Effects of **R**emote **I**schemic Pre-Conditioning on Neurologic Complications in Adult Ischemic **M**oyamoya Disease Patients Undergoing **E**ncephaloduroarteriosynangiosis（**RIME**）

—— A Prospective, Multi-center, Randomized Controlled Trial ——

Study Protocol

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1. Protocol Synopsis

Title	Effects of **R**emote **I**schemic Pre-Conditioning on Neurologic Complications in Adult Ischemic **M**oyamoya Disease Patients Undergoing **E**ncephaloduroarteriosynangiosis
Acronym	**RIME**
Objectives	• To evaluate the safety of remote ischemic preconditioning in adult ischemic MMD patients undergoing indirect revascularization; • To evaluate the clinical benefit of remote ischemic preconditioning in adults with ischemic MMD who underwent indirect revascularization.
Study Design	This study was a multi-center, prospective, randomized, controlled trial of randomized (1:1) adult ischemic MMD patients undergoing indirect revascularization into two groups: 1. RIPC group Remote limb ischemic preconditioning (RIPC) is consisted of five 5-min cycles of bilateral arm ischemia/reperfusion, it is induced by a sphygmomanometer placed on bilateral arm and inflated to 200 mmHg for 5-min followed by deflating the cuff for 5-min, patients in the RIPC group will do it twice a day for at least five days before EDAS. 2. sham RIPC group Sham RIPC group is consisted of five 5-min cycles of bilateral arm ischemia/reperfusion, induced by a sphygmomanometer placed on bilateral arm and inflated to 60 mmHg for 5-min followed by deflating the cuff for 5-min, they will do it twice a day for at least five

	days before EDAS.
Primary endpoint	• All cerebrovascular events (ischemic stroke, cerebral hemorrhage, transient neurological deficits) within 30 days post-surgery • All death or dependent (mRS > 2) within 30 days post-surgery
Secondary endpoint	• The severity of the ischemic stroke after surgery • Number of patients occurred restroke at Follow-up Period • Number of patients dependent or death at follow-up period • Number of patients with improved neurological function at follow-up period • Perfusion status of patients at follow-up period • Number of patients with any side effects of remote ischemic preconditioning (RIPC) treatment.
Inclusion Criteria	• Patients who diagnosed with moyamoya disease • Adults 18 to 65 years of age • The onset symptoms manifested as ischemic symptoms (TIA or stroke) or atypical symptoms (headache, epilepsy or asymptomatic) • Able to receive the necessary imaging examination • Patients who pre-agreed to the study
Exclusion Criteria	• Prior cerebral hemorrhage history • Other brain or cerebrovascular disease • Previous history of revascularization surgery • Dependent (mRS > 2) • Receive other type of revascularization surgery • Peripheral blood vessel disease (especially subclavian arterial and upper limb artery stenosis or occlusion).

	• Patients who do not agree with the study
Sample Size	Sample size and power were calculated based on previous studies and postoperative neurological complications, which were much better to indicate the efficacy of RIPC. We calculated the simple size and power with PASS, version 11 (NCSS, LLC, Kaysville, UT, USA). We expected ≈10% of subjects in the RIPC group and 20% of subjects in the other 2 groups would have new postoperative neurological complications. The intended target sample size was 328 subjects allowing 15% loss to follow-up and with 90% power and an α of 0.05 (2-sided) of significance.
Follow-up	The face-to-face interview will be performed by study neurologists at discharge, at 6 months and at 12 months (or by telephone) after the recruitment of patients.

2. Study Rationale

2.1 Background

Moyamoya disease (MDD) is a chronic ischemic cerebrovascular disease characterized by chronic progressive stenosis of the bilateral internal carotid artery.[1] Chronic progression of the disease can lead to the formation of abnormal vascular networks, including vascular network compensation for the formation of the skull base and the initial pathological changes in the area of cerebral infarction.[2] MMD is common among East Asians, including Japan, South Korea and China.[3-5] The clinical manifestations of MMD are mainly divided into two types in the Asian population: ischemic and hemorrhagic. The ischemic type accounts for about 70%, and the

hemorrhagic type accounts for about 30%. [6, 7]

For the treatment of patients with MMD, the main purpose is to prevent further stroke events and reduce the rate of recurrent stroke.[8] There are two types of treatment for patients with MMD: surgery and conservative treatment.[9] Surgical treatment includes direct revascularization and indirect revascularization. Surgical treatment has been widely recognized for reducing ischemic MMD re-stroke, but there is still controversy about hemorrhagic MMD.[10, 11] Indirect revascularization is a simpler, less laborious technique than direct revascularization requiring manual anastomosis of extracranial donor vessels and intracranial recipient vessels, with a lower risk of postoperative complications.[12, 13] Furthermore, many recent studies demonstrated that the long-term efficacy of indirect revascularization has no significant difference with direct revascularization.[13-15] However, due to insufficient blood supply to the brain in patients with MMD, the vascular reactivity of the cerebral vessels is decreased,[16] leading to poor tolerance to hemodynamic changes.[17] Cerebral hypoperfusion may occur after indirect revascularization surgery, leading to postoperative ischemic events and postoperative neurological deterioration,[12] which may increase postoperative morbidity and mortality. Therefore, patients undergoing cerebral revascularization require an effective neuroprotective strategy.

Several animal and human studies have shown that non-fatal ischemic injury has an overall protective effect on pretreated tissues and other distal organs, which is called distal ischemic preconditioning (RIPC).[18, 19] RIPC has cardioprotective effects on patients undergoing cardiac surgery.[20] In terms of neuroprotection, RIPC reduces

recurrence of transient ischemic attack (TIA), improves recovery and increases cerebral perfusion in patients with a history of stroke or TIA and intracranial stenosis.[21] Vasodilation prevents ischemia in patients with subarachnoid hemorrhage.[22]

When RIPC is applied to adult ischemic MMD patients undergoing indirect cerebral revascularization, whether it can reduce the incidence of postoperative neurological complications in MMD patients and improve the neurological prognosis of patients with MMD, there is still no evidence-based medical evidence.

2.2 Research status

Many literatures have reported risk factors for neurological complications in patients with MMD after revascularization,[12, 27, 28] however, there is a lack of effective measures and clear criteria for how to reduce the incidence of neurological complications after revascularization in patients with MMD. A recent study reported the effect of combined remote ischemic treatment on neurological complications after STA-MCA anastomosis in patients with MMD.[29] This study demonstrated the potential of combined RIPC and RIPostC to reduce neurologic complications and the duration of hospitalization in patients undergoing STA-MCA anastomosis for MMD. However, since this study is a single-center study and only 108 patients were enrolled, the effectiveness of RIPC remains to be confirmed. In addition, the effect of direct revascularization varies greatly depending on the surgeon's experience and technique. When conducting a multicenter study, the results may be biased. At the same time, because this study enrolled MMD patients undergoing direct revascularization, it is

unclear whether RIPC can reduce the incidence of postoperative neurological complications in adults with ischemic MMD undergoing indirect revascularization. Whether RIPC is effective enough in adult ischemic MMD patients undergoing indirect revascularization to reduce postoperative neurological complications and improve prognosis? The current research quality is not sufficient to support clinical decision making. In adult ischemic MMD patients undergoing indirect revascularization, prospective clinical trials to confirm the clinical benefits and risks of RIPC procedure have become clinical problems that need to be addressed.

3. Primary Aim

- To evaluate the safety of remote ischemic preconditioning in adult ischemic MMD patients undergoing indirect revascularization
- To evaluate the clinical benefit of remote ischemic preconditioning in adults with ischemic MMD who underwent indirect revascularization

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4. Study Plan and Procedure

Study Design and Flow Chart

This study was a multi-center, prospective, randomized, controlled trial of

randomized (1:1) adult ischemic MMD patients undergoing indirect revascularization into two groups:

1. RIPC group

Remote limb ischemic preconditioning (RIPC) is consisted of five 5-min cycles of bilateral arm ischemia/reperfusion, it is induced by a sphygmomanometer placed on bilateral arm and inflated to 200 mmHg for 5-min followed by deflating the cuff for 5-min, patients in the RIPC group will do it twice a day for at least five days before EDAS.

2. sham RIPC group

Sham RIPC group is consisted of five 5-min cycles of bilateral arm ischemia/reperfusion, induced by a sphygmomanometer placed on bilateral arm and inflated to 60 mmHg for 5-min followed by deflating the cuff for 5-min, they will do it twice a day for at least five days before EDAS.

5. Study Endpoints

5.1 Primary Endpoint

- All cerebrovascular events (ischemic stroke, cerebral hemorrhage, transient neurological dysfunction) within 30 days post-surgery
- All death or dependent (mRS > 2) within 30 days post-surgery

5.2 Clinical Secondary Endpoint

- The severity of the ischemic stroke after surgery

- Number of patients occurred restroke at follow-up period
- Number of patients dependent (mRS > 2)or death at follow-up period
- Number of patients with improved neurological function at follow-up period
- Perfusion status of patients at follow-up period
- Number of patients with any side effects of remote ischemic preconditioning (RIPC) treatment.

6. Patient Selection Criteria

6.1 Inclusion criteria

- Patients who diagnosed with moyamoya disease
- Adults 18 to 65 years of age
- The onset symptoms manifested as ischemic symptoms (TIA or stroke) or atypical symptoms (headache, epilepsy or asymptomatic)
- Able to receive the necessary imaging examination
- Patients who pre-agreed to the study

6.2 Exclusion Criteria

- Prior cerebral hemorrhage history
- Other brain or cerebrovascular disease
- Previous history of revascularization surgery
- Dependent (mRS > 2)
- Receive other type of revascularization surgery

- Peripheral blood vessel disease (especially subclavian arterial and upper limb artery stenosis or occlusion).
- Patients who do not agree with the study

7. Informed Consent

The principles of Informed Consent, according to FDA Regulations and ICH guidelines on GCP, will be followed. Investigator will submit a copy of the proposed consent form, together with the study protocol, to the central Institutional Review Board (IRB) at Beijing Tiantan Hospital for approval. Each eligible patient who wishes to participate in this study will be invited to give written informed consent. Before the consent is signed, a trained researcher will explain study purpose, description, duration, potential risks and anticipated benefits, cost and compensation, voluntary nature of participation, appropriate alternatives, treatment for study-related injury, whom to contact with questions or concerns or study-related injuries, maintenance of confidentiality of record, and funding source. Patients will be encouraged to consent for the blood drawing for biomarker testing only if they would be prepared to enroll in the trial.

8. Enrollment of Patients

All patients with moyamoya disease who visit the research center will be asked if they are involved in the study as long as they meet the inclusion criteria. This study is included in patients who have voluntarily participated in the study and signed

informed consent and did not meet the exclusion criteria.

9. Randomization of Patients

Patients was randomized by random number table

10. Image Data Evaluation

In this study, Suzuki staging was determined by DSA technique; subarachnoid hemorrhage, ischemic stroke (cerebral infarction), and cerebral hemorrhage were diagnosed using the Fourth National Conference on Cerebrovascular Diseases (1995). In order to prevent errors in the research due to the interpretation technique, this study set up a decision-making committee to uniformly judge the imaging data of the patients enrolled. Two experienced neuroimaging physicians conducted mutual blind interpretation, and the results of the inconsistent report should be ranked third. The senior neuroimaging chief physician will conduct a trial and finally submit true and reliable imaging results for all cases. The interpreter does not participate in the study design and does not know the patient's clinical information.

11. Bio sample test

Blood samples were drawn from the cubital vein; the points of measurement included baseline, pre-EDAS, right 1 hour and 24 hours post-EDAS. The collected blood samples were sent for examination, and plasma neuron specific enolase (NSE) and human S protein 100B (S-100B) levels were examined in the test samples.

11. Schedule of Follow-up and Post-study Follow-up Period

All patients will be followed up until the primary endpoint or the end of the trial. Complete endpoint information will be obtained with the best effort irrespective of patient study status, unless patients withdraw consent to participate the trial. The face-to-face interview will be performed by study neurologists at discharge, at 6 months and at 12 months (or by telephone) after the recruitment of patients.

Visits	**Windows**	**Definition**
Randomization	0 day	Study Day 0 day
At discharge	0 day	Based on the number of hospitalization days
At 6 months	14 days	Day 166-194
At 12 months	30 days	Day 330-390

12. Quality Assurance

Periodic monitoring and auditing will be performed at each site to ensure that data generated during the study reflect what is specified in the protocol, and data consistence by comparing data in the case report form (CRF) and data collected in source documents for (CRF vs. source documents). If patients who have events go to non-study sites for treatment, source documents will be photocopied for review. It should be guaranteed that the study investigators and relevant study personnel are available during the monitoring visits and possible audits.

13. Statistical Consideration

13.1 Sample size estimates

This study was a cohort study of prospective, multicenter, hospital-based, continuous enrollment patients. It is planned to choose three hospitals in Beijing. The investigation and registration of the ending events are carried out through hospital follow-up examinations, investigations, registration and hotline reports, face-to-face or telephone follow-up, and monitoring information database supplementation. Sample size and power were calculated based on previous studies and postoperative neurological complications, which were much better to indicate the efficacy of RIPC. We calculated the simple size and power with PASS, version 11 (NCSS, LLC, Kaysville, UT, USA). We expected $\approx$10% of subjects in the RIPC group and 20% of subjects in the other 2 groups would have new postoperative neurological complications. The intended target sample size was 328 subjects allowing 15% loss to follow-up and with 90% power and an α of 0.05 (2-sided) of significance.

13.2 Statistical Analyses

The results of the study were analyzed using IBM SPSS Statistics 23.0 (IBM Corp, Armonk, NY, USA) data analysis software. Charting was performed using GraphPad Prism 7.0a (GraphPad Software, La Jolla, CA, USA). Continuous variables obeying the normal distribution were expressed as mean ± standard deviation, and two independent sample t-tests or paired t-tests were used for comparison between the two groups. Continuous variables with unknown distributions were expressed using median and interquartile range and compared between the two groups by Mann-Whitney U test or Wilconxon rank sum test. The normality of the continuous variables

was tested using the Shapiro-Wilk W test. The categorical variables were expressed as frequency and percentage, and comparisons between the two groups were made using the Pearson chi-square test or the McNemar paired chi-square test. Correlation between the two variables was analyzed using Pearson, Kendall's tau-b or spearman correlation coefficients according to the corresponding variable types. Prognostic information was analyzed by Kaplan-Meier survival analysis based on least squares method and compared between the two groups using log-rank test. All statistical tests were two-sided, and the results were considered statistically significant at $P < 0.05$.

13.3 Clinical Site Effect

All revascularization surgeries will be performed by experienced neurosurgeon.

14. Data Safety Monitoring Committee

A Data Safety Monitoring Board (DSMB) is composed of Academic Members, including an independent statistician, who are not otherwise participating in the trial. A DSMB charter including membership role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial. DSMB will meet approximately every three months to review the progress of this study (e.g enrollment, site performance, meeting risk factor targets) as well as data on the safety of both treatment arms (e.g., side effects of RIPC) to ensure that the study meets the highest standards of ethics and patient safety. Using guidelines established by the committee and the principal investigators before the study begins, the DSMB may

recommend termination of the study if one treatment arm is found to be unequivocally more efficacious than the other or if one of the treatment arms is found to be unsafe. Additionally, the DSMB may recommend modifications to the protocol if a reversible safety issue is identified. A letter including written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting. This letter will be provided to the central IRBs at their request.

Committee member: Xun Ye, Rong Wang, Yuanli Zhao

15. Institutional Review Board/Independent Ethics Committee(IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the central IRB located at Beijing Tiantan Hospital, and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The following information should be clearly stated on the written approval/favorable opinion: The Clinical Trial information (study number, Clinical Trial Protocol title and version number), the documents reviewed (Protocol, Informed Consent Form, Investigator's Brochure, etc.), the list of voting members along with their qualification and the date of the review.

Investigational Product will not be released at the study site and the Clinical Trial will not be initiated until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial

Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

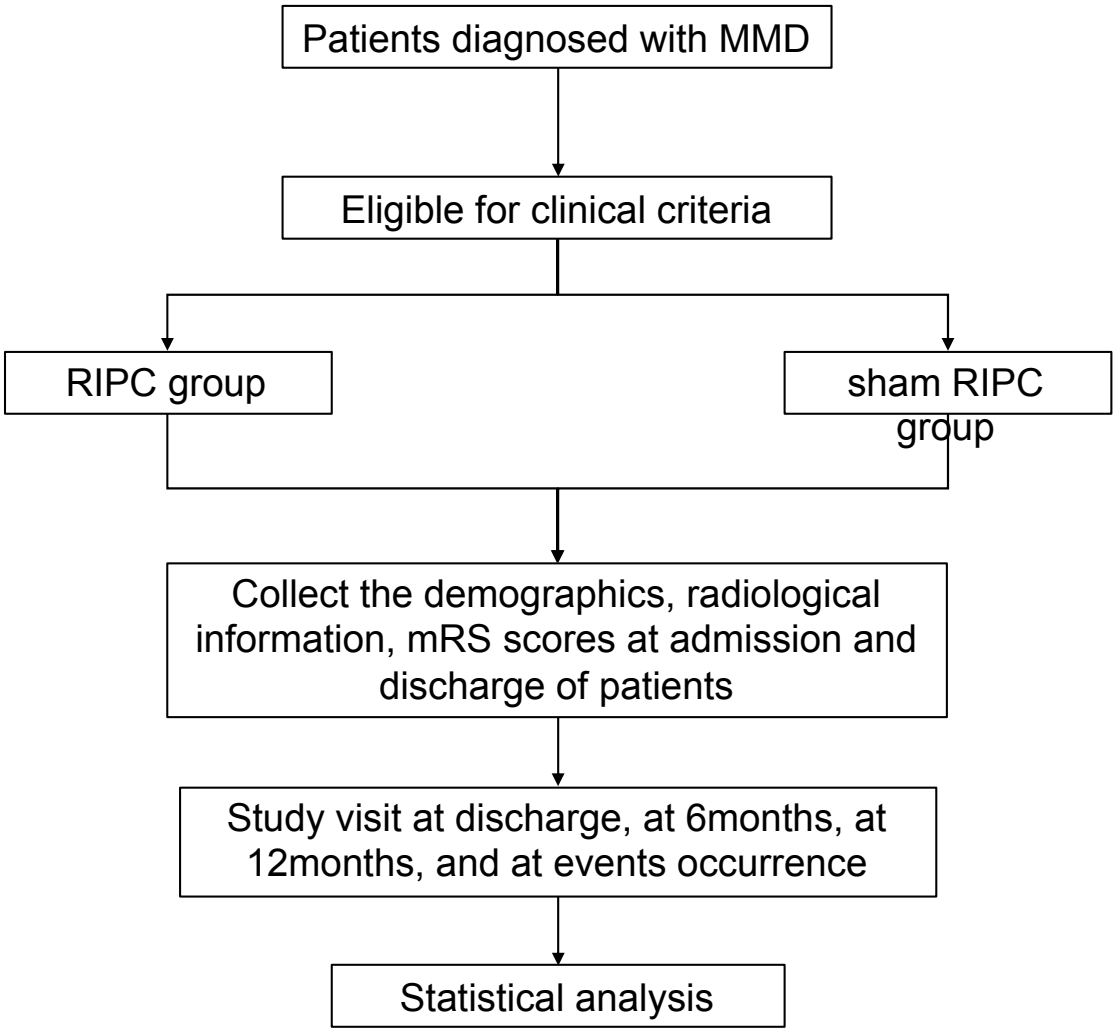
If requested, a progress report will be sent to the Ethics Committee (IRB/IEC) annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

16. Safety Outcomes Assessment

The following adverse events were defined as safety outcomes: (1) elevation of plasma NSE and S-100B levels beyond normal limits after RIPC and sham RIPC procedure; (2) inability to tolerate RIPC or sham RIPC procedure that leads to the discontinuation from the study; (3) objective signs of tissue or neurovascular injury resulting from RIPC and sham RIPC procedure. An inspection that was done by staffs blinded to the study protocol included palpation of distal radial pulses, visual inspection for local edema, erythema and skin lesions, and palpation for tenderness. These safety outcomes were evaluated by observers blinded to the treatment assignment, and any suspicious adverse event associated with RIPC or sham RIPC procedure was reported to the investigators.

APPENDIXS

Study Flow Chart



Schedule of Visits and Test

	Visit 1	Visit 2	Visit 3	Visit 4	Event visit
Assessments	**Screening/Randomize**	**At discharge**	**At 1 year ± 1 month**	**Every 12 months ±1 month**	
Informed Consent	✔				
Eligibility criteria	✔				
Patient Randomization	✔				
Relevant medical history	✔				
Demographics	✔				
MRI before Surgery	✔				
CTP before Surgery	✔				
DSA before Surgery					
Vital signs	✔				✔
Modified Rankin Score	✔	✔	✔	✔	✔
MRI after surgery		✔	✔	✔	
CTP after surgery		✔	✔	✔	✔
DSA after surgery		✔	✔		✔
Current Medications	✔	✔	✔	✔	✔
Endpoints		✔	✔	✔	✔

modified Rankin Scale

The modified Rankin Scale (mRS) is a scale commonly used for measuring the degree of disability or dependence in the daily activities of individuals who have suffered a stroke, and it has become the most widely used clinical outcome measure for stroke clinical trials.

Description	**Score** (select one)
No symptoms at all	**0** ☐
No significant disability despite symptoms; able to carry out all usual duties and activities	**1** ☐
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	**2** ☐
Moderate disability; requiring some help, but able to walk without assistance	**3** ☐
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	**4** ☐
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	**5** ☐

Dead	**6** ☐

Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders.
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) acute onset of a new focal neurological deficit with clinical or imaging evidence of infarction lasting more than 24 hours and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or (2) acute onset of a new focal neurological deficit and not attributable to a non-ischemic etiology lasting less than 24 hours, but accompanied by neuroimaging evidence of new brain infarction; or, (3) rapid worsening of an existing focal neurological deficit lasting more than 24 hours and not attributable to a non-ischemic etiology, and accompanied by new ischemic changes on brain MRI or CT, and clearly

	distinct from the index ischemic event.
Hemorrhagic stroke	An acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms.
TIA	A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Transient neurological deficits (TNDs)	Either any reversible neurological deficit observed objectively (e.g., hemiparesis, dysarthria) or any reversible neurological deficit recognized and reported subjectively (e.g., facial palsy), without evidence of intracranial hemorrhage and cerebral

	infarction on imaging studies.
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy
Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on

	the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or

	any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage
Dependent	Unable to look after own affairs without assistance, mRS score > 2