="list-style-type: none">1. Received intravenous or intraarterial thrombolytic therapy such as rtPA within 24 hours prior to inclusion2. Progressive deterioration of neurological manifestations within 24 hours prior to inclusion

NCT03105141 (Continued)

3. Intracranial arterial stenosis due to any of the following non-atherosclerotic aetiologies, for instance, Moyamoya disease, artery dissection, any known vasculitic disease, any intracranial infection, radiation induced vasculopathy, cerebrospinal fluid pleocytosis-associated intraarterial stenosis, genetic or developmental abnormalities such as fibromuscular dysplasia, neurofibromatosis, sickle cell disease, and mitochondrial encephalopathy, intracranial granulomatous arteritis, postpartum angiopathy, suspected vasospasm or embolism, iatrogenic trauma
4. Intracranial abnormalities such as tumour, abscess, vascular malformation, cerebral venous sinus stenosis or thrombosis
5. Any haemorrhagic transformation or large area of cerebral infarction (more than 1/3 of MCA perfusion territory)
6. Any type of intracranial haemorrhage within 90 days prior to inclusion
7. Potential cardiac source of embolism such as rheumatic mitral and or aortic stenosis, prosthetic heart valves, atrial flutter, atrial fibrillation, left atrial myxoma, sick sinus syndrome, patent foramen ovale, left ventricular mural thrombus or valvular vegetation, congestive heart failure, and bacterial endocarditis
8. Previous stent, angioplasty, or other mechanical device in the target lesion, or plan to receive any of the above procedures within 12 months after inclusion
9. Refractory hypertension (systolic blood pressure > 180 mmHg; diastolic blood pressure > 110 mmHg) that cannot be controlled by medical intervention
10. Above 50% stenosis of extracranial artery (carotid artery or vertebral artery)
11. Above 50% stenosis of subclavian artery or subclavian steal syndrome
12. Retinal haemorrhage or visceral bleeding within 30 days prior to inclusion
13. Myocardial infarction within previous 30 days prior to inclusion
14. Previous history of major surgery within 30 days prior to inclusion, or arranged for any of the procedure within 12 months after inclusion
15. Severe haemostatic or coagulation disorders (haemoglobin <10 g/dL, blood platelet count < 100 × 10⁹/L)
16. Hepatic or renal dysfunctions (aspartate transaminase and/or alanine transaminase > 3 x upper limit of normal range, creatinine clearance < 0.6 ml/s and/or serum creatinine > 265 µmol/l (> 3.0 mg/dl))
17. Current or having a history of chronic physical diseases or mental disorders
18. Life expectancy < 3 years due to concomitant life-threatening illness
19. Contraindications for RIC: significant peripheral arterial disease, soft tissue or vascular injury, wounds, and fracture affecting the upper limbs
20. Pregnant or lactating women
21. Patients unlikely to be compliant with intervention or return for follow-up visits
22. No consent obtained from the patient or available legally authorised representatives
23. Patients recruited into another clinical investigation with medication or device, which is likely to impact the outcome of this study

Interventions

Substudy 1: optimising inflating pressure

Group 1: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Group 2: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 40 mmHg above systolic pressure for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Substudy 2: optimising cycles for application

Group 1: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 4 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

NCT03105141 (Continued)

Group 2: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Group 3: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 6 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Substudy 3: optimising ischaemia duration

Group 1: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 4 minutes of reperfusion by cuff deflation.

Group 2: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Group 3: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 6 minutes of reperfusion by cuff deflation.

Substudy 4: optimising times daily

Group 1: participants will be treated with RIC twice daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Group 2: participants will be treated with RIC once daily for 12 months. RIC treatment is comprised of 5 cycles of bilateral upper limb ischaemia and reperfusion, which will be induced by 2 cuffs placed around the upper arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation.

Outcomes	Primary outcome
	1. Recurrent rate of ischaemic stroke and/or TIA (time frame: within 12 months)
	Secondary outcomes
	1. Treatment of related adverse events (time frame: within 12 months)
	2. The incidence of composite vascular events (time frame: within 12 months)
	3. The incidence of each component of composite vascular events (time frame: within 12 month)
	4. The incidence of all cause mortality (time frame: within 12 months)
	5. The evaluation of cognitive function (time frame: baseline, within 3, 6 and 12 months)
	6. The evaluation of neurological impairment caused by a stroke (time frame: baseline, within 3, 6 and 12 months)
	7. The evaluation of degree of disability or dependence in the daily activities (time frame: baseline, within 3, 6 and 12 months)
	8. The evaluation of performance in activities of daily living (time frame: baseline, within 3, 6 and 12 months)
	9. Mean changes in cerebral blood perfusion and/or collateral circulation (time frame: baseline, within 12 months)
	10. Mean change in brain function (time frame: baseline, within 12 months)
	11. Changes in cerebral white matter lesions (WMLs) (time frame: baseline, within 12 months)
	12. The occurrence of additional neurological events (time frame: within 12 months)

NCT03105141 (Continued)

	13. The evaluation of serum biomarkers (time frame: baseline, within 1, 3, 6 and 12 months)
Starting date	1 June 2017
Contact information	Ran Meng, MD, PhD; +86-10-83198952; Ranmeng2011@pku.org.cn Da Zhou, MD, PhD candidate; +86-10-83198952; popdoctor@foxmail.com
Notes	The study is currently recruiting participants. The estimated study completion date is January 2020. Results not yet published

NCT03208166

Trial name or title	Pilot study of pre-ischaemic conditioning for intracranial atherosclerosis (PICASSO)
Methods	RCT (2 groups) Open label Follow-up: 30 days
Participants	10 participants Inclusion criteria <ol style="list-style-type: none"> 1. Symptomatic cerebral infarction within 30 days of enrolment attributed to 70% to 99% stenosis of a major intracranial artery (carotid artery, MCA stem (M1), vertebral artery, or basilar artery) that is documented by any of the following: MRA, CTA, or catheter angiography. Percent stenosis will be measured according to WASID criteria ($= 1 - (Ds / Dn) \times 100\%$ with Ds (diameter of stenosis) and Dn (diameter of normal vessel)) 2. Modified Rankin score of ≤ 3 3. Age ≥ 30 years and ≤ 90 years. Participants of 30-49 years are required to meet at least one additional criteria. This additional requirement is to increase the likelihood that the symptomatic intracranial stenosis in participants of 30-49 years is atherosclerotic: a) insulin dependent diabetes for at least 15 years; b) at least 2 of the following atherosclerotic risk factors: hypertension (BP $> 140/90$ or on antihypertensive therapy); dyslipidaemia (LDL > 130 mg/dl or HDL < 40 mg/dl or fasting triglycerides > 150 mg/dl or on lipid lowering therapy); smoking; non-insulin dependent diabetes or insulin dependent diabetes of less than 15 years duration; family history of any of the following: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, stroke, carotid endarterectomy or stenting, peripheral vascular surgery in parent or sibling who was < 55 years of age for men or < 65 for women at the time of the event; c) history of any of the following: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, carotid endarterectomy or stenting, or peripheral vascular surgery for atherosclerotic disease; d) any stenosis of an extracranial carotid or vertebral artery, another intracranial artery, subclavian artery, coronary artery, iliac or femoral artery, other lower or upper extremity artery, mesenteric artery, or renal artery that was documented by non-invasive vascular imaging or catheter angiography and is considered atherosclerotic; e) aortic arch atheroma documented by non-invasive vascular imaging or catheter angiography; f) any aortic aneurysm documented by non-invasive vascular imaging or catheter angiography that is considered atherosclerotic 4. Recent (within 30 days) negative pregnancy test in a woman who has had any menses in the last 12 months 5. Participant is willing and able to return in 30 days for close-out visit for the study 6. Participant is available by phone 7. Participant is able to apply the conditioning device or has access to another person (family member, friend) who can assist with application of conditioning device if needed 8. Participant understands the purpose and requirements of the study, can make him/herself understood, and has provided informed consent

NCT03208166 (Continued)

9. Participant is able to undergo brain MRI

Exclusion criteria

1. Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, or plan to perform one of these procedures
2. Plan to perform concomitant angioplasty or stenting of an extracranial vessel tandem to an intracranial stenosis
3. Intracranial tumour (except meningioma) or any intracranial vascular malformation
4. Thrombolytic therapy within 24 hours prior to enrolment
5. Progressive neurological signs within 24 hours prior to enrolment
6. Any intracranial haemorrhage (parenchymal, subarachnoid, subdural, epidural) within 90 days
7. Any untreated chronic subdural haematoma
8. Intracranial arterial stenosis due to arterial dissection, Moya Moya disease; any known vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with CSF pleocytosis; radiation induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; post-partum angiopathy; suspected vasospastic process, suspected recanalised embolus
9. Presence of any of the following unequivocal cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, dilated cardiomyopathy, left atrial spontaneous echo contrast, ejection fraction less than 30%
10. History of upper extremity ischaemia, known subclavian or brachial artery stenosis, subclavian steal syndrome, any upper extremity soft tissue, orthopedic or vascular injury, or mastectomy or other procedure that may contraindicate taking blood pressure or having a cuff on the arm for the conditioning treatment
11. Difference in systolic blood pressure of > 15 mmHg between both arms
12. Known allergy to aspirin or clopidogrel
13. Active peptic ulcer disease, major systemic haemorrhage within 30 days, active bleeding diathesis, platelets < 100,000, hematocrit < 30, INR > 1.5, clotting factor abnormality that increases the risk of bleeding, current alcohol or substance abuse, uncontrolled severe hypertension (systolic pressure > 180 mmHg or diastolic pressure > 115 mmHg), severe liver impairment (AST or ALT > 3 x normal, cirrhosis), subject on dialysis
14. Major surgery (including open femoral, aortic, or carotid surgery, cardiac) within previous 30 days or planned in the next 30 days after enrolment
15. Indication for warfarin or heparin beyond enrolment (note: exceptions allowed for subcutaneous heparin for deep vein thrombosis prophylaxis while hospitalised)
16. Diabetics taking sulfonylurea drugs
17. Severe neurological deficit that renders the person incapable of living independently
18. Dementia or psychiatric problem that prevents the person from following the protocol reliably
19. Co-morbid conditions that may limit survival to < 3 months
20. Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study
21. Claustrophobia requiring sedation for MRI
22. Enrollment in another study that would conflict with the current study

Interventions	<p>RIC group: RIC and standard medical care. RIC consist of 4 cycles of 5-minute inflations of both blood pressure cuffs simultaneously to a pressure of 200 mmHg with 5 minutes of reperfusion between each inflation.</p> <p>Control group: standard medical care alone</p>
Outcomes	Primary outcome: cerebral blood flow (time frame: baseline and 30 days)
Starting date	15 June 2017

NCT03208166 (Continued)

Contact information	Marc I Chimowitz, MD; 843-792-3020; mchimow@musc.edu
Notes	The study is currently recruiting participants. The estimated study completion date is December 2017. Results not yet published.

NCT03231384

Trial name or title	Rt-PA thrombolytic therapy in combination with remote ischaemic conditioning for acute ischaemic stroke
Methods	RCT (2 groups) Single-blind (outcomes assessor) Follow-up: 7 days, 90 days
Participants	30 participants Inclusion criteria <ol style="list-style-type: none"> 1. Male or female, age ≥ 18 2. Acute ischaemic stroke 3. modified Rankin Scale (mRS) score of 2-5 4. mRS score less than 1 before onset of stroke symptom 5. Onset of stroke symptoms within 4.5h before initiation of intravenous rt-PA thrombolytic therapy 6. Good compliance for RIC therapy 7. Informed consent obtained Exclusion criteria <ol style="list-style-type: none"> 1. Stroke or serious head trauma within the previous 3 months 2. Major surgery or severe trauma within the preceding 3 months 3. Intracranial haemorrhage 4. Systolic pressure greater than 185 mmHg or diastolic pressure greater than 110 mmHg, or aggressive treatment intravenous medication necessary to reduce blood pressure to these limits 5. Symptoms rapidly improving 6. Symptoms suggestive of subarachnoid haemorrhage, even if CT scan was normal 7. Gastrointestinal haemorrhage or urinary tract haemorrhage within the previous 21 days 8. Arterial puncture at a noncompressible site within the previous 7 days 9. Seizure at the onset of stroke 10. Platelet count of less than 100,000 per cubic millimetre 11. Received heparin within the 48 hours preceding the onset of stroke and had an elevated partial-thromboplastin time 12. Received oral anticoagulation therapy preceding the onset of stroke and INR greater than 1.7 or prothrombin times greater than 15 seconds 13. CT showed a multiple infarction (low density area greater than 1/3 cerebral hemisphere) 14. Use or plan to use intervention for diagnosis or treating 15. Intracranial neoplasm, cerebral aneurysm or arteriovenous malformation 16. Severe hepatic or renal dysfunction 17. Contraindication for RIC: severe soft tissue injury, fracture, or peripheral vascular disease in the upper limbs 18. Life expectancy < 1 year 19. Pregnant or breastfeeding women 20. Unwilling to be followed up or poor compliance for treatment

NCT03231384 (Continued)

21. Patients being enrolled or having been enrolled

Interventions	<p>1. RIC group: RIC will be performed twice daily for 7 consecutive days. The upper limb ischaemic conditioning is composed of 5 cycles of upper limb ischaemia intervened by reperfusion, which is induced by 2 cuffs placed on bilateral arms respectively and inflated to 200 mmHg for 5 minutes followed by 5 minutes of reperfusion by cuff deflation. RIC starts within 2 hours after intravenous thrombolysis. All participants receive a standard clinical management.</p> <p>2. Control group: all participants received intravenous thrombolysis and standard clinical management.</p>
Outcomes	<p>Primary outcome</p> <p>1. Feasibility of RIC after acute ischaemic stroke (time frame: 7 days): assessed by the proportion of enrolled participants that completed all the designed RIC procedures</p> <p>Secondary outcome</p> <p>1. Objective signs of tissue or neurovascular injury (time frame: within 7 ($\pm$ 1) days): palpation of distal radial pulses, visual inspection (for local oedema, redness, skin lesion), and palpation for tenderness</p> <p>2. Number of participants suffering from intracranial haemorrhage (time frame: 7 ($\pm$ 1) days)</p> <p>3. Scores assessed by National Institutes of Health Stroke Scale (NIHSS) (time frame: 7 ($\pm$ 1) days)</p> <p>4. The functional outcome of all participants (time frame: 90 ($\pm$ 7) days): functional outcomes will be assessed by the mRS and BI</p> <p>5. Cerebral infarct volume (time frame: 3-7 days): the infarct volume will be calculated on MRI and CT imaging</p> <p>6. Blood pressure and heart rate during 7 days of RIC treatment (time frame: 7 days)</p> <p>7. Plasma biomarkers (time frame: 7 ($\pm$ 2) days): including myoglobin, IL-6, HS-CRP and HCY</p> <p>8. Any adverse events (time frame: 90 ($\pm$ 7) days)</p>
Starting date	30 July 30 2017
Contact information	Xunming Ji, MD, PhD; Tel: 86-10-83198952; email: jixm@ccmu.edu.cn
Notes	The study is currently recruiting participants. The estimated study completion date is 31 January 2018. Results not yet published

ADL: activities of daily living

ASL: arterial spin-labelled perfusion magnetic resonance

BI: Barthel Index

CTA: computed tomography angiography

DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging

DWI: diffusion weighted imaging

ITT: intention-to-treat

MoCA: Montreal Cognitive Assessment

MMSE: Mini Mental State Examination

MRA: magnetic resonance angiography

MRI: magnetic resonance imaging

mRS: modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

PP: per protocol

RCT: randomised controlled trial

RIC: remote ischaemic conditioning

rtPA: recombinant tissue plasminogen activator

SPECT: single-photon emission computed tomography

TCD: transcranial Doppler

TIA: transient ischaemic attack

WMHs: white matter hyperintensities

Remote ischaemic conditioning for preventing and treating ischaemic stroke (Review)

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

Comparison 1. RIC versus non-RIC for preventing ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up	3	371	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.76]
1.1 Ischaemic stroke	1	189	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.03]
1.2 Recurrent ischaemic stroke	2	182	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.12, 0.83]
2 Death or dependency at completion of follow-up	2	292	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 Death	2	292	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Dependency	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Stroke severity	1	189	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.23, -0.11]
3.1 RIC vs sham control	1	94	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.22, -0.08]
3.2 RIC vs blank control	1	95	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.30, -0.12]
4 Improvement in neurological impairment	0		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Improvement in psychological and cognitive impairment at completion of follow-up	0		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Cardiovascular events	2	292	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.1 RIC vs sham control	1	94	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 RIC vs blank control	2	198	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Haemorrhagic stroke	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Adverse events associated with RIC treatment	3	371	Risk Ratio (M-H, Random, 95% CI)	10.91 [2.01, 59.28]
8.1 RIC vs sham control	2	173	Risk Ratio (M-H, Random, 95% CI)	9.78 [1.23, 77.71]
8.2 RIC vs blank control	2	198	Risk Ratio (M-H, Random, 95% CI)	13.58 [0.72, 255.07]

Analysis 1.1. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 1 Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up.

Analysis 1.2. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 2 Death or dependency at completion of follow-up.

Analysis 1.3. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 3 Stroke severity.

Analysis 1.6. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 6 Cardiovascular events.

Analysis 1.8. Comparison 1 RIC versus non-RIC for preventing ischaemic stroke, Outcome 8 Adverse events associated with RIC treatment.

Comparison 2. RIC versus non-RIC treating ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ischaemic stroke or recurrent ischaemic stroke at completion of follow-up	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Death or dependency at the completion of follow up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Stroke severity	2	175	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-1.02, 0.54]
3.1 NIHSS scores	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.53, 0.07]
3.2 Infarct volume	1	149	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.24, 0.41]
4 Improvement in neurological impairment	0		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Improvement in psychological and cognitive impairment at completion of follow-up	3	105	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.68, 0.11]
5.1 Psychological impairment	1	26	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.15, 0.41]
5.2 Cognitive impairment	3	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.72, 0.21]
6 Cardiovascular events	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Hemorrhagic stroke	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Adverse events associated with RIC treatment	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.2. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 2 Death or dependency at the completion of follow up.

Study or subgroup	RIC n/N	non-RIC n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hougaard 2014	30/160	10/125		2.34[1.19,4.61]
Favours RIC 0.01 0.1 1 10 100 Favours non-RIC				

Analysis 2.3. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 3 Stroke severity.

Study or subgroup	N	RIC Mean(SD)	N	non-RIC Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.3.1 NIHSS scores							
England 2016	13	2.7 (3)	13	6.1 (5.6)		39.6%	-0.73[-1.53,0.07]
Subtotal ***	13		13			39.6%	-0.73[-1.53,0.07]
Heterogeneity: Not applicable Test for overall effect: Z=1.8(P=0.07)							
2.3.2 Infarct volume							
Hougaard 2014	81	7.4 (15.2)	68	6.2 (12.3)		60.4%	0.08[-0.24,0.41]
Subtotal ***	81		68			60.4%	0.08[-0.24,0.41]
Heterogeneity: Not applicable Test for overall effect: Z=0.51(P=0.61)							
Total ***	94		81			100%	-0.24[-1.02,0.54]
Heterogeneity: Tau ² =0.24; Chi ² =3.46, df=1(P=0.06); I ² =71.08% Test for overall effect: Z=0.6(P=0.55) Test for subgroup differences: Chi ² =3.46, df=1 (P=0.06), I ² =71.08%							
Favours RIC -100 -50 0 50 100 Favours non-RIC							

Analysis 2.5. Comparison 2 RIC versus non-RIC treating ischaemic stroke, Outcome 5 Improvement in psychological and cognitive impairment at completion of follow-up.

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1[mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"basal ganglia cerebrovascular disease"] or [mh ^"vertebral artery dissection"]

#2isch*mi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*):ti,ab,kw (Word variations have been searched)

#3(brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation" or "basilar artery" or "vertebral artery") near/5 (stroke* or isch*mi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*):ti,ab,kw (Word variations have been searched)

#4#1 or #2 or #3

#5[mh ^"ischemic postconditioning"] or [mh ^"ischemic preconditioning"]

#6((isch?emic near/5 (condition or precondition* or postcondition*)) or IPC or RIC or RIPC):ti,ab,kw (Word variations have been searched)

#7((limb or vascular) near/5 (isch?emia or occlusi*)):ti,ab,kw (Word variations have been searched)

#8[mh Sphygmomanometers]

#9sphygmomanometer*:ti,ab,kw (Word variations have been searched)

#10(blood pressure near/5 (cuff or device or monitor or meter or guage)):ti,ab,kw (Word variations have been searched)

#11{or #5-#10}

#12#4 and #11

Appendix 2. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/

2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.

3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. ischemic postconditioning/ or exp ischemic preconditioning/
6. ((isch?emic adj5 (condition\$ or precondition\$ or postcondition\$)) or IPC or RIC or RIPC).tw.
7. ((limb or vascular) adj5 (isch?emia or occlusi\$)).tw.
8. exp Sphygmomanometers/
9. sphygmomanometer\$.tw.
10. (blood pressure adj5 (cuff or device or monitor or meter or guage)).tw.
11. or/5-10
12. Randomized Controlled Trials as Topic/
13. Random Allocation/
14. Controlled Clinical Trials as Topic/
15. control groups/
16. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
17. double-blind method/
18. single-blind method/
19. Placebos/
20. placebo effect/
21. cross-over studies/
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
25. (random\$ or RCT or RCTs).tw.
26. (controlled adj5 (trial\$ or stud\$)).tw.
27. (clinical\$ adj5 trial\$).tw.
28. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
29. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
30. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
31. (cross-over or cross over or crossover).tw.
32. (placebo\$ or sham).tw.
33. trial.ti.
34. (assign\$ or allocat\$).tw.
35. controls.tw.
36. or/12-35
37. 4 and 11 and 36

Appendix 3. Embase (Ovid) search strategy

1. cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (isch?emi\$ adj5 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. ischemic postconditioning/ or ischemic preconditioning/
6. ((isch?emic adj5 (condition\$ or precondition\$ or postcondition\$)) or IPC or RIC or RIPC).tw.
7. ((limb or vascular) adj5 (isch?emia or occlusi\$)).tw.
8. sphygmomanometer/
9. sphygmomanometer\$.tw.
10. (blood pressure adj5 (cuff or device or monitor or meter or guage)).tw.
11. or/5-10
12. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
13. Randomization/
14. Controlled clinical trial/ or "controlled clinical trial (topic)"/
15. control group/ or controlled study/
16. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
17. Crossover Procedure/
18. Double Blind Procedure/

19. Single Blind Procedure/ or triple blind procedure/
20. placebo/ or placebo effect/
21. (random\$ or RCT or RCTs).tw.
22. (controlled adj5 (trial\$ or stud\$)).tw.
23. (clinical\$ adj5 trial\$).tw.
24. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
25. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
26. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
27. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
28. (cross-over or cross over or crossover).tw.
29. (placebo\$ or sham).tw.
30. trial.ti.
31. (assign\$ or allocat\$).tw.
32. controls.tw.
33. or/12-32
34. 4 and 11 and 33

Appendix 4. Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S)search strategy

1 TI=(stroke or poststroke or post-stroke or cerebrovasc* or brain vas* or cerebral vas* or cva* or apoplex* or SAH)
Indexes=SCI-EXPANDED Timespan=1950-2018
2 TI=(isch\$emic *conditioning)
Indexes=SCI-EXPANDED Timespan=1950-2018
3 #1 AND #2
Indexes=SCI-EXPANDED Timespan=1950-2018

Appendix 5. China Biological Medicine Database (CBM) search strategy

#1 脑缺血 OR 脑梗塞 OR 颈动脉疾病 OR 颈动脉血栓形成 OR 颈动脉血栓解剖 OR 颅内动脉疾病 OR 脑动脉疾病 OR 脑梗死 OR 颅内栓塞和血栓形成 OR 缺血性卒中
#2 主题词="脑梗死"[不加权:扩展] OR "脑血管障碍"[不加权:扩展] OR "脑梗死"[不加权:扩展] OR "脑梗死"[不加权:扩展] OR "脑干梗死"[不加权:扩展]
#3 中风 OR CVA OR 脑血管意外
#4 缺血\$处理 OR IPC or RIC or RIPC OR 缺血\$适应 OR 远隔缺血\$处理 OR 远隔缺血\$适应 OR 预处理
#5 (#3) OR (#2) OR (#1)
#6 (#5) AND (#4) AND (临床试验[文献类型] OR 随机对照试验[文献类型] OR 多中心研究[文献类型])

Appendix 6. China Doctoral Dissertations Full-text Database (CDFS) search strategy

(SU= '缺血处理' OR SU= 'IPC' OR SU= 'RIC' OR SU= 'RIPC' OR SU= '缺血预处理' OR SU= '缺血适应' OR SU= '缺血预适应' OR SU= '缺血后适应' OR SU= '缺血后处理' OR SU= '预处理' OR SU= '远隔缺血处理' OR SU= '远隔缺血适应') AND (SU= '脑缺血' OR SU= '脑梗塞' OR SU= '颈动脉疾病' OR SU= '颈动脉血栓形成' OR SU= '颈动脉血栓解剖' OR SU= '颅内动脉疾病' OR SU= '脑动脉疾病' OR SU= '脑梗死' OR SU= '颅内栓塞和血栓形成' OR SU= '缺血性卒中' OR SU= '脑血栓形成' OR SU= '脑血管意外' OR SU= '脑中风')

Appendix 7. China Academic Journal Network Publishing Database (CAJD) search strategy

((SU= '缺血处理' OR SU= 'IPC' OR SU= 'RIC' OR SU= 'RIPC' OR SU= '缺血预处理' OR SU= '缺血适应' OR SU= '缺血预适应' OR SU= '缺血后适应' OR SU= '缺血后处理' OR SU= '预处理' OR SU= '远隔缺血处理' OR SU= '远隔缺血适应') AND (SU= '脑缺血' OR SU= '脑梗塞' OR SU= '颈动脉疾病' OR SU= '颈动脉血栓形成' OR SU= '颈动脉血栓解剖' OR SU= '颅内动脉疾病' OR SU= '脑动脉疾病' OR SU= '脑梗死' OR SU= '颅内栓塞和血栓形成' OR SU= '缺血性卒中' OR SU= '脑血栓形成' OR SU= '脑血管意外' OR SU= '脑中风')) NOT (SU= '基因' OR SU= '分子' OR SU= '大鼠' OR SU= '小鼠' OR SU= '动物')

Appendix 8. World Health Organization (WHO) International Clinical Trials Registry Platform search strategy

Ischemic *conditioning [Intervention] AND Stroke [Condition]

Appendix 9. ClinicalTrials.gov search strategy

ischaemic conditioning AND Cerebrovascular Disorders [DISEASE]

Appendix 10. Stroke Trials Registry search strategy

("Ischemic Conditioning" or "Remote Ischemic Conditioning" or "Remote ischemic preconditioning stimulus" or "Remote ischemic preconditioning (RIPC)" or "Remote ischemic preconditioning" or "Remote Ischemic Pre-conditioning" or "Sham Remote Ischemic Preconditioning" or "Remote Ischemic Conditioning (using Sphygmomanometer)" or "Remote ischemic postconditioning" or "Remote ischemic perconditioning") [INTERVENTIONS] AND Stroke [CONDITIONS]

Appendix 11. ISRCTN Registry search strategy

Ischaemic *conditioning [Interventions] AND Stroke [Condition]

WHAT'S NEW

Date	Event	Description
28 September 2019	Amended	Two sections were amended: (1) the "Declarations of interest" section; and (2) the "3 Embase (Ovid) search strategy" of Appendices section (#37 was updated as "4 and 11 and 36").

CONTRIBUTIONS OF AUTHORS

WBZ and JZ assessed all trials for eligibility, extracted data, and assessed the risk of bias. RM performed literature searches of the Chinese language studies. MGS helped with the related trials selection and looked for the full texts. YCD and XMJ drafted the review text with input from the other authors and revised the manuscript. All review authors contributed to writing and revising this review.

DECLARATIONS OF INTEREST

Wenbo Zhao: none known.

Jing Zhang: none known.

Mordechai G Sadowsky: none known.

Ran Meng: none known.

Yuchuan Ding: none known.

Xunming Ji: is one of the inventors of the electric auto-control device that induces remote ischaemic conditioning. This device has been used in many studies, including the ones mentioned in this review. There is no conflict of interest in the conduct of this review. The ownership of the patent belongs to Xuanwu Hospital, Capital Medical University. Dr Ji does not participate in any commercial activities or profits related to the device.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Key R&D Program of China (No. 2017YFC1308400), China.

Grant for the research of remote ischaemic conditioning for chronic cerebrovascular diseases

- Beijing Municipal Administration of Hospitals Incubating Program (Code:PX2018033), China.

Grants for the research of remote ischaemic conditioning for intracranial atherosclerosis

- Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding (ZYLX201706), China.

Grant for the research of ischaemic stroke

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned to include participants undergoing cardiovascular intervention therapies, coronary artery bypass grafting, and any other type of cardiac surgery. However, we found that cardioembolism is the main cause of stroke in the above participants, which is closely related with operative procedures. In conventional studies focusing on ischaemic stroke, the above participants were excluded. In addition, all cardiac studies investigated the effects of RIC on cardiovascular events, plasma biomarkers or imaging outcomes; many of them did

not report cerebrovascular events if they occurred. Some bias may be caused unintentionally if the above participants were included. Therefore, we did not include these participants in this review.

We had intended to perform subgroup analyses to investigate heterogeneity by analysing differences in the number of RIC cycles and their length, and the position and length of RIC treatment. However, in this review only seven trials were eligible for analysis, including three studies for the analysis of RIC for preventing ischaemic stroke, and another four studies for the analysis of RIC for treating ischaemic stroke. Given the limited number of included studies, there were not enough data for subgroup analyses.

We had intended to perform sensitivity analyses if the results were substantially heterogeneous. However, we did not perform any sensitivity analyses because of the limited number of included studies, and we found no substantial heterogeneity in this review.

We had intended to include 'quality of life' as an outcome in the 'Summary of findings' table. However, no included study measured this outcome. Instead, we included 'stroke severity', which has been assessed by NIHSS scores or infarct volume in several studies, as an outcome in the 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

*Neuroprotection; Bias; Cerebral Arterial Diseases [complications]; Extremities [blood supply]; Ischemic Preconditioning [*methods] [mortality]; Randomized Controlled Trials as Topic; Stroke [mortality] [prevention & control] [*therapy]; Thrombolytic Therapy [mortality]

MeSH check words

Humans