ONLINE SUPPLUMENT

Clinical Practice Guidelines of Remote Ischemic Conditioning for the Management of Cerebrovascular Diseases

On recommendation for clinical practice by the *American Association of Conditioning Medicin*e

Table of Contents

1. Formulation of the clinical questions

Clinical questions were formulated by experts based on their extensive clinical experience, which helped shape their current opinions. By the end, eleven specific questions were identified and discussed in this document. The latter questions were deemed to be of the greatest importance to patients who use RIC, their caregivers, and clinicians who use RIC for the management of cerebrovascular disease. A list of outcomes tied to each of the clinical questions was created. Outcomes were rated as "less important", "important", or "critical". According to the GRADE method, only outcomes that were "important" and "critical" were considered.

2. Literature search

For clinical questions II to VI, literature searches for published clinical studies were conducted using the standard methodology provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook-5-1.cochrane.org/) and recommended by the *American Association of Conditioning Medicine*. We searched for studies within MEDLINE Ovid (from 1946 to 16 November 2018), Embase Ovid (from 1974 to 16 November 2018), and the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11) in the Cochrane Library (search date 16 November 2018). The search strategies used were described in this online supplemental material in the "Search Strategies" section.

Two authors independently screened the titles and abstracts of records identified through literature search activities and excluded those that were duplicates or clearly irrelevant. We retrieved the full text of remaining articles, and these two authors independently screened full-text articles to identify clinical studies investigating remote ischemic conditioning in patients with stroke. The two authors resolved any disagreements through discussion or by consulting a third author.

3. Evidence review and development of clinical recommendations.

We used the GRADEproGDT Guideline Development Tool line software (https://gdt.gradepro.org) to develop evidence profiles for clinical questions II to VI. The evidence profiles summarized the quality of the evidence and results for each outcome of importance. Results of randomized trials and observational studies were pooled separately. When data from the included studies were not available or inconclusive, we drafted a simple narrative review. For other clinical questions, we created a narrative literature review.

The overall quality of evidence for each outcome was defined as the degree of confidence that an estimate of the effect is correct. The evidence quality therefore depends on the overall risk of bias, precision, consistency, directness of the evidence, risk of publication bias, presence of dose-effect, magnitude of effect, and the effect of plausible residual confounding. The quality of evidence was categorized as high, moderate, low or very low (E-Table 1).

Recommendations were described as 'strong' or 'conditional' (also referred to as 'weak') and the categorization was based on the evidence-to-decision framework, which includes the following items: priority of the clinical problem, magnitude of the desirable effects, magnitude of the undesirable effects, overall certainty of the evidence (quality of evidence), variability in patient values, the balance of desirable and undesirable effects of the intervention, acceptability of the intervention, and feasibility of implementing the recommendation. For clinical questions II to VI, recommendations were made based on historical studies; for clinical questions I and VII, we performed a narrative review to solve the clinical questions and no recommendation was made; for clinical questions VIII to XI, the recommendations were based on the consensus of expert clinical experience.

4. Quality of the Evidence

E-Table 1. Quality of Evidence Grade.

Grade	Definition
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	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	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

5. Search Strategies

5.1 Search strategies for clinical question II: Should RIC be used to improve the functional outcomes in patients with acute ischemic stroke?

Database 1. MEDLINE (via Ovid) search strategy

1 cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or hypoxia-ischemia, brain/ or ischemic attack, transient/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2 (isch?emi$ and (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) and (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4 1 or 2 or 3
5 ischemic postconditioning/ or ischemic preconditioning/
6 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
7 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC).tw.
8 exp Sphygmomanometers/
9 sphygmomanometer$.tw.
10 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
11 5 or 6 or 7 or 8 or 9 or 10
12 (limb$ or arm$ or remote or regional).tw.
13 11 and 12
14 4 and 13
15 Randomized controlled trials as Topic/
16 Randomized controlled trial/
17 Random allocation/
18 Double blind method/
19 Single blind method/
20 Clinical trial/
21 exp Clinical Trials as Topic/
22 or/15-21
23 (clinic$ adj trial$1).tw.
24 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
25 Placebos/
26 (Placebo$ or sham).tw.
27 Randomly allocated.tw.
28 (allocated adj2 random).tw.
29 or/23-28
30 22 or 29
31 Case report.tw.
32 Letter/
33 Historical article/
34 Review of reported cases.pt.
35 Review, multicase.pt.
36 or/31-35
37 30 not 36
38 Epidemiologic studies/
39 exp case control studies/

40 exp cohort studies/
41 Case control.tw.
42 (cohort adj (study or studies)).tw.
43 Cohort analy$.tw.
44 (Follow up adj (study or studies)).tw.
45 (observational adj (study or studies)).tw.
46 Longitudinal.tw.
47 Retrospective.tw.
48 Cross sectional.tw.
49 Cross-sectional studies/
50 or/38-49
51 37 or 50
52 14 and 51

Database 2. Embase (via Ovid) search strategy

1 brain infarction/ or brain infarction size/ or brain stem infarction/ or cerebellum infarction/
2 exp brain ischemia/
3 carotid artery disease/ or exp carotid artery obstruction/ or carotid atherosclerosis/
4 stroke patient/ or cerebrovascular disease/ or exp cerebrovascular accident/
5 cerebral artery disease/ or exp occlusive cerebrovascular disease/
6 (isch?emi$ and (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
7 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) and (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 ischemic postconditioning/ or ischemic preconditioning/
10 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
11 sphygmomanometer/ or mercury sphygmomanometer/
12 sphygmomanometer$.tw.
13 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
14 9 or 10 or 11 or 12 or 13
15 (limb$ or arm$ or remote or regional).tw.
16 14 and 15
17 8 and 16
18 Clinical trial/
19 Randomized controlled trial/
20 Randomization/
21 Single blind procedure/
22 Double blind procedure/
23 Crossover procedure/
24 Placebo/
25 Randomi?ed controlled trial$.tw.
26 Rct.tw.
27 Random allocation.tw.
28 Randomly allocated.tw.
29 Allocated randomly.tw.
30 (allocated adj2 random).tw.
31 Single blind$.tw.
32 Double blind$.tw.

33 ((treble or triple) adj blind$).tw.
34 (Placebo$ or sham).tw.
35 Prospective study/
36 or/18-35
37 Case study/
38 Case report.tw.
39 Abstract report/ or letter/
40 or/37-39
41 36 not 40
42 Clinical study/
43 Case control study/
44 Family study/
45 Longitudinal study/
46 Retrospective study/
47 Prospective study/
48 Randomized controlled trials/
49 47 not 48
50 Cohort analysis/
51 (Cohort adj (study or studies)).mp.
52 (Case control adj (study or studies)).tw.
53 (follow up adj (study or studies)).tw.
54 (observational adj (study or studies)).tw.
55 (epidemiologic$ adj (study or studies)).tw.
56 (cross sectional adj (study or studies)).tw.
57 or/42-46,49-56
58 41 or 57
59 17 and 58

Database 3. CENTRAL (via the Cochrane Library) search strategy

#1 MeSH descriptor: [Stroke] explode all trees
#2 MeSH descriptor: [Cerebrovascular Disorders] this term only
#3 MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] this term only
#4 MeSH descriptor: [Brain Ischemia] explode all trees
#5 MeSH descriptor: [Carotid Artery Thrombosis] this term only
#6 MeSH descriptor: [Carotid Stenosis] this term only
#7 MeSH descriptor: [Cerebral Small Vessel Diseases] this term only
#8 MeSH descriptor: [Intracranial Arterial Diseases] this term only
#9 MeSH descriptor: [Infarction, Anterior Cerebral Artery] this term only
#10 MeSH descriptor: [Infarction, Middle Cerebral Artery] this term only
#11 MeSH descriptor: [Infarction, Posterior Cerebral Artery] this term only
#12 MeSH descriptor: [Intracranial Arteriosclerosis] this term only
#13 MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#14 (isch*mi* and (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)):ti,ab,kw(Word variations have been searched)
#15 ((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) and (isch*mi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw(Word variations have been searched)
#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 MeSH descriptor: [Ischemic Postconditioning] this term only

#18 MeSH descriptor: [Ischemic Preconditioning] this term only
#19 (isch*mic and (condition* or precondition* or postcondition* or percondition*)):ti,ab,kw(Word variations have been searched)
#20 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC):ti,ab,kw(Word variations have been searched)
#21 MeSH descriptor: [Sphygmomanometers] explode all trees
#22 (Sphygmomanometer*):ti,ab,kw(Word variations have been searched)
#23 ("blood pressure" and (cuff or device or monitor or meter or guage)):ti,ab,kw(Word variations have been searched)
#24 #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 (limb* or arm* or remote or regional):ti,ab,kw(Word variations have been searched)
#26 #24 and #25
#27 #16 and #26

5.2 Search strategies for Clinical question III: Should RIC be used to reduce recurrent cerebrovascular events in patients with symptomatic intracranial atherosclerosis?

Database 1. MEDLINE (via Ovid) search strategy

1 arteriosclerosis/ or arteriolosclerosis/ or arteriosclerosis obliterans/ or exp atherosclerosis/ or intracranial arteriosclerosis/ or carotid stenosis/ or Plaque, Atherosclerotic/
2 ((aort* or brain or carotid or cerebr$ or intracranial) and (atherosclero$ or plaque? or sclerosis or arteriosclero$ or presclerosis)).tw.
3 ((athero$ or arteriosclero$ or intima) and plaque?).tw.
4 (atherosclerosis or atherogen$ or atheroma$).tw.
5 1 or 2 or 3 or 4
6 ischemic postconditioning/ or ischemic preconditioning/
7 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
8 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC).tw.
9 exp Sphygmomanometers/
10 sphygmomanometer$.tw.
11 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
12 6 or 7 or 8 or 9 or 10 or 11
13 (limb$ or arm$ or remote or regional).tw.
14 12 and 13
15 5 and 14
16 Randomized controlled trials as Topic/
17 Randomized controlled trial/
18 Random allocation/
19 Double blind method/
20 Single blind method/
21 Clinical trial/
22 exp Clinical Trials as Topic/
23 or/16-22
24 (clinic$ adj trial$1).tw.
25 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
26 Placebos/
27 (Placebo$ or sham).tw.
28 Randomly allocated.tw.
29 (allocated adj2 random).tw.
30 or/24-29

31 23 or 30
32 Case report.tw.
33 Letter/
34 Historical article/
35 Review of reported cases.pt.
36 Review, multicase.pt.
37 or/32-36
38 31 not 37
39 Epidemiologic studies/
40 exp case control studies/
41 exp cohort studies/
42 Case control.tw.
43 (cohort adj (study or studies)).tw.
44 Cohort analy$.tw.
45 (Follow up adj (study or studies)).tw.
46 (observational adj (study or studies)).tw.
47 Longitudinal.tw.
48 Retrospective.tw.
49 Cross sectional.tw.
50 Cross-sectional studies/
51 or/39-50
52 38 or 51
53 15 and 52

Database 2. Embase (via Ovid) search strategy

1 atherosclerosis/ or aortic atherosclerosis/ or atherogenesis/ or atheroma/ or atheromatosis/ or atherosclerotic plaque/ or brain atherosclerosis/ or carotid atherosclerosis/
2 ((aort* or brain or carotid or cerebr$ or intracranial) and (atherosclero$ or plaque? or sclerosis or arteriosclero$ or presclerosis)).tw.
3 ((athero$ or arteriosclero$ or intima) and plaque?).tw.
4 (atherosclerosis or atherogen$ or atheroma$).tw.
5 1 or 2 or 3 or 4
6 ischemic postconditioning/ or ischemic preconditioning/
7 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
8 sphygmomanometer/ or mercury sphygmomanometer/
9 sphygmomanometer$.tw.
10 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
11 6 or 7 or 8 or 9 or 10
12 (limb$ or arm$ or remote or regional).tw.
13 11 and 12
14 5 and 13
15 Clinical trial/
16 Randomized controlled trial/
17 Randomization/
18 Single blind procedure/
19 Double blind procedure/
20 Crossover procedure/
21 Placebo/
22 Randomi?ed controlled trial$.tw.

23 Rct.tw.
24 Random allocation.tw.
25 Randomly allocated.tw.
26 Allocated randomly.tw.
27 (allocated adj2 random).tw.
28 Single blind$.tw.
29 Double blind$.tw.
30 ((treble or triple) adj blind$).tw.
31 (Placebo$ or sham).tw.
32 Prospective study/
33 or/15-32
34 Case study/
35 Case report.tw.
36 Abstract report/ or letter/
37 or/34-36
38 33 not 37
39 Clinical study/
40 Case control study/
41 Family study/
42 Longitudinal study/
43 Retrospective study/
44 Prospective study/
45 Randomized controlled trials/
46 44 not 45
47 Cohort analysis/
48 (Cohort adj (study or studies)).mp.
49 (Case control adj (study or studies)).tw.
50 (follow up adj (study or studies)).tw.
51 (observational adj (study or studies)).tw.
52 (epidemiologic$ adj (study or studies)).tw.
53 (cross sectional adj (study or studies)).tw.
54 or/39-43,46-53
55 38 or 54
56 14 and 55

Database 3. CENTRAL (via the Cochrane Library) search strategy

#1 MeSH descriptor: [Arteriosclerosis] this term only
#2 MeSH descriptor: [Arteriolosclerosis] this term only
#3 MeSH descriptor: [Arteriosclerosis Obliterans] this term only
#4 MeSH descriptor: [Atherosclerosis] explode all trees
#5 MeSH descriptor: [Intracranial Arteriosclerosis] this term only
#6 MeSH descriptor: [Carotid Stenosis] this term only
#7 MeSH descriptor: [Plaque, Atherosclerotic] this term only
#8 (((aort* or brain or carotid or cerebr* or intracranial) and (atherosclero* or plaque* or sclerosis or arteriosclero* or presclerosis))):ti,ab,kw (Word variations have been searched)(Word variations have been searched)
#9 (((athero* or arteriosclero* or intima) and plaque*)):ti,ab,kw (Word variations have been searched)(Word variations have been searched)
#10 ((atherosclerosis or atherogen* or atheroma*)):ti,ab,kw (Word variations have been searched)(Word

variations have been searched)
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10(Word variations have been searched)
#12 MeSH descriptor: [Ischemic Postconditioning] this term only
#13 MeSH descriptor: [Ischemic Preconditioning] this term only
#14 ((isch*mic and (condition* or precondition* or postcondition* or percondition*))):ti,ab,kw (Word variations have been searched)
#15 ((IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC)):ti,ab,kw (Word variations have been searched)
#16 MeSH descriptor: [Sphygmomanometers] explode all trees
#17 ((Sphygmomanometer*)):ti,ab,kw (Word variations have been searched)
#18 (("blood pressure" and (cuff or device or monitor or meter or guage))):ti,ab,kw (Word variations have been searched)
#19 #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 ((limb* or arm* or remote or regional)):ti,ab,kw (Word variations have been searched)
#21 #19 and #20
#22 #11 and #21

5.3 Search strategies for Clinical questions IV: Should RIC be used to improve the neurological outcomes in patients with cerebral small vessel disease?

Database 1. MEDLINE (via Ovid) search strategy

1 cerebral small vessel diseases/ or cadasil/ or cerebral amyloid angiopathy, familial/ or microscopic polyangiitis/ or stroke, lacunar/
2 (cerebr$ and (microangiopath$ or small vessel disease$ or amyloid$)).tw.
3 (lacunar and (infarct$ or stroke$ or syndrome$)).tw.
4 (microscopic polyangiiti$ or CADASIL).tw.
5 1 or 2 or 3 or 4
6 ischemic postconditioning/ or ischemic preconditioning/
7 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
8 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC).tw.
9 exp Sphygmomanometers/
10 sphygmomanometer$.tw.
11 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
12 6 or 7 or 8 or 9 or 10 or 11
13 (limb$ or arm$ or remote or regional).tw.
14 12 and 13
15 5 and 14

Database 2. Embase (via Ovid) search strategy

1 cerebrovascular accident/ or lacunar stroke/ or brain infarction/ or cadasil/ or vascular amyloidosis/ or microscopic polyangiitis/
2 (cerebr$ and (microangiopath$ or small vessel disease$ or amyloid$)).tw.
3 (lacunar and (infarct$ or stroke$ or syndrome$)).tw.
4 (microscopic polyangiiti$ or CADASIL).tw.
5 1 or 2 or 3 or 4
6 ischemic postconditioning/ or ischemic preconditioning/
7 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
8 sphygmomanometer/ or mercury sphygmomanometer/
9 sphygmomanometer$.tw.
10 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
11 6 or 7 or 8 or 9 or 10

12 (limb$ or arm$ or remote or regional).tw.
13 11 and 12
14 5 and 13
15 Clinical trial/
16 Randomized controlled trial/
17 Randomization/
18 Single blind procedure/
19 Double blind procedure/
20 Crossover procedure/
21 Placebo/
22 Randomi?ed controlled trial$.tw.
23 Rct.tw.
24 Random allocation.tw.
25 Randomly allocated.tw.
26 Allocated randomly.tw.
27 (allocated adj2 random).tw.
28 Single blind$.tw.
29 Double blind$.tw.
30 ((treble or triple) adj blind$).tw.
31 (Placebo$ or sham).tw.
32 Prospective study/
33 or/15-32
34 Case study/
35 Case report.tw.
36 Abstract report/ or letter/
37 or/34-36
38 33 not 37
39 Clinical study/
40 Case control study/
41 Family study/
42 Longitudinal study/
43 Retrospective study/
44 Prospective study/
45 Randomized controlled trials/
46 44 not 45
47 Cohort analysis/
48 (Cohort adj (study or studies)).mp.
49 (Case control adj (study or studies)).tw.
50 (follow up adj (study or studies)).tw.
51 (observational adj (study or studies)).tw.
52 (epidemiologic$ adj (study or studies)).tw.
53 (cross sectional adj (study or studies)).tw.
54 or/39-43,46-53
55 38 or 54
56 14 and 55

Database 3. CENTRAL (via the Cochrane Library) search strategy

#1 MeSH descriptor: [Cerebral Small Vessel Diseases] this term only
#2 MeSH descriptor: [CADASIL] this term only

#3 MeSH descriptor: [Cerebral Amyloid Angiopathy, Familial] this term only
#4 MeSH descriptor: [Microscopic Polyangiitis] this term only
#5 MeSH descriptor: [Stroke, Lacunar] this term only
#6 ((cerebr* and (microangiopath* or small vessel disease* or amyloid*))):ti,ab,kw (Word variations have been searched)
#7 ((lacunar and (infarct* or stroke* or syndrome*))):ti,ab,kw (Word variations have been searched)
#8 ((microscopic polyangiiti* or CADASIL)):ti,ab,kw (Word variations have been searched)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Ischemic Postconditioning] this term only
#11 MeSH descriptor: [Ischemic Preconditioning] this term only
#12 ((isch*mic and (condition* or precondition* or postcondition* or percondition*))):ti,ab,kw (Word variations have been searched)
#13 ((IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC)):ti,ab,kw (Word variations have been searched)
#14 MeSH descriptor: [Sphygmomanometers] explode all trees
#15 ((Sphygmomanometer*)):ti,ab,kw (Word variations have been searched)
#16 (("blood pressure" and (cuff or device or monitor or meter or guage))):ti,ab,kw (Word variations have been searched)
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 ((limb* or arm* or remote or regional)):ti,ab,kw (Word variations have been searched)
#19 #17 and #18
#20 #9 and #19

5.4 Search strategies for clinical questions V: Should RIC be used to reduce perioperative complications in patients with carotid artery stenosis who are treated with carotid stenting?

Database 1. MEDLINE (via Ovid) search strategy

1 carotid artery diseases/ or carotid stenosis/ or arterial occlusive diseases/
2 (((carotid or arter$) and narrow$) or plaque$ or stenos$).tw.
3 1 or 2
4 ischemic postconditioning/ or ischemic preconditioning/
5 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
6 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC).tw.
7 exp Sphygmomanometers/
8 sphygmomanometer$.tw.
9 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
10 4 or 5 or 6 or 7 or 8 or 9
11 (limb$ or arm$ or remote or regional).tw.
12 10 and 11
13 3 and 12
14 Randomized controlled trials as Topic/
15 Randomized controlled trial/
16 Random allocation/
17 Double blind method/
18 Single blind method/
19 Clinical trial/
20 exp Clinical Trials as Topic/
21 or/14-20
22 (clinic$ adj trial$1).tw.
23 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

24 Placebos/
25 (Placebo$ or sham).tw.
26 Randomly allocated.tw.
27 (allocated adj2 random).tw.
28 or/22-27
29 21 or 28
30 Case report.tw.
31 Letter/
32 Historical article/
33 Review of reported cases.pt.
34 Review, multicase.pt.
35 or/30-34
36 29 not 35
37 Epidemiologic studies/
38 exp case control studies/
39 exp cohort studies/
40 Case control.tw.
41 (cohort adj (study or studies)).tw.
42 Cohort analy$.tw.
43 (Follow up adj (study or studies)).tw.
44 (observational adj (study or studies)).tw.
45 Longitudinal.tw.
46 Retrospective.tw.
47 Cross sectional.tw.
48 Cross-sectional studies/
49 or/37-48
50 36 or 49
51 13 and 50

Database 2. Embase (via Ovid) search strategy

1 exp carotid artery obstruction/ or artery occlusion/ or artery reocclusion/
2 (((carotid or arter$) and narrow$) or plaque$ or stenos$).tw.
3 1 or 2
4 ischemic postconditioning/ or ischemic preconditioning/
5 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
6 sphygmomanometer/ or mercury sphygmomanometer/
7 sphygmomanometer$.tw.
8 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
9 4 or 5 or 6 or 7 or 8
10 (limb$ or arm$ or remote or regional).tw.
11 9 and 10
12 3 and 11
13 Clinical trial/
14 Randomized controlled trial/
15 Randomization/
16 Single blind procedure/
17 Double blind procedure/
18 Crossover procedure/
19 Placebo/

20 Randomi?ed controlled trial$.tw.
21 Rct.tw.
22 Random allocation.tw.
23 Randomly allocated.tw.
24 Allocated randomly.tw.
25 (allocated adj2 random).tw.
26 Single blind$.tw.
27 Double blind$.tw.
28 ((treble or triple) adj blind$).tw.
29 (Placebo$ or sham).tw.
30 Prospective study/
31 or/13-30
32 Case study/
33 Case report.tw.
34 Abstract report/ or letter/
35 or/32-34
36 31 not 35
37 Clinical study/
38 Case control study/
39 Family study/
40 Longitudinal study/
41 Retrospective study/
42 Prospective study/
43 Randomized controlled trials/
44 42 not 43
45 Cohort analysis/
46 (Cohort adj (study or studies)).mp.
47 (Case control adj (study or studies)).tw.
48 (follow up adj (study or studies)).tw.
49 (observational adj (study or studies)).tw.
50 (epidemiologic$ adj (study or studies)).tw.
51 (cross sectional adj (study or studies)).tw.
52 or/37-41,44-51
53 36 or 52
54 12 and 53

Database 3. CENTRAL (via the Cochrane Library) search strategy

#1 MeSH descriptor: [Carotid Artery Diseases] this term only
#2 MeSH descriptor: [Carotid Stenosis] this term only
#3 MeSH descriptor: [Arterial Occlusive Diseases] this term only
#4 (((carotid or arter$) and narrow$) or plaque$ or stenos$):ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Ischemic Postconditioning] this term only
#7 MeSH descriptor: [Ischemic Preconditioning] this term only
#8 ((isch*mic and (condition* or precondition* or postcondition* or percondition*))):ti,ab,kw (Word variations have been searched)
#9 ((IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC)):ti,ab,kw (Word variations have been searched)
#10 MeSH descriptor: [Sphygmomanometers] explode all trees
#11 ((Sphygmomanometer*)):ti,ab,kw (Word variations have been searched)

#12 (("blood pressure" and (cuff or device or monitor or meter or guage))):ti,ab,kw (Word variations have been searched)
#13 #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 ((limb* or arm* or remote or regional)):ti,ab,kw (Word variations have been searched)
#15 #13 and #14
#16 #5 and #15

5.5 Search strategies for clinical questions VI: Can RIC can be performed safely and should RIC be used to improve functional outcomes in patients with intracranial hemorrhage?

Database 1. MEDLINE (via Ovid) search strategy

1 exp intracranial hemorrhages/ or hematoma, epidural, cranial/ or hematoma, subdural/
2 (((brain or cerebral or cranial or callosum or stroke$ or intrac$ or apoplex$ or subdural or intraventricular or periventricular or fossa) and (hemorrhag$ or haemorrhag$ or bleed$ or hemat$)) or encephalorrhagia).tw.
3 1 or 2
4 ischemic postconditioning/ or ischemic preconditioning/
5 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
6 (IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC).tw.
7 exp Sphygmomanometers/
8 sphygmomanometer$.tw.
9 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
10 4 or 5 or 6 or 7 or 8 or 9
11 (limb$ or arm$ or remote or regional).tw.
12 10 and 11
13 3 and 12
14 Randomized controlled trials as Topic/
15 Randomized controlled trial/
16 Random allocation/
17 Double blind method/
18 Single blind method/
19 Clinical trial/
20 exp Clinical Trials as Topic/
21 or/14-20
22 (clinic$ adj trial$1).tw.
23 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
24 Placebos/
25 (Placebo$ or sham).tw.
26 Randomly allocated.tw.
27 (allocated adj2 random).tw.
28 or/22-27
29 21 or 28
30 Case report.tw.
31 Letter/
32 Historical article/
33 Review of reported cases.pt.
34 Review, multicase.pt.
35 or/30-34
36 29 not 35

37 Epidemiologic studies/
38 exp case control studies/
39 exp cohort studies/
40 Case control.tw.
41 (cohort adj (study or studies)).tw.
42 Cohort analy$.tw.
43 (Follow up adj (study or studies)).tw.
44 (observational adj (study or studies)).tw.
45 Longitudinal.tw.
46 Retrospective.tw.
47 Cross sectional.tw.
48 Cross-sectional studies/
49 or/37-48
50 36 or 49
51 13 and 50

Database 2. Embase (via Ovid) search strategy

1 exp brain hemorrhage/
2 (((brain or cerebral or cranial or corpus callosum or stroke$ or intrac$ or apoplex$ or subdural or intraventricular or periventricular or fossa) and (h?emorrhag$ or bleed$ or hemat$)) or encephalorrhagia).tw.
3 1 or 2
4 ischemic postconditioning/ or ischemic preconditioning/
5 (isch?emic and (condition$ or precondition$ or postcondition$ or percondition$)).tw.
6 sphygmomanometer/ or mercury sphygmomanometer/
7 sphygmomanometer$.tw.
8 (blood pressure and (cuff or device or monitor or meter or guage)).tw.
9 4 or 5 or 6 or 7 or 8
10 (limb$ or arm$ or remote or regional).tw.
11 9 and 10
12 3 and 11
13 Clinical trial/
14 Randomized controlled trial/
15 Randomization/
16 Single blind procedure/
17 Double blind procedure/
18 Crossover procedure/
19 Placebo/
20 Randomi?ed controlled trial$.tw.
21 Rct.tw.
22 Random allocation.tw.
23 Randomly allocated.tw.
24 Allocated randomly.tw.
25 (allocated adj2 random).tw.
26 Single blind$.tw.
27 Double blind$.tw.
28 ((treble or triple) adj blind$).tw.
29 (Placebo$ or sham).tw.
30 Prospective study/
31 or/13-30

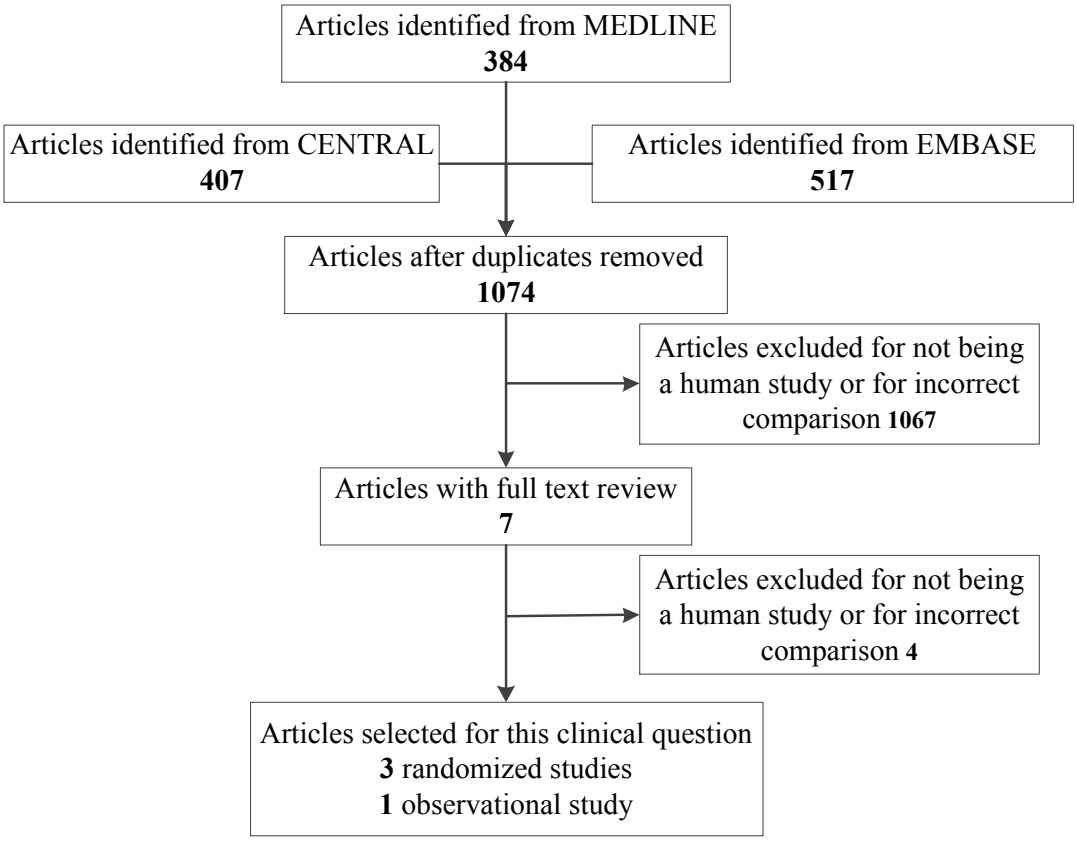
32 Case study/
33 Case report.tw.
34 Abstract report/ or letter/
35 or/32-34
36 31 not 35
37 Clinical study/
38 Case control study/
39 Family study/
40 Longitudinal study/
41 Retrospective study/
42 Prospective study/
43 Randomized controlled trials/
44 42 not 43
45 Cohort analysis/
46 (Cohort adj (study or studies)).mp.
47 (Case control adj (study or studies)).tw.
48 (follow up adj (study or studies)).tw.
49 (observational adj (study or studies)).tw.
50 (epidemiologic$ adj (study or studies)).tw.
51 (cross sectional adj (study or studies)).tw.
52 or/37-41,44-51
53 36 or 52
54 12 and 53

Database 3. CENTRAL (via the Cochrane Library) search strategy

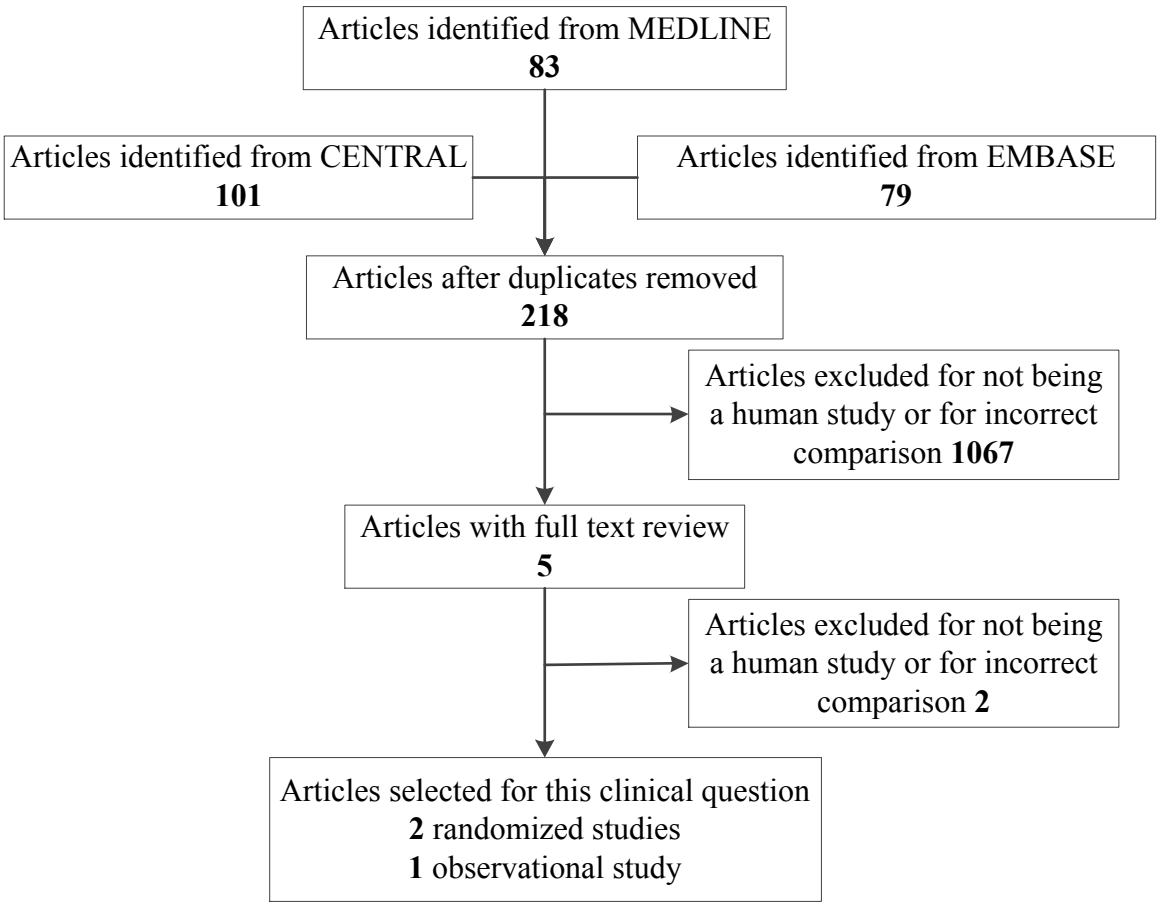
#1 MeSH descriptor: [Intracranial Hemorrhages] explore all trees
#2 MeSH descriptor: [Hematoma, Epidural, Cranial] this term only
#3 MeSH descriptor: [Hematoma, Subdural] this term only
#4 ((((brain or cerebral or cranial or callosum or stroke* or intrac* or apoplex* or subdural or intraventricular or periventricular or fossa) and (hemorrhag* or haemorrhag* or bleed* or hemat*)) or encephalorrhagia)):ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Ischemic Postconditioning] this term only
#7 MeSH descriptor: [Ischemic Preconditioning] this term only
#8 ((isch*mic and (condition* or precondition* or postcondition* or percondition*))):ti,ab,kw (Word variations have been searched)
#9 ((IPC or RIC or RIPC or RIPreC or RIPerC or RIPostC)):ti,ab,kw (Word variations have been searched)
#10 MeSH descriptor: [Sphygmomanometers] explode all trees
#11 ((Sphygmomanometer*)):ti,ab,kw (Word variations have been searched)
#12 (("blood pressure" and (cuff or device or monitor or meter or guage))):ti,ab,kw (Word variations have been searched)
#13 #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 ((limb* or arm* or remote or regional)):ti,ab,kw (Word variations have been searched)
#15 #13 and #14
#16 #5 and #15

6. Flow diagram of Search Results

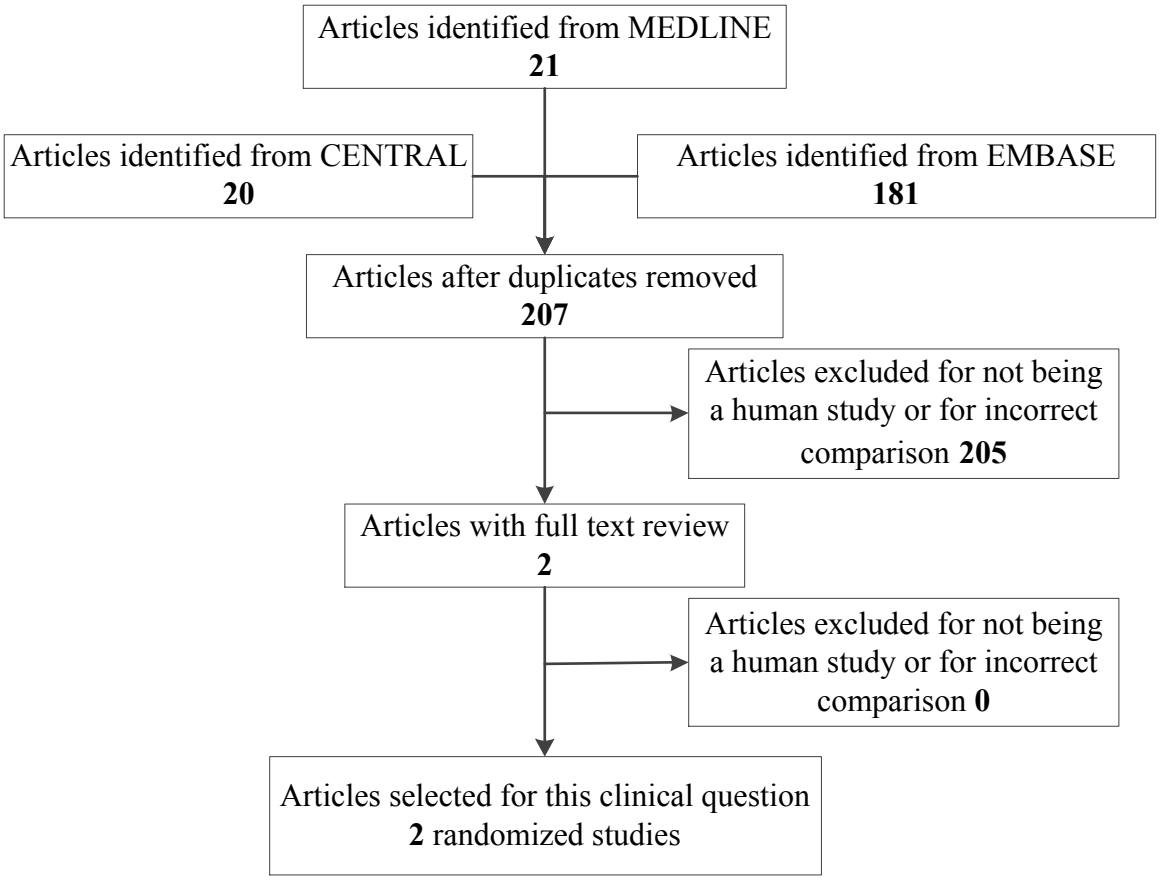
E-Figure 1. Flow diagram for the systematic review selection of studies pertaining to clinical question II: Should RIC be used to improve functional outcomes in patients with acute ischemic stroke?



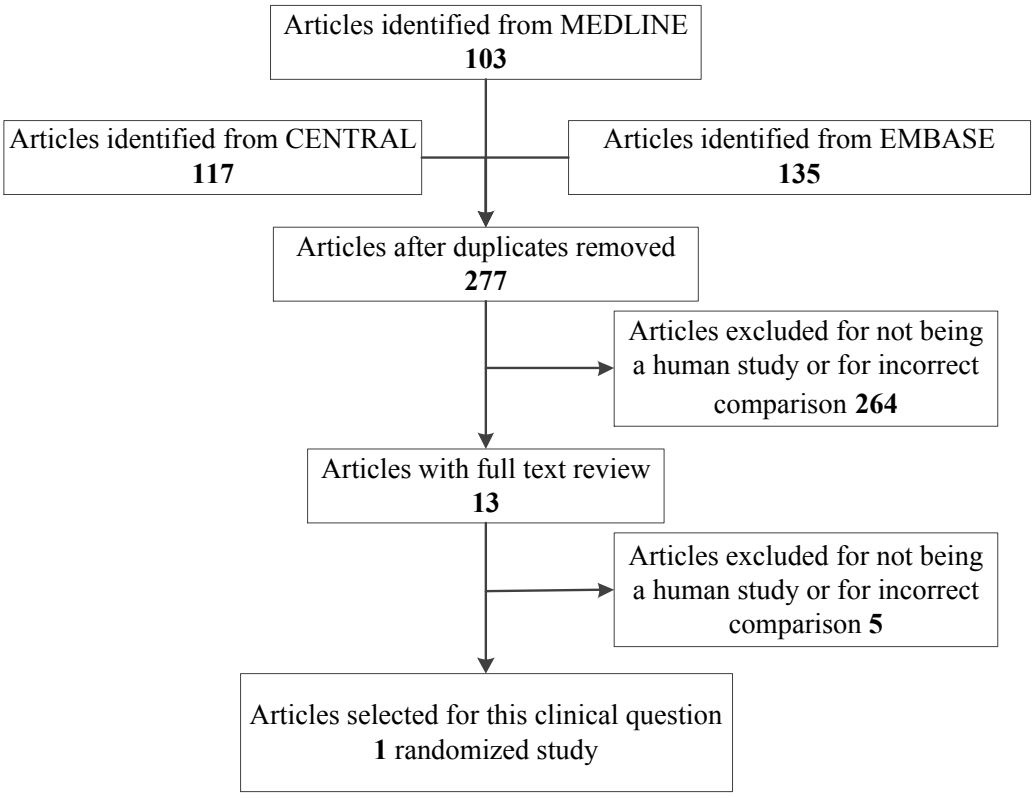
E-Figure **2. Flow diagram for the systematic review selection of studies pertaining to clinical question III: Should RIC be used to reduce recurrent cerebrovascular events in patients with symptomatic intracranial atherosclerosis?**



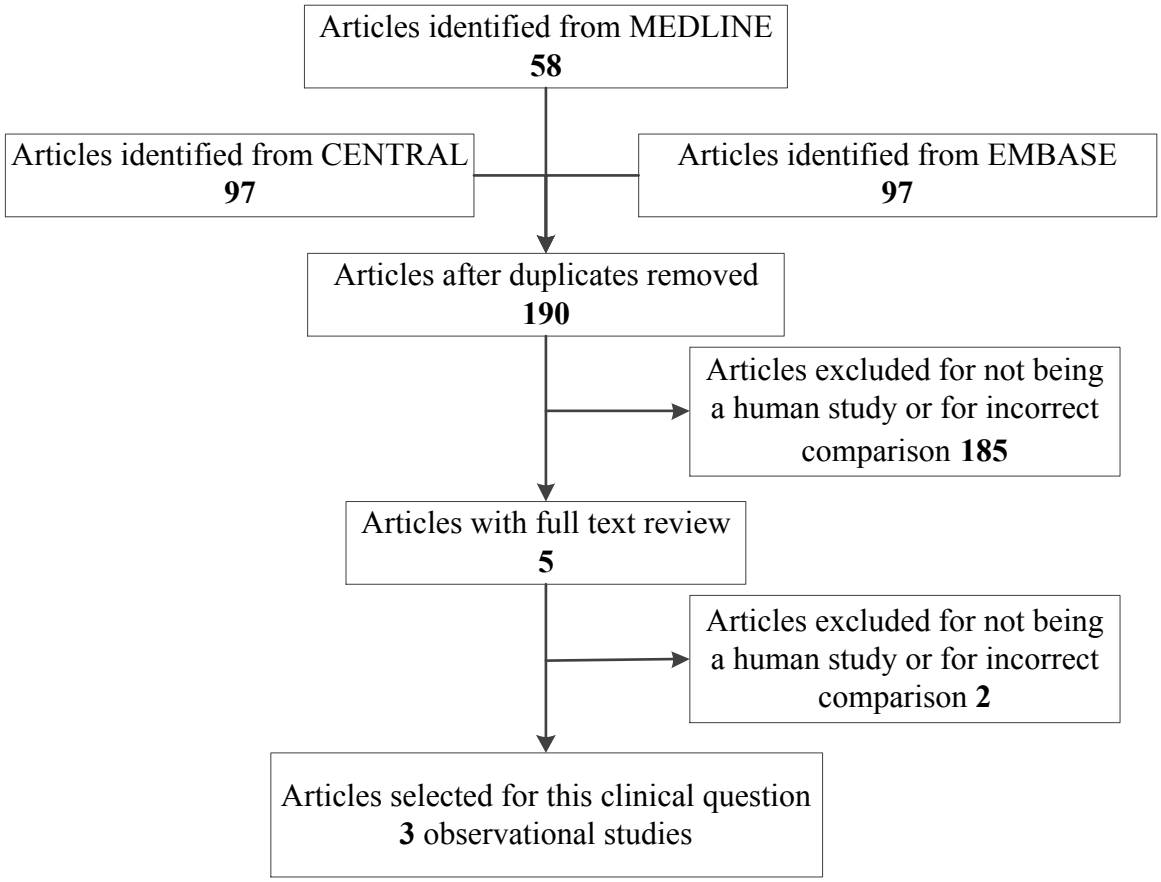
E-Figure **3. Flow diagram for the systematic review selection of studies pertaining to clinical question IV: Should RIC be used to improve neurological outcomes in patients with cerebral small vessel disease?**



E-Figure **4. Flow diagram for the systematic review selection of studies pertaining to clinical question V: Should RIC be used to reduce perioperative complications in patients with carotid artery stenosis who are treated with carotid stenting?**



E-Figure 5. Flow diagram for the systematic review selection of studies pertaining to clinical question VI: Can RIC be performed safely to improve functional outcomes in patients with intracranial hemorrhage?



7. Evidence Profile

E-Table A1. Evidence Profile for Clinical Question II: Should RIC be used to improve functional outcomes in patients with acute ischemic stroke?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
Safety outcome												
1 [1]	observational studies	serious [a]	not serious	not serious	not serious	none	RIC is safe and well tolerated in AIS patients treated with thrombectomy				⊕◯◯◯ VERY LOW	CRITICAL
Safety outcome												
3 [2,3,4]	randomised trials	serious [b,c]	not serious	not serious	not serious	none	RIC is safe in AIS patients whether or not they received intravenous thrombolysis.				⊕⊕⊕◯ MODERATE	CRITICAL
Modified Rankin Scale (follow up: mean 3 months; Scale from: 0 to 6)												
3 [2,3,4]	randomised trials	serious [b,c]	not serious	not serious	not serious	none	175	135	-	MD **0.23 lower** (1.46 lower to 1 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
NIHSS score (follow up: mean 3 months; Scale from: 0 to 40)												
2 [2,4]	randomised trials	very serious [b]	not serious	not serious	not serious	none	42	44	-	MD **3.4 lower** (6.85 lower to 0.05 lower)	⊕⊕◯◯ LOW	CRITICAL
Final infarct volume (follow up: mean 1 months)												
2 [3,4]	randomised trials	serious [c]	not serious	not serious	not serious	none	110	99	-	MD **0.79 higher** (3.44 lower to 5.03 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Penumbral salvage volume												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
1 [3]	randomised trials	serious [c]	not serious	not serious	not serious	none	64	57	-	MD **5.48 lower** (22.58 lower to 11.62 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

RIC: Remote ischemic conditioning; **CI:** Confidence interval; **MD:** Mean difference; **NIHSS:** national institutes of health stroke scale

Explanations

a. Data from a case series without controls.

b. Only a small number of subjects were recruited and the sample sizes were not calculated.

c. A large number of randomized participants were excluded from the final analysis

References

1. Zhao, Wenbo, Che, Ruiwen, Li, Sijie, Ren, Changhong, Li, Chuanhui, Wu, Chuanjie, Lu, Hui, Chen, Jian, Duan, Jiangang, Meng, Ran, Ji, Xunming. Remote ischemic conditioning for acute stroke patients treated with thrombectomy. Annals of Clinical and Translational Neurology; 2018.

2. England, T. J., Hedstrom, A., O'Sullivan, S., Donnelly, R., Barrett, D. A., Sarmad, S., Sprigg, N., Bath, P. M.. RECAST (Remote Ischemic Conditioning After Stroke Trial): A Pilot Randomized Placebo Controlled Phase II Trial in Acute Ischemic Stroke. Stroke; May 2017.

3. Hougaard, K. D., Hjort, N., Zeidler, D., Sorensen, L., Norgaard, A., Hansen, T. M., von Weitzel-Mudersbach, P., Simonsen, C. Z., Damgaard, D., Gottrup, H., Svendsen, K., Rasmussen, P. V., Ribe, L. R., Mikkelsen, I. K., Nagenthiraja, K., Cho, T. H., Redington, A. N., Botker, H. E., Ostergaard, L., Mouridsen, K., Andersen, G.. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. Stroke; 2014.

4. Li, Y., Liang, K., Zhang, L., Hu, Y., Ge, Y., Zhao, J.. Upper Limb Ischemic Postconditioning as Adjunct Therapy in Acute Stroke Patients: A Randomized Pilot. J Stroke Cerebrovasc Dis; Nov 2018.

E-Table A2. Evidence Profile for Clinical Question III: Should RIC be used to reduce recurrent cerebrovascular events in patients with symptomatic intracranial atherosclerosis?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
Safety												
1 [1]	observational studies	very serious [a]	not serious	not serious	not serious	none	RIC was safe and well tolerated in both patients with intracranial atherosclerosis.				⊕◯◯◯ VERY LOW	IMPORTANT
Adverse event related with RIC												
2 [2,3]	randomised trials	very serious [b]	not serious	not serious	not serious	none	3/68 (4.4%)	0/58 (0.0%)	**RR 6.55** (0.35 to 121.37)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Recurrent ischemic cerebrovascular evnets												
2 [2,3]	randomised trials	very serious [b]	not serious	not serious	not serious	none	25/68 (36.8%)	37/58 (63.8%)	**RR 0.58** (0.37 to 0.91)	**268 fewer per 1,000** (from 402 fewer to 57 fewer)	⊕⊕◯◯ LOW	CRITICAL
Excellent outcome												
1 [3]	randomised trials	very serious [b]	not serious	not serious	not serious	none	25/38 (65.8%)	4/30 (13.3%)	**RR 5.53** (2.18 to 14.03)	**604 more per 1,000** (from 157 more to 1,000 more)	⊕⊕◯◯ LOW	
Modified Rankin Scale												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	very serious [b]	not serious	not serious	not serious	none	30	28	-	MD **0.9 lower** (1.44 lower to 0.36 lower)	⊕⊕◯◯ LOW	IMPORTANT
NIHSS score												
1 [2]	randomised trials	very serious [b]	not serious	not serious	not serious	none	30	28	-	MD **1.85 lower** (3.08 lower to 0.62 lower)	⊕⊕◯◯ LOW	IMPORTANT
Cerebral hemodynamics changes												
1 [3]	randomised trials	very serious [b]	not serious	not serious	not serious	none	38	30	-	MD **23.4 higher** (15.83 higher to 3097 higher)	⊕⊕◯◯ LOW	

RIC: Remote ischemic conditioning; **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **NIHSS:** National Institutes of Health Stroke Scale

Explanations

a. Only a small number of patients with intracranial atherosclerosis were recruited.

b. A large number of patients were lost during follow up.

References

1. Li, S., Ma, C., Shao, G., Esmail, F., Hua, Y., Jia, L., Qin, J., Ren, C., Luo, Y., Ding, Y., Borlongan, C. V., Ji, X.. Safety and Feasibility of Remote Limb Ischemic Preconditioning in Patients With Unilateral Middle Cerebral Artery Stenosis and Healthy Volunteers. Cell Transplant; 2015.

2. Meng, R., Ding, Y., Asmaro, K., Brogan, D., Meng, L., Sui, M., Shi, J., Duan, Y., Sun, Z., Yu, Y., Jia, J., Ji, X.. Ischemic Conditioning Is Safe and Effective for Octo- and Nonagenarians in Stroke Prevention and Treatment. Neurotherapeutics; 2015.

3. Meng, R., Asmaro, K., Meng, L., Liu, Y., Ma, C., Xi, C., Li, G., Ren, C., Luo, Y., Ling, F., Jia, J., Hua, Y., Wang, X., Ding, Y., Lo, E. H., Ji, X.. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology; 2012.

E-Table A3. Evidence Profile for Clinical Question IV: Should RIC be used to improve neurological outcomes in patients with cerebral small vessel disease?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
Cognitive function												
2 [1,2]	randomised trials	very serious [a,b]	not serious	serious [c]	not serious	none	46	48	-	SMD **0.58 SD higher** (0.45 lower to 1.61 higher)	⊕◯◯◯ VERY LOW	CRITICAL
White matter hyperintensities volume												
2 [1,2]	randomised trials	very serious [a,b]	not serious	serious [d]	not serious	none	23	24	-	MD **1.57 lower** (3.98 lower to 0.83 higher)	⊕◯◯◯ VERY LOW	CRITICAL

RIC: Remote ischemic conditioning; **CI:** Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. A small number of participants were recruited in the studies.

b. A high percentage of participants were lost during follow up.

c. Cognitive impairment is just a clinical manifestation of cerebral small vessel disease.

d. White matter hyperintensities is only a radiological manifestation of cerebral small vessel disease.

References

1. 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. Eur Neurol; 2016.

2. Wang, Y., Meng, R., Song, H., Liu, G., Hua, Y., Cui, D., Zheng, L., Feng, W., Liebeskind, D. S., Fisher, M., Ji, X.. Remote Ischemic Conditioning May Improve Outcomes of Patients With Cerebral Small-Vessel Disease. Stroke; Nov 2017.

E-Table A4. Evidence Profile for Clinical Question V: Should RIC be used to reduce perioperative complications in patients with carotid artery stenosis who are treated with carotid stenting?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RIC	non-RIC	Relative (95% CI)	Absolute (95% CI)		
Ischemic cerebrovascular events												
1 [1]	randomised trials	serious [a,b]	not serious	not serious	not serious	none	1/63 (1.6%)	5/126 (4.0%)	**RR 0.40** (0.05 to 3.35)	**24 fewer per 1,000** (from 38 fewer to 93 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Ischemic brain lesion												
1 [1]	randomised trials	serious [a,b]	not serious	not serious	not serious	none	10/63 (15.9%)	49/126 (38.9%)	**RR 0.41** (0.22 to 0.75)	**229 fewer per 1,000** (from 303 fewer to 97 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Infarct volume												
1 [1]	randomised trials	serious [a,b]	not serious	serious [c]	not serious	none	63	126	-	MD **0.53 lower** (0.59 lower to 0.48 lower)	⊕⊕◯◯ LOW	IMPORTANT
RIC related adverse events												
1 [1]	randomised trials	serious [a,b]	not serious	not serious	not serious	none	6/63 (9.5%)	0/126 (0.0%)	**RR 25.80** (1.48 to 450.77)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

RIC: Remote ischemic conditioning; **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. A large number of participants were lost during follow up.
b. Participants were not blinded to the treatment protocol.
c. The infarct volume was used as a surrogate endpoint to assess stroke severity.

References

1. Zhao, W., Meng, R., Ma, C., Hou, B., Jiao, L., Zhu, F., Wu, W., Shi, J., Duan, Y., Zhang, R., Zhang, J., Sun, Y., Zhang, H., Ling, F., Wang, Y., Feng, W., Ding, Y., Ovbiagele, B., Ji, X.. 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; Apr 04 2017.

E-Table A5. Evidence Profile for Clinical Question VI: Can RIC be performed safely and should RIC be used to improve functional outcomes in patients with intracranial hemorrhage?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Safety and feasibility									
2 [1,2]	observational studies	very serious [a,b]	not serious	not serious	not serious	none	RIC is safe and well tolerated in critically ill patients with subarachnoid hemorrhage.	⊕◯◯◯ VERY LOW	CRITICAL
Functional outcome									
1 [3]	observational studies	serious [b,c]	not serious	not serious	not serious	none	RIC was independently associated with good outcome.	⊕◯◯◯ VERY LOW	CRITICAL
Incidence of stroke or death									
1 [3]	observational studies	serious [b,c]	not serious	not serious	not serious	none	RIC shows a trend toward lower incidence of stroke and death.	⊕◯◯◯ VERY LOW	

RIC: Remote ischemic conditioning; **CI:** Confidence interval

Explanations

a. Only a single arm of participants was recruited, and the outcomes were not compared to controls.

b. There is a relatively small sample size.

c. This study is a retrospective study that used historic controls.

References

1. Gonzalez, N. R., Connolly, M., Dusick, J. R., Bhakta, H., Vespa, P.. Phase I clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. Neurosurgery; Nov 2014.

2. Koch, S., Katsnelson, M., Dong, C., Perez-Pinzon, M.. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. Stroke; 2011.

3. Laiwalla, A. N., Ooi, Y. C., Liou, R., Gonzalez, N. R.. Matched Cohort Analysis of the Effects of Limb Remote Ischemic Conditioning in Patients with Aneurysmal Subarachnoid Hemorrhage. Translational stroke research; Feb 2016.

8. Evidence to Decision Framework

E-Table B1. Evidence to Decision Framework for Clinical Question II: Should RIC be used to improve functional outcomes in patients with acute ischemic stroke?

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or		

variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE	Large	**Moderate**	Small	Trivial		Varies	Don't

	JUDGEMENT						
EFFECTS							know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

In patients with acute ischemic stroke, RIC can be considered in those not receiving reperfusion therapy, however, the currently available evidence suggests that RIC should not be used as routine adjunctive therapy in those receiving reperfusion therapy.

Justification

Overall justification

Two studies showed RIC could improve functional outcome of 90 days in acute ischemic stroke patients that not receiving reperfusion therapy. Three clinical trials of acute stroke patients that treated with reperfusion therapy, but all these three studies did not prove the safety profile of RIC

Detailed justification

Balance of effects

Two studies that investigated acute ischemic stroke patients receiving reperfusion therapy, these two studies only recruited a small simple size and the power was low. In addition, three clinical trials include patients treated with intravenous thrombolysis and endovascular thrombectomy, all the studies did not prove the safety and efficacy profile of RIC in these patients.

Implementation considerations

The protocols of RIC used in acute ischemic stroke patients depend on specific conditions of the patients population.

Research priorities

Larger efficacy trials are warranted to determine both the safety profiles and efficacy against acute ischemic stroke patients with or without reperfusion therapy. In addition, the benefits of RIC in cerebral infarct size also needed to be confirmed.

E-Table B2. Evidence-to-Decision Framework for Clinical Question III: Should RIC be used to reduce recurrent cerebrovascular event in patients with symptomatic intracranial atherosclerosis?

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability		

● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with symptomatic ICAS, long-term repeated RIC can be used to prevent recurrent ischemic cerebrovascular events.

Justification

Overall justification

This recommendation was mainly based on two RCTs, both of which demonstrated that repeated RIC—applied after ischemic cerebrovascular events and consecutively for 180 or 300 days—could not only prevent the recurrence of ischemic cerebrovascular events, but also promote the recovery of neurological deficits.

Detailed justification

Desirable Effects

Long-term repeated RIC has been demonstrated to prevent the recurrence of ischemic cerebrovascular events and promote the recovery of neurological deficits.

Implementation considerations

As recurrent ischemic cerebrovascular events were more common during the days after index ischemic events, it might be better to apply RIC as early as possible after the index ischemic events.

Research priorities

Much larger studies are needed to confirmed these results. In addition, the RIC protocol urgently needs to be investigated, and whether the use of RIC every 3 days, 7 days, or much longer times is also effective needs to be evaluated.

E-Table B3. Evidence to Decision Framework for Clinical Question IV: Should RIC be used to improve neurological outcomes in patients with cerebral small vessel disease?

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Important uncertainty or variability		

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

In patients with cerebral small vessel disease and those who have suffered from cerebral small vessel disease-related cognitive impairment, we suggest that RIC not be deployed as the first-line therapy.

Justification

Overall justification

The recommendations are based on two single-centre RCTs that recruited a very small number of patients with inconclusive results.

Detailed justification

Desirable Effects

One RCT recruited 17 patients and did not find any significant differences between the RIC group and the control group, the other RCT reported significant differences and recruited 36 patients, but 16.7% of patients were lost during follow-up. Furthermore, many key variables that may impact the results were not properly evaluated in either study, and these limitations could have biased the authors' results and interpretations.

Implementation considerations

Not considered.

Research priorities

Additional studies should be conducted to validate the findings of the aforementioned studies and further assess whether RIC may be superior to pharmacological treatments for improving cognitive function. Many key variables that may impact the study results (including the management of blood pressure, glucose and lipid) should be addressed in future studies. Additionally, assessments of the benefits of RIC for patients with vascular cognitive impairment would be a worthy research goal.

E-Table B4. Evidence-to-Decision Framework for Clinical Question V: Should RIC be used to reduce perioperative complications in patients with carotid artery stenosis who are treated with carotid stenting?

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with carotid artery stenosis who are treated with carotid stenting, pretreatment with two weeks of RIC may be considered as a strategy to prevent perioperative complications.

Justification

Overall justification

This recommendation is based on a RCT in which two weeks of RIC before operation significantly reduced the incidence of posttreatment brain lesion and infarct volume, and the incidence of ischemic cerebrovascular events tended to be lower in the RIC group.

Detailed justification

Balance of effects

Although RIC was associated with much higher rates of arm skin petechiae from repeated cuff applications, the adverse events caused by RIC were not serious.

Implementation considerations

Two weeks of repeated RIC before the operation may be considered to reduce the perioperative complications for patients

who will undergo carotid stenting.

Monitoring and evaluation

If using RIC before the carotid stenting, RIC-related adverse events (such as arm skin petechiae) should be monitored.

Research priorities

Future studies should be conducted to validate the findings of this study, and studies recruiting much higher patient numbers with severe carotid artery stenosis are needed to properly assess the benefits of RIC in prevention of ischemic cerebrovascular events after carotid stenting. Furthermore, future studies should include long-term cognitive and psychological functions in their outcome assessments. Additionally, postprocedural silent cerebral ischemic lesions are not an uncommon complication in many endovascular or vascular surgeries; therefore, whether or not RIC prevents silent cerebral embolisms during other procedures also needs to be assessed.

E-Table B5. Evidence-to-Decision Framework for Clinical Question VI: Can RIC be performed safely to improve functional outcomes in patients with intracranial hemorrhage?

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Important uncertainty or variability		

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

In patients with aneurysm subarachnoid hemorrhage who have been treated with endovascular coiling or surgical clipping, there is insufficient evidence to recommend routine use of RIC as an adjunctive therapy.

Justification

Overall justification

In patients with subarachnoid hemorrhage, RIC is safe and feasible, and may benefit these patients by improving the recovery of neurological outcomes. However, there are only two case series and one matched cohort study, supporting role of RIC in patients with aneurysm subarachnoid hemorrhage after endovascular coiling or surgical clipping.

Detailed justification

Balance of effects

RIC is safe and well tolerated in aneurysm subarachnoid hemorrhage after endovascular coiling or surgical clipping, and it may benefit these patients. A randomized controlled trial demonstrating efficacy is lacking.

Implementation considerations

The application of RIC through the arm or leg depends on specific circumstances, such as the availability of the arms or legs, comorbidities such as venous thrombosis, and the tolerance of patients, etc.

Research priorities

Much powerful studies are needed to confirm these results. In addition, as subarachnoid hemorrhage and intracerebral hemorrhage share many common pathophysiological mechanisms, the safety, feasibility, and efficacy of RIC in patients with intracerebral hemorrhage urgently deserve to be investigated.