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Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis (BASIS): protocol of a prospective, multicentre, randomised, controlled trial

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ABSTRACT

Background The superiority of balloon angioplasty plus aggressive medical management (AMM) to AMM alone for symptomatic intracranial artery stenosis (sICAS) on efficacy and safety profiles still lacks evidence from randomised controlled trials (RCTs).

Aim To demonstrate the design of an RCT on balloon angioplasty plus AMM for sICAS.

Design Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis (BASIS) trial is a multicentre, prospective, randomised, open-label, blinded end-point trial to investigate whether balloon angioplasty plus AMM could improve clinical outcome compared with AMM alone in patients with sICAS. Patients eligible in BASIS were 35–80 years old, with a recent transient ischaemic attack within the past 90 days or ischaemic stroke between 14 days and 90 days prior to enrolment due to severe atherosclerotic stenosis (70%–99%) of a major intracranial artery. The eligible patients were randomly assigned to receive balloon angioplasty plus AMM or AMM alone at a 1:1 ratio. Both groups will receive identical AMM, including standard dual antiplatelet therapy for 90 days followed by long-term single antiplatelet therapy, intensive risk factor management and life-style modification. All participants will be followed up for 3 years.

Study outcomes Stroke or death in the next 30 days after enrolment or after balloon angioplasty procedure of the qualifying lesion during follow-up, or any ischaemic stroke or revascularisation from the qualifying artery after 30 days but before 12 months of enrolment, is the primary outcome.

Discussion BASIS trail is the first RCT to compare the efficacy and safety of balloon angioplasty plus AMM to AMM alone in sICAS patients, which may provide an alternative perspective for treating sICAS.

Trial registration number NCT03703635; https://www.clinicaltrials.gov.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Optimal treatment for patients with symptomatic intracranial artery stenosis (sICAS), especially those accompanied by haemodynamic compromise, remains unclear.

WHAT THIS STUDY ADDS

⇒ Balloon angioplasty alone may be another feasible treatment option for sICAS for lower rates of perioperative complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis trial aims to explore whether balloon angioplasty plus aggressive medical management (AMM) is superior to AMM alone for sICAS patients.

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is a main aetiology of stroke worldwide, which is associated with stroke recurrence, substantial morbidity and mortality, accounting for up to 50% of ischaemic strokes in south and east Asia.[1] Although receiving treatment with aspirin and standard medical management of vascular risk factors, patients with symptomatic ICAS (sICAS) still had as high as 23% at a 1-year stroke recurrence rate.[2 3] Therefore, how to prevent stroke recurrence and death in patients with sICAS is a global major issue. Currently, treatment options for sICAS include aggressive medical management (AMM), balloon angioplasty and stenting (balloon angioplasty plus stenting); however, the optimal treatment for sICAS remains unclear.

SAMMPRIS (Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) and VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trials have shown high perioperative complication rates and no significant advantage of endovascular stents compared with AMM in the long term.[4 5] However, the CASSISS (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis)

trial reported that stenting by experienced operators did not add additional risks of stroke and death within 30 days to AMM for sICAS, although it failed to demonstrate a benefit by stenting.[6] As lower rates of short-term stroke or mortality (peri-procedural or mean follow-up ≤3 months) were found in balloon angioplasty than stenting,[7] balloon angioplasty alone may be a feasible alternative treatment to stenting for sICAS treatment. Moreover, several previous meta-analyses also proved the safety and efficacy of balloon angioplasty for sICAS, which suggested that balloon angioplasty alone may be potentially promising for sICAS.[8–10]

To date, limited evidence is available from randomised controlled trials (RCTs) to determine the safety and efficacy of balloon angioplasty for patients with sICAS. Hence, we designed the Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis (BASIS) RCT to explore whether balloon angioplasty plus AMM is superior to AMM alone in patients with sICAS.

METHODS

Hypothesis

Balloon angioplasty combined with AMM may be superior to AMM alone in patients with sICAS.

Design and patient population

BASIS trial is an investigator-initiated, multicentre, prospective, randomised, open-label, blinded endpoint trial that plans to enrol 512 patients with a 3-year follow-up, including a neurovascular imaging examination (digital subtraction angiography (DSA), CT angiography (CTA) or magnetic resonance angiography (MRA)) at 1 year after enrolment. Patients with sICAS (defined as a recent transient ischaemic attack (TIA) or ischaemic stroke attributed to a 70%–99% atherosclerotic stenosis of a major intracranial artery) determined by DSA and conform to the inclusion/exclusion criteria of BASIS trial will be considered for enrolment at 31 comprehensive stroke centres across China (online supplemental table 1). The ethics committee of each participating centre approved the BASIS trial study protocol. The inclusion and exclusion criteria are listed in table 1.

Randomisation

BASIS trial used an interactive web response system (IWRS) for central randomisation stratified by study centres. After inputting eligible patients' necessary information into the web-based system, the researchers in each centre will obtain a random code as well as the corresponding group allocation information from the IWRS. Eligible patients will be randomly, at a 1:1 ratio, assigned to the following one treatment group (figure 1).

- Experimental group: patients with sICAS will undergo balloon angioplasty plus AMM.
- Control group: patients with sICAS will undergo AMM alone.

Intervention

Endovascular treatment

Antithrombotic protocol

Preprocedure

All patients who are scheduled to undergo balloon angioplasty should receive dual antiplatelet therapy (aspirin 100 mg per day and clopidogrel 75 mg per day) for ≥3 days prior to the procedure.

Intraprocedure

Intravenous anticoagulant such as heparin during the procedure.

Postprocedure

Aspirin 100 mg per day must be used throughout the follow-up duration, and clopidogrel 75 mg per day or ticagrelor 90 mg two times per day must be used for 90 days after randomisation.

Anesthesia strategy and arterial access

The procedure should be performed under general anaesthesia. Femoral artery access is recommended (radial artery access is allowed for patients with tortuosity of the aortic arch or aorta abdominals).

Procedure steps

1. A stable vascular access with a long sheath or guiding catheter (an intermediate catheter is recommended for participants with tortuous access), which should be placed as distal as possible, is suggested to provide adequate support for performing the balloon angioplasty. Collateral status assessment based on a whole brain DSA is recommended before balloon angioplasty according to ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology) collateral flow grading system (poor collateral: ASITN/SIR <3).[11]
2. A 0.014-inch microwire with a microcatheter or not passes through the lesion to reach the distal branch of the target artery.
3. The microwire guides a balloon to the lesion of the target artery (the Neuro RX and Neuro LPS Intracranial Balloon Dilation Catheter (Sinomed, Tianjin, China) is recommended).
   Balloon size selection: balloon length should cover the lesion completely and cover at least 2 mm beyond each end of the lesion. The balloon diameter is determined according to surgeon's opinion (submaximal angioplasty is suggested: balloon with a diameter no more than 70% of the proximal artery diameter).
4. The balloon should be slowly inflated to the nominal pressure and maintain this pressure for 10–30 s before deflating slowly. This step can be repeated 2–3 times if the dilation effect of balloon angioplasty is not satisfactory. For patients with extremely severe stenosis, a relatively smaller balloon can be used for predilation.

Table 1 Inclusion and exclusion criteria of BASIS trial

Inclusion criteria
(1) 35–80 years old.
(2) Primary or recurring sICAS patients defined as a recent TIA within the past 90 days or ischaemic stroke between 14 days and 90 days prior to enrolment caused by severe atherosclerotic stenosis (70%–99%) of a major intracranial artery, who underwent at least one antithrombotic drug and/or standard vascular risk factors medical management.
(3) Severe atherosclerotic stenosis (70–99% according to WASID method diagnosed by DSA with≤10 mm-lesion length, ≥1.5 mm diameter, and normal distal artery occurs in a major intracranial artery including terminal internal carotid artery (ICA) C4-C7 segments, middle cerebral artery (MCA) M1 segment, basilar artery (BA), and vertebral artery (VA) V4 segment. (Whether the patient is enrolled in BASIS depends on the investigator's judgement of the patient's situation with respect to the curvature and angle of the lesion).
(4) Patients or their legally authorised representatives signed the informed consent before enrollment in the study.
Exclusion criteria
(1) The patient who plans to undergo more than three-grade surgery in the next 90 days or underwent surgery in the last 30 days.
(2) In the last 24 hours prior to enrolment, the patient received thrombolysis treatment.
(3) In the last 24 hours prior to enrolment, the patient suffered neurological deficits worsened.
(4) In the last 14 days prior to enrolment, the patient with acute ischaemic stroke onset.
(5) In addition to the lesion artery and its supplying artery, other intracranial arteries with 70%–99% stenosis.
(6) More than 50% stenosis of the supplying artery of the lesion artery (eg, MCA severe stenosis (lesion artery) with more than 50% stenosis of ipsilateral ICA (supplying artery) should be excluded; BA severe stenosis (lesion artery) with more than 50% stenosis of dominant VA (supplying artery) stenosis should be excluded), non-lesion side extracranial arteries with more than 70% stenosis, and bilateral VA stenosis with more than 70% stenosis in patients with balanced VA should be excluded (cannot identify lesion VA) should be excluded. But we don't exclude that the dominant VA is the lesion artery with contralateral VA is dysplasia or slender or the contralateral VA terminating at the posteroinferior cerebellar artery.
(7) Perforator stroke (except stenotic degree >70% of supplying artery, accompanied by poor collaterals or haemodynamic compromise).[21]
(8) Pre-enrolment modified Rankin Scale (mRS) 4–6.
(9) Non-atherosclerotic diseases (eg, vascular inflammatory lesions due to infection, post-irradiation, postpartum status, sickle cell anaemia, autoimmune diseases, suspected vasospasm, moyamoya disease, fibromuscular dysplasia and arterial dissection).
(10) Lesion artery with severe calcification and close neighbour stenosis.
(11) Accompanied by intracranial aneurysms or intracranial arteriovenous malformations or intracranial tumours.
(12) In the last 90 days, the patient with intracranial haemorrhage such as intraventricular haemorrhage, epidural haemorrhage, subarachnoid haemorrhage, parenchymal haematoma or subdural haemorrhage, etc.
(13) The patient undergoing balloon angioplasty, endarterectomy or stenting for original lesion vessel or its primary supplying vessel, or planning to undergo stenting.
(14) For other diseases, the patient can not undergo dual antiplatelet therapy.
(15) The ischaemic event that is highly suspected to be due to vascular embolism from an extracranial arterial segment such as ipsilateral neck/chest arterial occlusion) or cardio embolism such as left ventricular thrombus, mitral stenosis, atrial fibrillation, myocardial infarction within 6 weeks, patent foramen ovale, etc.
(16) Tortuous arterial route unable to acquire stable arterial access.
(17) The patient who is allergy response to aspirin, contrast agents, balloon components, clopidogrel, heparin or anaesthetics.
(18) Severe liver dysfunction (ALT>3 time normal value upper limit or AST>3 time of normal value upper limit) or severe kidney dysfunction (serum creatinine>2 time normal value upper limit).
(19) Women who are pregnant or lactating.
(20) Hb<100 g/L, INR>1.5 (irreversible), platelet<100×10^9/ L, coagulation dysfunction or irreversible bleeding.
(21) The patient with radial artery, renal artery or coronary artery disease that need simultaneous interventional therapy.
(22) Life expectancy is<1 year.
(23) Due to cognitive or emotional disorders or mental illness, the patient who cannot finish the follow-up.
(24) The patient who joins other clinical trials (medical device or drug) and has not finished programme need yet.
(25) Investigators consider the patient who is not suitable for enrolling in the present trial.

Continued

Table 1 Continued

Inclusion criteria
BASIS, Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis; Hb, haemoglobin; INR, international normalized ratio; sICAS, symptomatic intracranial artery stenosis.

5. Technical success: residual stenosis ≤50% of the proximal artery diameter with modified Thrombolysis in Cerebral Infarction (mTICI)[12] of 3 grade without arterial dissection that impairs the distal blood flow.
6. Rescue stent implantation is allowed when: (1) residual stenosis ≥70% after balloon dilation or the antegrade flow is unstable (mTICI <2b); (2) arterial dissection impairing the distal blood flow (mTICI <2b); (3) development of thrombosis or embolisation that jeopardises distal perfusion. Other measures such as intravenous/intraarterial thrombolysis, infusion of glycoprotein IIb/IIIa inhibitors, are based on the surgeon's experience, which can be used alone or in combination with rescue stenting.
7. A final DSA should be performed after 10–15 min of observation.

Aggressive medical management

Antiplatelet treatment

AMM will be identical in both arms. All the necessary blood and imaging tests are precollected in the screening period before randomisation for the following management of risk factors. Both arms are prescribed with an AMM regime (includes aspirin 100 mg per day throughout the follow-up duration and clopidogrel 75 mg per day for the first 90 days after enrollment). For the record: clopidogrel can be replaced with ticagrelor or cilostazol with appropriate dosage for patients with clopidogrel resistance (platelet aggregation rate of ADP >40% or loss-of-function alleles of CYP2C19 is detected).

Risk factors management

Neurologists and study investigators at each site will be responsible for the management of patients' risk factors. They receive training on risk factors management according to Chinese Stroke Association guidelines for the clinical management of cerebrovascular disorders.[13] All study investigators are regularly trained according to BASIS protocol every 6 months. If a patient fails to reach the target, a face-to-face follow-up with the local neurologist to modify their medical regime will be necessary.

Blood pressure management

Blood pressure will be checked at screening, randomisation, discharge, 30 days, 90 days, 180 days, 1 year and the end of the trial. Patients may need to visit local sites for blood pressure measurement and medical regime modification if necessary. The target blood pressure is no more than 140 mm Hg/90 mm Hg for patients without diabetes mellitus (DM) and no more than 130 mm Hg/80 mm Hg for patients with DM. Antihypertensive drugs include angiotensin-converting enzyme inhibitor (lisinopril 10 mg or 40 mg), angiotensin receptor blocker (candesartan 16 mg or 32 mg), beta-blocker (atenolol 50 mg or 100 mg), calcium channel antagonist (felodipine 5 mg or 10 mg), diuretic, vasodilator (hydralazine 50 mg), etc.

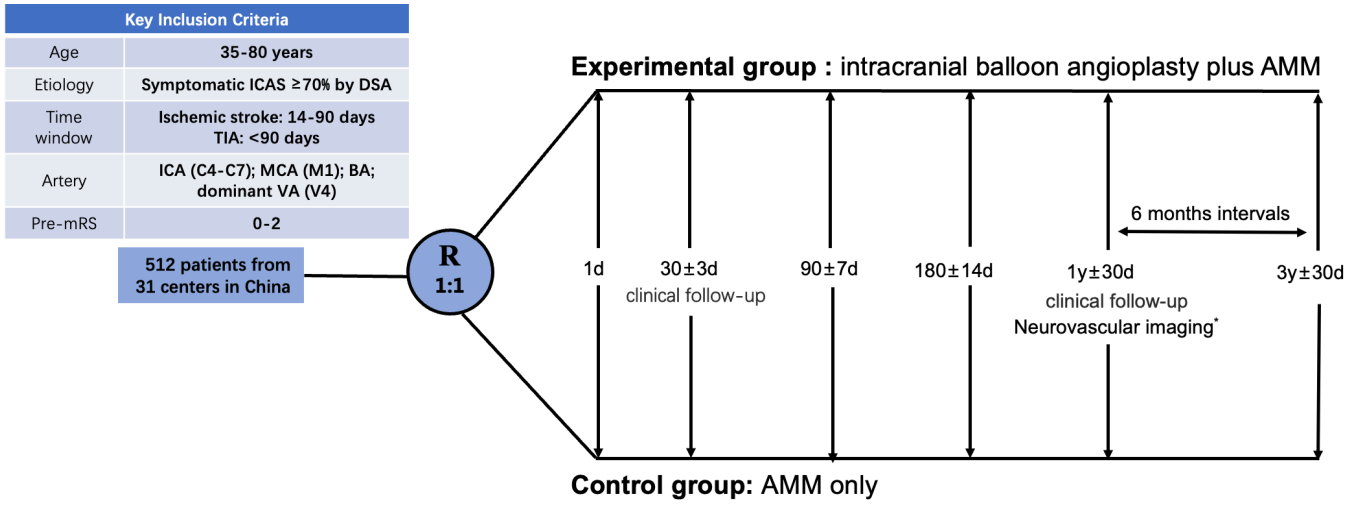

Figure 1 The flowchart of BASIS trial. *Neurovascular imaging includes digital subtraction angiography (DSA), CT angiography (CTA) or magnetic resonance angiography (MRA). AMM, aggressive medical management; BA, basilar artery; BASIS, Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis; ICA, internal carotid artery; MCA, middle cerebral artery; TIA, transient ischaemic attack; VA, vertebral artery.

Achieving target LDL cholesterol

The baseline serum low-density lipoprotein cholesterol (LDL-c) level is recorded before enrolment. The target LDL-c level is <1.8 mmol/L or 70 mg/dL. If the patient's LDL level is higher than the target level, he/she should modify the lipid-lowering drugs. Liver enzyme (Aspartate aminotransferase/Alaninetransaminase) levels will be measured at the beginning of the study and at each visit point.

Non-HDL cholesterol

The target level of nonhigh-density lipoprotein (HDL) cholesterol is <100 mg/dL. Non-HDL cholesterol includes low-density lipoproteins (LDL), very-low-density lipoproteins and intermediate-density lipoproteins. When a larger statin dosage fails to lower LDL level, while non-HDL cholesterol ≥100 mg/dL and triglycerides ≥200 mg/dL, other lipid-lowering drugs in addition to statin are recommended, such as ezetimibe or PCSK9 inhibitors.

Diabetes management

The target of DM management is to achieve HbA1c<7.0%. Fasting plasma glucose and HbA1c levels will be measured at baseline, 30 days, 90 days, and 1 year.

Lifestyle modification

Smoking cessation: investigators at each site will evaluate smoking status at each follow-up and encourage all subjects to quit smoking as soon as possible.

Weight management: investigators at each site will evaluate the weight according to body mass index.

Activity level: activity level for each patient is also assessed at each follow-up by trained investigators or coordinators, and moderate exercise of 30 minutes a day, three times per week is strongly recommended to all patients with athletic ability.

Follow-up schedule

All the participants will be followed up by the on-site neurologists at baseline, the day of DSA, discharge, 30±7 days, 90±7 days, 6 months±14 days, 1 year±30 days and up to 3 years (at 6 months intervals after 1 year). Follow-up visits will be conducted by telephone at 6-month and post-1-year period and will be evaluated in person at other visits. At each follow-up visits, the participants' medications, laboratory tests, risk factors management (as described above) and possible adverse event (AEs)/endpoints are reviewed by experienced neurologist and/or neurointerventionalist. All patients are required to undergo a neurovascular imaging examination including DSA, CTA or MRA at 1-year follow-up. Table 2 shows the complete study assessment schedule.

Study outcomes

Primary outcome

Stroke or death in the next 30 days after enrolment or after balloon angioplasty procedure of the qualifying lesion during follow-up or any ischaemic stroke or revascularisation from the qualifying artery after 30 days but before 12 months of enrolment. We defined ischaemic stroke as a new focal, sudden onset neurologic deficit, which is confirmed on brain NCCT or MRI. We define symptomatic intracranial haemorrhage as subarachnoid, parenchymal or intraventricular haemorrhage identified on brain MRI or NCCT, which leads to new neurologic symptoms (consciousness level change, headache or focal neurologic symptoms), lasting over 24 hours or a seizure. If symptomatic intracranial haemorrhage occurs in the next 30 days after enrolment or in the next 30 days after the balloon angioplasty during follow-up, we will consider it as a primary outcome. Revascularisation of the culprit artery will be considered a primary outcome if it occurs from 30 days though 12 months after enrolment and fulfils one of the following requirements:

1. Acute revascularisation: acute culprit artery occlusion accompanied by neurological deficit, requiring intravenous thrombolysis, intraarterial thrombolysis, mechanical thrombectomy or balloon/stent angioplasty (including intracranial–extracranial bypass grafting operations).
2. Selective revascularisation: neurologic symptom-driven selective revascularisation, including balloon angioplasty or stent implantation (including intracranial–extracranial bypass grafting operations), if the participants fulfil one of the following conditions:
   1. Ischaemic stroke caused by the culprit artery stenosis: a new focal neurological deficit of sudden onset attributed to the territory of the culprit artery, which is confirmed as a recurrent stroke on brain CT or MRI (follow-up imaging will be compared with baseline imaging for the detection of new lesions).
   2. Culprit artery stenosis that causes recurrent transient ischaemic attack lasting longer than 10 min or new disabling neurological symptoms (paroxysmal limb weakness/numbness, inarticulateness, diplopia or dyspraxia) compared with the baseline qualifying symptoms. All symptoms must be detected after 1 month of AMM (as described above).

Secondary outcomes

1. Any stroke (ischaemic or haemorrhagic stroke) or death due to any cause in the next 1 month after enrolment or after balloon angioplasty of the qualifying lesion during follow-up.
2. Any stroke (ischaemic or haemorrhagic stroke) within the lesion arterial territory or death from any cause in the next 3 months after enrollment.
3. Any stroke (ischaemic or haemorrhagic stroke) that occurs beyond the lesion arterial territory in the next 3 months after enrolment.
4. Modified Rankin Scale (mRS) at 3 months.
5. Any stroke (ischaemic or haemorrhagic stroke) within the lesion arterial territory or death from any cause in the next 1 year after enrollment.
6. Lesion arterial revascularisation in the next 1 year after enrollment.

Table 2 Assessment schedule

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 Telephone interview	Visit 7	Follow-up 1 year to 3 years (Visit 8, 9, 10, 11)
Assessment	**Baseline15 days ~ 0 day**	**Angiogram 0 day**	**Discharge**	**30 days±7 days**	**90 days±7 days**	**6 months±14 days**	**1 year±30 days**	**6 months intervals**
Informed consent	√							
Inclusion/exclusion criteria check	√							
History and physical examination	√							
Vital signs*	√	√	√	√	√		√	
Blood laboratory test† and urine routine test	√		√	√	√		√	
Coagulation function‡	√							
FBG, HbA1c§	√			√	√		√	
Platelet aggregation test and/or CYPC219 genotype test¶	√							
ECG	√							
MRI/CT	√						√	
CTP**	√				√		√	
DSA/CTA/MRA	√						√	
Life-style modification review††	√		√	√	√	√	√	√
mRS	√			√	√	√	√	√
NIHSS (neurological examination) examination)	√		√		√		√	
EQ-5D	√						√	√
MoCA¶	√						√	√
HR-VWI,TCD¶	√						√	
Medication review and patient compliance survey		√	√	√	√		√	
AE, SAE and endpoints‡‡	√	√	√	√	√	√	√	√

*Vital signs: body temperature, blood pressure, respiration rate, heart rate.
†Blood laboratory test includes blood routine and biochemistry examinations, hepatic and renal function tests.
‡Coagulation function: PT, APTT, TT, FIB, INR.
§HbA1c is an optional inspection but is recommended for patients with diabetes mellitus.
¶Platelet aggregation test, CYPC219 genotype test, MoCA, HR-VWI and TCD test are optional according to the actual situation of the centre.
**CTP is an optional inspection, but is recommended for patients with haemodynamic compromise, poor collateral or perforator stroke.
††Life-style modification review: including whether to smoke and the number of cigarettes per day; Weight: reflect the patient's weight control through the patient's weight and BMI; Exercise: number of exercises per week and duration of each exercise.
‡‡After 1 year of follow-up, follow-up will focus on AE, SAE and endpoint events;
AE, adverse event; CTA, CT angiography; CTP, CT perfusion; DSA, digital subtraction angiography; ECG, electrocardiograph; EQ-5D, quality-of-life EuroQol-5 Dimensions; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HR-VWI, high-resolution vessel wall imaging; INR, international normalized ratio; MoCA, montreal cognitive assessment; MRA, magnetic resonance angiography; mRS, modified Rankin scale; SAE, serious adverse event; TCD, transcranial Doppler.

7. Any stroke (ischaemic or haemorrhagic stroke) that occurs beyond the lesion arterial territory in the next 1 year after enrolment.
8. mRS at 1 year.
9. Restenosis rate of the lesion artery in the next 1 year after enrolment (defined as based on subsequent neurovascular imaging, stenotic degree >70% or increased by 30%).
10. Combined events such as myocardial infarction, stroke and vascular death in the next 1 year after enrolment.
11. EuroQol-5-Dimensions Scale questionnaire in the next 1 year after enrollment.
12. Any stroke (ischaemic or haemorrhagic stroke) within the lesion arterial territory or death from any cause in the next 2 years after enrolment.
13. Any stroke (ischaemic or haemorrhagic stroke) that occurs beyond the lesion arterial territory in the next 2 years after enrolment.
14. mRS at 2 years.
15. Combined events such as myocardial infarction, stroke and vascular death in the next 2 years after enrolment.
16. Any stroke (ischaemic or haemorrhagic stroke) within the lesion arterial territory or death from any cause in the next 3 years after enrolment.
17. Any stroke (ischaemic or haemorrhagic stroke) that occurs beyond the lesion arterial territory in the next 3 years after enrolment.
18. mRS at 3 years.
19. Combined events such as myocardial infarction, stroke and vascular death in the next 3 years after enrolment.

Assessment of AEs

We defined AE as the presence of all unexpected medical conditions during or after being treated with medical devices. It includes symptoms, signs or abnormal laboratory parameters that can be unrelated to treatment. We define severe AE as an AE meeting at least one criterion as follows: lead to death; need hospitalisation or extend the existing hospitalisation time; life-threatening; lead to serious disability or need medical intervention to prevent one of the above-mentioned outcomes. If a potential endpoint occurs, the committee board meeting will be convened to evaluate whether such an event can be categorised as the primary endpoint.

Data safety and monitoring board

An independent statistician and academic members consist of the data safety and monitoring board (DSMB) of the BASIS trial. DSMB is scheduled to have meetings annually to review the study progress to make sure that the trial is consistent with the standards of ethics and to guarantee all enrolled patients' safety. After every DSMB meeting, a report including all recommendations will be generated by the DSMB members and handed to the steering committee immediately after the meeting.

Sample size

According to VISSIT trial and a previous randomised trial in China, the composite event rate of the primary outcome in the control group is anticipated to be 15%.[4 14] As to the balloon angioplasty group, we assume a 7% of the primary outcome based on studies of angioplasty without stenting[9 15] and investigators' clinical practice experience in China. As a result, the sample size needs to detect an 8% absolute difference. A total of 512 patients (256 per group) will be enrolled considering an 80% statistical power at a one-sided α of 2.5% and a 10% dropout rate.

Statistical analyses

The composite event rates and corresponding 95% CIs of the primary outcome in the two treatment groups will be estimated by Kaplan-Meier survival analysis and compared by log-rank test. We will perform a Cox proportional hazards regression model to calculate the HR between the two groups and its 95% CI. Time-to-event endpoints of secondary outcomes will also be analysed by Kaplan-Meier survival analysis and Cox regression, and common ORs of mRS will be estimated using ordinal logistic regression. The widths of the intervals will not be adjusted for multiplicity for secondary outcomes. The main analysis of this study will be conducted based on intention-to-treat principle, and a per-protocol analysis will also be conducted as a sensitivity analysis. Subgroup analyses on the primary outcome will be performed in the following subgroups: age (<65 years old vs ≥65 years old), sex (men vs women), hypertension (yes vs no), DM (yes vs no), smoking (yes vs no), baseline renal function (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 vs eGFR≥60 mL/min/1.73 m^2), target vessel stenosis degree (<80% vs ≥80%), body mass index (<25 Kg/m^2 vs 25–30 Kg/m^2 vs ≥30 Kg/m^2), hypoperfusion (yes vs no), lesion location (anterior circulation vs posterior circulation) and mechanism (ischaemic stroke vs TIA). We will use SAS software, V.9.4 (SAS Institute) to conduct all analyses. Detailed statistical methods, missing data imputation and subgroup analyses are described in the statistical analysis plan.

Study organisation

Twice a year, the steering committee will meet to oversee the trial and provide strategic guidance. Periodically, the clinical research team of the leading centre will meet online with the project team of the clinical research organisation to review the trial progress and data monitoring each week. An independent clinical events adjudication committee will ensure that defined outcomes are reported and judged uniformly using the same definition by experts who are blinded to the treatment status (online supplemental table 2).

Core lab and quality assurance

Imaging will be adjudicated by an independent neuroimaging core laboratory (China National Clinical Research Center for Neurological Diseases, Tiantan Neuroimaging

Center of Excellence). We will collect, transport and persevere all blood samples and imaging data according to the study protocol. The diagnosis of sICAS and regional hypoperfusion that is attributed to the target artery will be blindly assessed by experienced neuroradiologists and neurologists (over 10-year working experience). To make sure that the collected data reveal what is illustrated in the protocol, each subcentre of the BASIS trial will be regularly scrutinised, and by comparing data in the Electronic Data Capture System and data in the original documents (case report form vs source documents) to confirm data consistency. If a patient develops AE/severe AE or completes a 1-year observation after receiving treatment from non-study sites, duplicate copies of the medical documents will be collected for future reviews.

DISCUSSION

Up till now, no consensus has been achieved on the optimal treatment for patients with sICAS to prevent stroke recurrence and death. The SAMMPRIS trial failed to show positive results and suggested stenting could add additional perioperative risks of stroke or death within 30 days to the AMM for sICAS patients (14.7% vs 5.8%, p=0.002).[5 16] However, in the AMM group of the SAMMPRIS trial, patients in the haemodynamic insufficiency subgroup still had as high as 37% rate of stroke recurrence.[17] As a result, the phenomenon indicates that further RCT with more rigorous patient selection and an eligible endovascular strategy with an acceptable safety and efficacy profile may be necessary for the treatment of sICAS. The subsequent VISSIT study also showed no advantage of balloon-expandable stenting over medical therapy.[4] A registry study of stenting for symptomatic intracranial artery stenosis in China reported the rate of TIA, death or stroke within 1 month after stenting for sICAS was only 4.3%, which may suggest the safety of stenting for sICAS in real-world practice.[18] Eleven years after SAMMPRIS, the CASSSIS study reported that stenting plus AMM had a similar effect on preventing stroke and death with AMM alone in patients with sICAS (8.0% vs 7.2%, p=0.82).[6]

Patients with sICAS, especially those accompanied by haemodynamic disorders, not only have a high risk of recurrent stroke but may also be associated with cognitive decline.[19] For such patients, it is necessary to identify safer and more effective revascularisation methods to improve blood flow and further reduce stroke recurrence. Balloon angioplasty alone may be another feasible treatment option for sICAS due to its easy operation and lower rates of perioperative morbidity and mortality.[7] Three recent meta-analyses all suggested that submaximal balloon angioplasty may be a potentially promising intervention for sICAS.[8–10] However, compared with medical therapy, the long-term effectiveness of balloon angioplasty, including recurrent stroke and restenosis of target vessels, is still unknown.

Therefore, we designed the BASIS trial to investigate a new perspective on endovascular treatment for sICAS. BASIS trial has several unique aspects that may contribute to previous clinical trials and cohort studies. First, unlike previous trials, balloon angioplasty (submaximal angioplasty and slow inflation/deflation of the balloon are recommended) alone is performed in the experimental group instead of balloon angioplasty plus stenting; and a 1-year neurovascular imaging follow-up is used to assess its long-term efficacy. Second, before the BASIS trial, our centre conducted a prospective, multicentre registry study of stenting for symptomatic intracranial artery stenosis in China,[20] which helped us screen the comprehensive centres with rich experience in angioplasty to ensure consistency in performing the procedure in the BASIS trial. Finally, stricter patient selection criteria and preprocedure assessments will be conducted in the BASIS trial, such as perfusion imaging or collateral assessment. Participants with perforator stroke will fulfil the inclusion criteria only with simultaneous perfusion compromise and poor collateral duo to the culprit stenosis.

CONCLUSIONS

BASIS trial will provide objective evidence on whether balloon angioplasty plus AMM is superior to AMM alone in patients with sICAS, which may propose an alternative perspective for treating sICAS.

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Contributors ZM, YW and YW designed the study; XS, MY and DS drafted the manuscript; GP, YD, XZ, LL, NM, FG, DM and WY provided critical comments/revisions of the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of Beijing Tiantan Hosptial and corresponding branch centres. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

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Supplemental Table 1. List of Basis site

Basis site	Investigator
Beijing Tian Tan Hospital, Capital Medical University	Zhongrong Miao
Beijing Tian Tan Hospital, Capital Medical University	Yilong Wang
The Affiliated Hospital of Qingdao University	Yong Zhang
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	Yun Xu
Henan Provincial People's Hospital	Tianxiao Li
The Second Affiliated Hospital of Guangzhou Medical University	Yunxiang Ji
Beijing Luhe Hospital,Capital Medical University	Xiaokun Geng
The First Hospital of Jilin University	Shouchun Wang
Qilu Hospital of Shandong University	Wei Wu
Hunan Provincial People's Hospital	Xiaoping Gao
The First Affiliated Hospital,Sun Yat-sen University	Jinsheng Zeng
The Affiliated Hospital of Guizhou Medical University	Xin Xiang
Shandong Provincial Hospital	Yifeng Du
General Hospital of The Northern Theater of The Chinese People's Liberation Army	Huisheng Chen
Guangdong Sanjiu Brain Hospital	Peiming Wang
Shenzhen Hospital of Southern Medical University	Yajie liu
West China Hospital Sichuan University	Hongbo Zheng
Wuhan NO.1 Hospital	Wenhua Liu
The First Affiliated Hospital of Anhui Medical University	Weimin Yang
Jiangxi Provincial People's Hospital	Wenfeng Cao
Liaocheng People's Hospital	Guisheng Jiang
The First Affiliated Hospital of Xi'an Jiaotong University	Jianfeng Han
The First People's Hospital of Changzhou	Ya Peng
Chinese PLA General Hospital	Jun Wang
Beijing Chao-Yang Hospital, Capital Medical University	Yang Wang
The First Affiliated Hospital of Anhui University of CM	Weimin Yang
Beijing Fengtai You Anmen Hospital	Shiyong Zhang
Dongfang Hospital Beijing University of Chinese Medicine	Gesheng Wang

Basis site	Investigator
Beijing ShunYi Hospital	Liyu Wang
The Second Affiliated Hospital Of NanJing Medical University	Jin Wu
Guangdong Provincial Hospital of Traditional Chinese Medicine	Guifu Li
The Affiliated Hospital of Northwest University	Mingze Chang

Supplemental Table 2. Cooperation team of trial and Study Committee

Cooperation team	Unit or Hospital name	Investigator Name
Sponsor	Beijing Tian Tan Hospital, Capital Medical University	NA
CRO	Beijing Jingchengtong Medicine Technology Co., Ltd.	NA
Statistical analysis	Medical Statistics Office, Peking University First Hospital, Beijing, China	NA
Imaging core lab	China National Clinical Research Center for Neurological Diseases, Tiantan Neuroimaging Center of Excellence	Jing Jing
	China National Clinical Research Center for Neurological Diseases, Tiantan Neuroimaging Center of Excellence	Nan Qi
CEC team	Tangdu Hospital of Air Force Medical University	Zhenwei Zhao
	Beijing Tian Tan Hospital, Capital Medical University	Kehui Dong
	The First Affiliated Hospital of Harbin Medical University	Huaizhang Shi
DSMB	People's Liberation Army Air Force General Hospital	Jin Shi
	Strategic Support Force Specialty Medical Center	Yiling Cai
	China National Clinical Research Center for Neurological Diseases	Yuesong Pan
AE	Beijing Tian Tan Hospital, Capital Medical University	Xuan Sun
Committee	Beijing Tian Tan Hospital, Capital Medical University	Yiming Deng
	Beijing Tian Tan Hospital, Capital Medical University	Ning Ma
Steering Committee	Beijing Tian Tan Hospital, Capital Medical University	Zhongrong Miao
	Beijing Tian Tan Hospital, Capital Medical University	Yilong Wang
	Beijing Tian Tan Hospital, Capital Medical University	Yongjun Wang
	Comprehensive Stroke Center, University of California, Irvine, USA	Wengui Yu
	Beijing Tian Tan Hospital, Capital Medical University	Xingquan Zhao
	Neurovascular Imaging Research Core and Department of Neurology, University of California, USA	David S Liebeskind
	Department of Neurosurgery, Neuropsychiatric Institute, University of Illinois at Chicago, USA	Sepideh Amin-Hanjani