

Measurement of cerebrovascular reserve by multimodal image for cerebral arterial occlusion or stenosis patients: study protocol of a randomized paralleled controlled trial

xiao zhipeng

renji hospital, medicine of school of Shanghai jiaotong university

ji ke

renji hospital, medicine of school of Shanghai jiaotong university

lin yong

renji hospital, medicine of school of Shanghai jiaotong university

wan jieqing

renji hospital, medicine of Shanghai jiaotong university

pan yaohua

renji hospital, medicine of school of Shanghai jiaotong university

jin yichao

renji hospital, medicine of school of Shanghai jiaotong university

zhang xiaohua (✉ zhh1969@aliyun.com)

<https://orcid.org/0000-0001-5845-9787>

Study protocol

Keywords: stroke; cerebrovascular reactivity; cerebral blood flow; multimodal image; recurrence

Posted Date: August 7th, 2019

DOI: <https://doi.org/10.21203/rs.2.12484/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 8th, 2020. See the published version at <https://doi.org/10.1186/s13063-019-3967-2>.

Abstract

Background Cerebrovascular reactivity (CVR), index of cerebral hemodynamics, might guide the treatment of ischemic stroke. However, the previous studies that the therapeutic strategy of stroke mainly depends on the degree of vascular stenosis with steady-state vascular parameters, such as cerebral blood flow, and CVR factors are not under consideration. Measurement of CVR by multimodal image might improve the prognosis for ischemic stroke. Methods/design The study is a prospective, randomized, paralleled controlled clinical trial to examine the multimodal image evaluation for CVR. A total of 66 eligible patients will be recruited from Renji hospital, Shanghai Jiaotong University School of Medicine. The patients will be categorized based on CVR into two subgroups as follows: CVR>10% group and CVR<10% group. And the patients will be randomly assigned to medical management, percutaneous transluminal angioplasty and stenting, and intracranial and extra-cranial bypass groups in a 1:1:1 ratio. The primary end point is all adverse events and ipsilateral stroke recurrence at 6, 12, 24 months after the management. The secondary outcomes include the CVR, the National Institute of Health stroke scale and the Modified Rankin Scale at 6, 12, 24 months. Discussion Measurement of cerebrovascular reserve by multimodal image is recommended by most recent studies to guide the treatment of ischemic stroke, and thus its efficacy and evaluation accuracy need to be established in randomized controlled settings. This prospective, randomized, paralleled controlled registry study, together with other ongoing studies, will present more evidence for optimal individualized accurate treatment of ischemic stroke.

Introduction

Stroke is the second most common cause of death and major cause of disability worldwide after ischemia heart disease, especially in developing countries[1]. Ischemic is the primary classification of stroke, accounting for about 87% of all strokes. Patients with symptomatic major cerebral arterial occlusion or stenosis have a substantial risk of recurrent ischemic stroke[2]. Therefore, an effective imagine digital evaluation method and a good treatment for intracranial artery stenosis and occlusive disease is necessarily.

The treatment of ischemic stroke has been investigated by some high-quality trials: The Japanese EC-IC bypass trial (JET2) study revealed that patients with cerebral blood flow (CBF) < 80% and CVR < 10% had significantly lower incidence of ipsilateral stroke recurrence compared to the medical group and EC-IC bypass surgery is unlikely to benefit patients with CBF > 80% or CVR > 10%[3]. Another recent trials, including the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRISS) trial and the Carotid Occlusion Surgery Study, demonstrated that recurrent stroke rates have decreased over time when patients are treated with maximal medical therapy[4]. AL Hasan reported a study about Ischemic Stroke Therapy trial also show that the 30-day incidence of any transient ischemic attack, stroke, intracranial hemorrhage, or death was higher in the stent group (14.7%) vs the medical group (5.8%). Although the current trial show that medical management, PTAS, and IC-EC bypass can be selected for ischemic stroke patient, but which treatment is more benefit to what typical stroke patients is unclear. However, the treatment strategy of intracranial

arterial stenosis or occlusion mainly depends on the degree of vascular stenosis, with or without considering about the distal hemodynamic factors and CVR factors, or steady-state vascular parameters, such as CBF and cerebral blood volume (CBV). So we consider this to plan a study protocol that measurements of cerebrovascular reserve by multimodal image for cerebral arterial occlusion or stenosis patients.

Cerebrovascular reactivity(CVR) is an important measure to impaired cerebral hemodynamics and provides vascular reserve information that is complementary to steady-state vascular parameters, such as CBF and cerebral blood volume (CBV)[5, 6]. CVR denotes the ability of cerebral vessels to dilate or constrict in response to challenges or defined as the change in CBF in response to a vasoactive stimulus such as an increase in the arterial partial pressure of CO₂ (PaCO₂)[7, 8]. There are two typical methods to measure CVR: one is to directly reflect CVR by image, such as PET, SPECT, CT and MRI; Another method is to indirectly reflect CVR by TCD[9-12]. we intend to precisely evaluate the change of CVR before and after surgery or medicine treatments by multimodal image including MR, CT and SPECT, so that we can make strategies of individualized accurate diagnosis and treatment for the ischemic stroke[3, 13].

Based on current uncertainty concerning the treatment of intracranial arterial stenosis or occlusion, the plan of a trial was conceived to Chinese Clinical Trial Registry and raised in Renji hospital cerebral vascular center. And hence the present trial is designed with intent to determine whether multimodal and digital image evaluation for CVR can effectively select the treatment strategy in adult patients with intracranial arterial stenosis or occlusion. Detail of the trial will be specified in the following.

Methods/design

2.1 overview

The study is a prospective, randomized, paralleled controlled clinical trial to examine the multimodal and digital image evaluation for cerebrovascular reserve on ischemic stroke treatments. A total of 66 eligible patients will enrolled at Shanghai Jiaotong University School of Medicine, Renji hospital cerebral vascular center. The eligible patients were categorized based on rest CBF and CVR into two subgroups as follows: CVR>10% group and CVR<10% group. And the two group patients will randomly be assigned to medical management, single angioplasty, PTAS, and IC-EC bypass group in a 1:1:1 ratio. The primary end point is all adverse events and ipsilateral stroke recurrence at 6, 12, 24 months after the management. The secondary outcomes include the CVR, the National Institute of Health stroke scale (NIHSS) and the Modified Rankin Scale (MRS) at 6, 12, 24 months after the management.

2.2. Inclusion and exclusion criteria for the trial

The patients will be deemed eligible for the trial if they meet the following criteria: 1. Clinical requirements:(1) Males and females aged between 18 and 70 years; (2) Independent of daily life

(modified Rankin disability scale score of 0–2) on admission or after resuscitation. 2. Radiological requirements: (1) Occlusion or severe stenosis in the main trunk of the middle cerebral artery or the internal carotid artery supraclinoid segment (MCA or /and ICA intracranial stenosis is 50% to 100%) (2) CT and MRI: No large infarction and no contrast enhancement in the infarcted area; 3. Informed consent

The exclusion criteria include: 1. Not independent in daily life (modified Rankin disability scale score of 3–5); 2. Major cerebral arterial occlusive lesions due to diseases other than atherosclerosis; 3. Malignant tumors or organ failure of the heart, liver, kidney, or lung; 4. Myocardial infarction within the past 6 months; 5. Uncontrolled diabetes mellitus showing a serumfasting blood glucose level > 300 mg/dL, or requires insulin; 6. Hypertension with a diastolic blood pressure of > 110 mmHg ;7. Artery to artery embolism; 8. Cardioembolism

2.3 Ethical approval and governmental funding

The study protocol and consent forms have been approved by the Ethics Committee of Renji Hospital (2016-143K). Furthermore, the trial is registered on Chinese Clinical Trial Registry with the ID number ChiCTR-IOR-16009635. The trial is to be performed in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. All informed consent was obtained from the patient legal representative[14].

2.4 Randomization and allocation concealment

Participants in each site will be randomly assigned to medical management, PTAS, and IC-EC bypass group in a 1:1:1 ratio. The randomization sequence is generated by an independent statistician who is not involved in the determination of eligibility.

2.5 treatment protocol (Fig. 1)

The eligible patients were sent to the department of neurosurgery for measurements of the rest CBF and CVR by multimodal imagine. Regional CBF was quantitatively measured more than 3 weeks after the last ischemic attacks using enhanced computed tomography perfusion (CTP) or SPECT(123I-MP). In 123I-MP SPECT and CTP with CO₂ challenge, the fixed concentration of CO₂ (5% CO₂ mixed 95% oxygen) was provided by a gas delivery system using an indicating pressure transmitters to controlled gas blender with prospective gas targeting algorithms. Before starting the scanner protocol, which allows to record for precise the resting End-tidal CO₂ (mmHg) and Paco₂(mmHg) that were measured by electrocardiograph monitoring and artery blood before and after with inhalation of CO₂ for 2 minutes. Subjects were positioned in the SPECT/CTP scanner and were asked to breath normally for 10 minutes to correct for

possible hyperventilation. ¹²³I-IMP SPECT with CO₂ challenge was performed within a week of the measurement of rest CBF. The region of interest (ROI) was designated manually in the cerebral cortex in the territory of ipsilateral MCA at the level of the anterior horn of the lateral ventricle. ROIs were also placed in bilateral cerebellar hemispheres and in the contralateral MCA territory as reference. Regional CBF was expressed as relative values (%) to normal control values of each institute obtained from volunteers free of cerebrovascular disease. CVR was calculated as follows: CVR (%) = [(CO₂ challenge CBF – rest CBF)/rest CBF] × 100. All patients were divided into two groups according to CVR as follows: A: CVR < 10%; B: CVR > 10%. And the two subgroups patients will randomly be assigned to medical management, PTAS, and IC-ECIC-EC bypass group in a 1:1:1 ratio. All treatment procedures and specific operating protocols for the management of ischemic stroke in our trial are standardized, based on current guidelines and consensus of all participating principle investigators.

Surgical intervention was microsurgical end-to-side anastomosis of a superficial temporal artery branch to a cortical branch of the middle cerebral artery. If the superficial temporal branch was unsuitable, the occipital artery could be used. For participants in the surgical group, preoperative and postoperative antithrombotic treatment was determined by the COSS neurosurgeon until they were returned to the antithrombotic treatment preferred by their physicians. Patients in the PTAS group will receive stenting when alarm symptoms are relieved after MT treatment. Participants in the nonsurgical group continued to receive the antithrombotic treatment preferred by their physicians. Target goals for risk factor control were 130/85 mm Hg for blood pressure, 100 mg/dL for low density lipoprotein cholesterol, 150 mg/dL for triglycerides, and 7% for hemoglobin A1C.

2.5 Study endpoints

Each patient was followed up for 2 years after enrollment by a pair of a neurologist and a neurosurgeon in participating institute. The primary end point is all adverse events and ipsilateral stroke recurrence at 6, 12, 24 months after the management. Neurological findings, intracranial CT/MRI, and CBF/CVR measurements were examined and reported at the time of enrollment and 6 months, 1 year, and 2 years after enrollment. Evaluation of the cognitive function and angiography were performed at the time of enrollment and 2 years after enrollment. The secondary outcomes include the National Institute of Health stroke scale (NIHSS) and the Modified Rankin Scale (MRS) at 6, 12, 24 months after the management.

2.6 Data collection

The Entry Form is used to collect baseline information including the following variables: hypertension, smoking and diabetes, clinical presentation (include the initial ischemic stroke, on admission, before treatment); neurological function (the NIHSS and MRS), vascular stenosis, timing of management,

treatment procedure, neurological condition within 72 hours after the treatment, complications during the hospitalization, follow-up imaging and the presumed reasons of death.

2.7 Follow-up and data quality

Follow-up CT perfusion (CTP) and SPECT will be taken in outpatient 6 months after treatment. All patients will be followed up after the management by a neurosurgeon using the telephone interview or in person interview. The neurosurgeon was trained before the registry and was not involved in the treatment of ischemic stroke patients. Outcomes at 6, 12 and 24 months was measured using the NIHSS and MRS. The MRS of 0–2 was identified as good outcome, and the score of 3–6 is generally as poor outcome.

All data were collected using a written case report form (CRF) and Clinical Trial Management Public platform, Neurological conditions and complications related to surgical procedure will be monitored during the whole period of follow-up. Data verification was undertaken in 20% of all cases to assess the accuracy of data recording. The monthly auditing, data quality and statistical analysis are managed by a third party who shall be responsible for notifying the principal investigator and Institutional Review Board of Renji Hospital of any issues that arise. Any serious adverse events will be reported to the Institutional Review Board. Recommendations will be forwarded to the principal investigators for a review of risk and benefit. The Institutional Review Board of the hospital shall have access to these interim results and make the final decision to terminate the trial.

2.8 Sample size and data analysis

The target number of patients included in the registry is 60, this study will enroll more than 66 eligible ischemic stroke patients in case there are about 10% of patients lost to follow-up. Data was presented as mean and standard deviation for continuous variables or frequency for categorical variables.

Significances between variables were analyzed using the t-test or Chi-square test. Association between clinical variables and outcome will be analyzed, and predictors of long-term outcome were identified using a univariate and multivariate analysis. The difference was expressed as an odds ratio (OR, with 95% confidence interval [CI]), and significance was considered if P value was <0.05.

Discussion

The current trials showed that medical management, PTAS, and IC-EC bypass can be selected for ischemic stroke patient, but which treatment is more benefit to stroke patients is not clear[4, 15]. And the present trial is designed with intent to whether multimodal and digital image evaluation for CVR can benefit to formulate the treatment strategy in adult patients with intracranial arterial stenosis or occlusion.

CVR denotes the ability of cerebral vessels to dilate or constrict in response to challenges or defined as the change in CBF in response to a vasoactive stimulus such as an increase in the arterial partial pressure of CO₂ (PaCO₂) or acetazolamide[10]. CO₂ inhalation as a physiological challenge in hemodynamic has been increasingly used in recent literature due to its potency in causing vasodilation, rapid onset and cessation of the effect, as well as recent advances in MRI-compatible gas delivery apparatus. Increased stroke risk associated with hemodynamic failure, which can be assessed with (15O-) H₂O positron emission tomography (PET) CBF measurements[16]. This gold standard technique, however, is not established for routine clinical imaging. Standardized blood oxygen-level-dependent functional MRI+CO₂ is a noninvasive and potentially widely applicable tool to assess whole-brain quantitative CVR. SPECT+CTP combined with CO₂ challenge enables us to measure CBF and CVR, which represent the degree of hemodynamic failure[17, 18]. We examined the agreement between the various imaging modalities and hypothesized that quantitative CVR can be a surrogate imaging marker to assess hemodynamic failure.

CVR is a metric of the compensatory ability of the cerebral blood vessels, enables us to assess the extent of hemodynamic compromise and the ensuing risk of recurrent ischemic stroke. The present study, accurately evaluate the CVR for ischemic stroke patients by multimodal MRI, CT or SPECT, and would explore the recurrence of ischemic stroke after treatment, so as to develop a new method for individualized accurate diagnosis and treatment of ischemic stroke[9, 19, 20]. It has some novel features in study design compared to other major ischemic stroke trials. Firstly, the CVR of the ischemic stroke patients is evaluated by multimodal imagine digital because recent studies suggest that PET; SPECT; CTP and MRI were widely applicable tool to assess whole-brain quantitative CVR. Some studies reported that SPECT is more sensitive than PET in evaluation of CBF and cerebral perfusion, but its spatial resolution is lower[21, 22]. However; MR perfusion and CT perfusion can also be used to analyze the changes of CVF and CBV to calculate the necrotic area and penumbra of cerebral ischemic tissue. Therefore, multimodal image can compensate for each other and more accurate evaluation of changes in CVR.

Secondly, our study trial categorized the eligible patients to medical management, PTAS, and IC-EC bypass group in a 1:1:1 ratio based on rest CBF and CVR. Our former study showed that different treatment strategy for ischemic stroke patient depend on artery stenosis; but have rare clinical trial pay attention on clinical management depend on CVR was evaluated by multimodal imagine digital.

Finally, the trial records all the detailed information about the changes of CVR before and after treatment in three groups by multimodal imagine. The adverse events during follow-up period are collected and categorized into ipsilateral stroke recurrence and all adverse events. We think that such data are useful to analyze the effect of relevant confounding factors.

Our trial will be able to answer the question “does the treatment strategy depend on CVR was effectively and safely and can improve the outcome in patients with intracranial arterial stenosis or occlusion?” Considering the great challenge in performing a clinical trial in ischemic stroke, it probably requires an

extremely high level of input in the coming years. However, due to the high incidence, poor outcomes and huge burden of ischemic stroke disease, the effort can be quite rewarding and the results will surely provide more evidence for the clinical quality of the diagnosis and treatment of ischemic stroke, reduce the mortality and disability, also reduce the burden of patients and society.

Trial status

This protocol is version 1, dated 12 May 2019. Recruitment began on 6 June 2018. We planned to achieve the recruitment target by September 2020.

Abbreviations

CVR: Cerebrovascular reserve **PTAS:** Percutaneous transluminal angioplasty and stenting

CBV:cerebral blood volume **CTP:** computed tomography perfusion

MRI: Magnetic Resonance Imaging **PET:** Positron Emission Tomography

SPECT: single photon emission computed tomography

MCA:Middle cerebral artery **ICA:**Internal cerebral artery

IC-EC: Intracranial and extra-cranial

Declarations

Acknowledgements

The authors express their gratitude to all members of the Clinical Research Center for their input for this study

Funding

This was funded by Shanghai Shen Kang Hospital Development Center Research Program(16CR2048B and 16CR2045B).

Availability of data and materials

Not applicable.

Authors' contributions

XZP, JK, LY, WJQ, PYH, JYC and ZXH designed the study and the protocol. XZP and JK wrote the manuscript. JYC and ZXH revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol and consent forms have been approved by the Ethics Committee of Renji Hospital (2016-143K). Informed consent will be obtained from all patients enrolled in the study.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Disclosures

No conflict of interest exists in the submission of this manuscript. All the authors listed have approved the manuscript that is enclosed.

Consent for publication

The study was done after agreement from the Renji Hospital Ethics Committee and with the patients' informed consent..

References

- [1]. Pandian, J.D., et al., Prevention of stroke: a global perspective. *Lancet*, 2018. 392(10154): p. 1269-1278.
- [2]. Donnan, G.A., et al., Stroke. *Lancet*, 2008. 371(9624): p. 1612-23.
- [3]. Kataoka, H., et al., Results of Prospective Cohort Study on Symptomatic Cerebrovascular Occlusive Disease Showing Mild Hemodynamic Compromise [Japanese Extracranial-Intracranial Bypass Trial (JET)-2 Study]. *Neurol Med Chir (Tokyo)*, 2015. 55(6): p. 460-8.
- [4]. Derdeyn, C.P., et al., Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet*, 2014. 383(9914): p. 333-41.
- [5]. Liu, P, J.B. De Vis and H. Lu, Cerebrovascular reactivity (CVR) MRI with CO₂ challenge: A technical review. *Neuroimage*, 2019. 187: p. 104-115.

- [6]. Gupta, A., et al., Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke*, 2012. 43(11): p. 2884-91.
- [7]. Smeling, D.P., et al., Arterial Spin Labeling and Blood Oxygen Level-Dependent MRI Cerebrovascular Reactivity in Cerebrovascular Disease: A Systematic Review and Meta-Analysis. *Cerebrovasc Dis*, 2016. 42(3-4): p. 288-307.
- [8]. Chen, D.W., et al., Assessment of the Cerebral Hemodynamic Benefits of Carotid Artery Stenting for Patients with Preoperative Hemodynamic Impairment Using Cerebral Single Photon Emission Computed Tomography (SPECT) and Carbon Dioxide Inhalation. *Med Sci Monit*, 2018. 24: p. 5398-5404.
- [9]. Boudiaf, N., et al., BOLD fMRI of cerebrovascular reactivity in the middle cerebral artery territory: A 100 volunteers' study. *J Neuroradiol*, 2015. 42(6): p. 338-44.
- [10]. Choksi, V., et al., Transient neurologic deficit after acetazolamide challenge for computed tomography perfusion imaging. *J Comput Assist Tomogr*, 2005. 29(2): p. 278-80.
- [11]. De Bortoli, M., et al., [Cerebral vasoreactivity: Concordance of breath holding test and acetazolamide injection in current practice: 20 cases of asymptomatic carotid artery stenosis]. *J Med Vasc*, 2017. 42(5): p. 272-281.
- [12]. Seo, H.J., et al., Hemodynamic Significance of Internal Carotid or Middle Cerebral Artery Stenosis Detected on Magnetic Resonance Angiography. *Yonsei Med J*, 2015. 56(6): p. 1686-93.
- [13]. Thomas, B.P., et al., Physiologic underpinnings of negative BOLD cerebrovascular reactivity in brain ventricles. *Neuroimage*, 2013. 83: p. 505-12.
- [14]. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*, 2013. 310(20): p. 2191-4.
- [15]. Al, H.M. and R. Murugan, Stenting versus aggressive medical therapy for intracranial arterial stenosis: more harm than good. *Crit Care*, 2012. 16(3): p. 310.
- [16]. Gruner, J.M., et al., Brain perfusion CT compared with ¹⁵⁰H₂O-PET in healthy subjects. *EJNMMI Res*, 2011. 1(1): p. 28.
- [17]. Muscas, G., et al., Feasibility and safety of intraoperative BOLD functional MRI cerebrovascular reactivity to evaluate extracranial-to-intracranial bypass efficacy. *Neurosurg Focus*, 2019. 46(2): p. E7.
- [18]. Taneja, K., et al., Evaluation of cerebrovascular reserve in patients with cerebrovascular diseases using resting-state MRI: A feasibility study. *Magn Reson Imaging*, 2019. 59: p. 46-52.
- [19]. Sebok, M., et al., BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis. *Neurology*, 2018. 91(14): p. e1328-e1337.

- [20]. Fierstra, J., et al., Staging Hemodynamic Failure With Blood Oxygen-Level-Dependent Functional Magnetic Resonance Imaging Cerebrovascular Reactivity: A Comparison Versus Gold Standard ((15)O)-H₂O-Positron Emission Tomography. *Stroke*, 2018. 49(3): p. 621-629.
- [21]. Choi, J.W., et al., Neural Correlates of Motor Recovery Measured by SPECT at Six Months After Basal Ganglia Stroke. *Ann Rehabil Med*, 2017. 41(6): p. 905-914.
- [22]. Eicker, S.O., et al., A comparative study of perfusion CT and 99m Tc-HMPAO SPECT measurement to assess cerebrovascular reserve capacity in patients with internal carotid artery occlusion. *Eur J Med Res*, 2011. 16(11): p. 484-90.

Figures

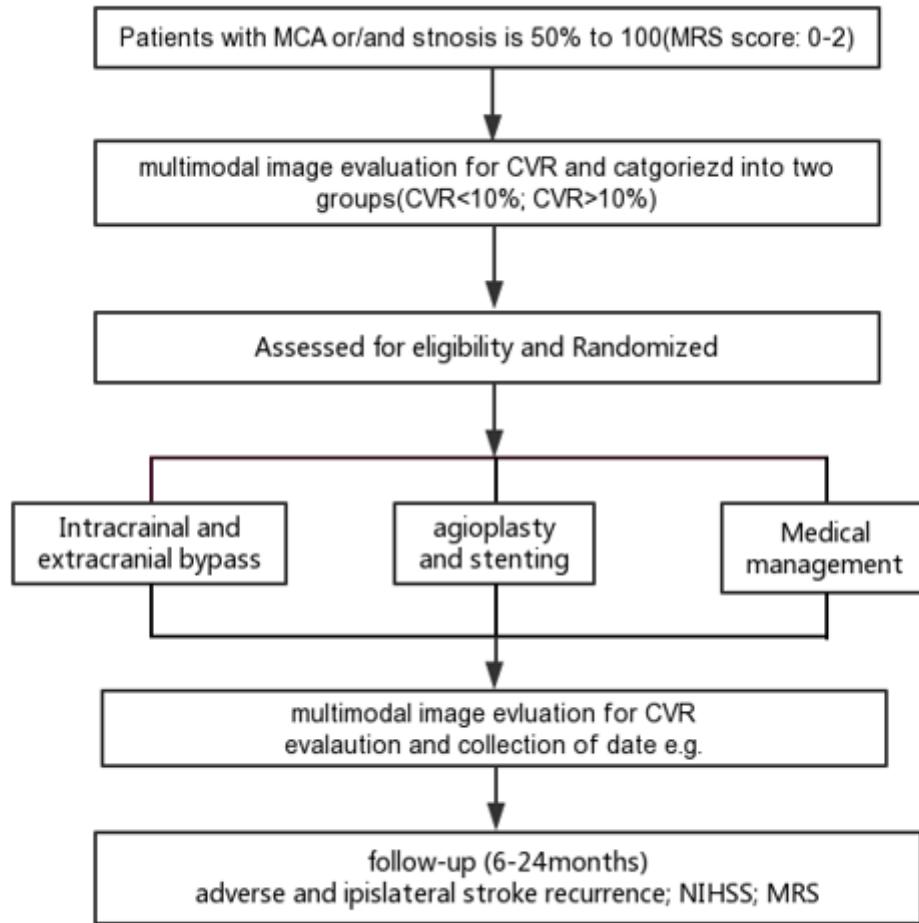


Figure 1

Study flowchart of our trial

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.pdf](#)