CASSISS TRIAL PROTOCOL

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China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial

15 # The CASSISS Trial

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Full Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS)：A prospective, multi-center, randomized controlled trial (RCT)
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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AHA	American Heart Association
ALT	Alanine transarninase
APTT	Activated Partial Thromboplastin Time
ASA	American Stroke Association
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System
AST	Aspartate aminotransferase
ATM	Atmosphere
BA	Basilar Artery
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
DSMB	Data Safety and Monitoring Board
DWI	Diffusion-weighted Imaging
ECG	Electrocardiogram
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
Cr	Creatine
CRF	Case Report Form
CRP	C-reactive protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DSA	Digital Subtraction Angiography
DAPT	Dural Anti-Platelet Therapy
DWI	Diffusion-Weighted Imaging
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EDC	Electronic Data Capture

FAS	Full Analysis Set
FBG	Fasting blood glucose
FIB	Fibrinogen
GCP	Good Clinical Practice
HDL	High-density Lipoprotein
HbA1c	Glycated Hemoglobin
ICA	Internal Carotid Artery
ICAS	IntraCranial Atherosclerotic Stenosis
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LDL	Low-density Lipoprotein
LOCF	Last Observed Carried Forward
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scales
MTT	Mean Transit Time
NIHSS	National Institute of Health Stroke Scale
PI	Principle Investigator
PPS	Per-Protocol Set
PT	Prothrombin Time
PWI	Perfusion Weighted Imaging
RCT	Randomized Control Trial
PTAS	Percutaneous Transluminal Angioplasty and Stenting
SAE	Serious Adverse Event
SIT	Stroke In the Territory of symptomatic intracranial stenosis
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding

	for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
TC	Total Cholesterol
TCD	TransCranial Doppler
TIA	Transient Ischemic Attack
TICI	Thrombolysis in Cerebral Infarction
TT	Thrombin Time
TTP	Time-to-Peak
USA	United States of America
VA	Vertebral Artery

2. SUMMARY

Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial
Objectives	To determine whether intracranial angioplasty and stenting with Gateway-Wingspan stent system adds benefit to medical therapy alone for preventing the primary outcome (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery).
Patient population	Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery.
Sample size	380 (ratio 1:1)
Intervention	Random 1:1 allocation to medical therapy alone versus medical therapy plus intracranial angioplasty and stenting with Gateway-Wingspan stent system. Superiority is prospectively defined if the stenting arm has a significantly lower stroke or death rate.
Study design	Prospective, open-label, multi-center, randomized controlled study.
Main parameters / Outcomes	Primary outcomes: • Stroke or death within 30 days after enrollment; • Stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year Secondary outcomes: • Disabling stroke or death beyond 30 days through 3 years in both arms; • Complication rates associated with stenting procedures; • Restenosis (>50%) related to stenting within a follow-up of 3 years; • Any stroke, severe TIA, or cardiovascular events within a

	follow-up of 3 years; • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index assessment within a follow-up of 3 years; • The compliance rate of patients with regular medical therapy within a follow-up of 3 years; • Death rate in both arms within a follow-up of 3 years.
Follow-up schedule	Baseline, 30-day, 1-year, 2-year, and 3-year
Statistical analysis plan	• The primary and secondary outcomes are compared between the groups using log-rank test by ITT. • An independent groups t-test or Wilcoxon rank test are used to compare the quantitative data between the groups. • Chi-square test or Fisher exact probability method is used for categorical data between the groups. • Kaplan-Meier curves is used to show the incidence of outcomes over time. • All statistical tests are performed by two-sided test. P-value less than 0.05 is considered as statistically significant. • All the analyses are performed with the use of SAS software (SAS Institute).

3. INTRODUCTION AND RATIONALE

3.1 Description of the disease

Stroke is one of the leading causes of death in China and confers a large burden and effort upon patients and health professionals.[1-3] In contrast to Western countries, intracranial atherosclerotic stenosis (ICAS) is the most common vascular lesion in patients with cerebrovascular disease, and is an important cause of ischemic stroke and future recurrent events in China.[4-7] Patients with ICAS have long been considered to be at high risk of recurrent stroke, which led to the development and wide use of percutaneous transluminal angioplasty and stenting (PTAS).[8-12]

3.2 Description of the intervention

In 2005, the Wingspan Stent system (Stryker Neurovascular, Fremont, CA, USA) was approved under a Humanitarian Device Exemption by the US Food and Drug Administration (FDA), and had been used to reduce the rate of recurrent ischemic events among patients with severe symptomatic ICAS.[13-17] However, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS trial, ClinicalTrials.gov number, NCT00576693), as the first RCT,[18] demonstrated that aggressive medical management was superior to PTAS with the Wingspan stent among patients with symptomatic severe ICAS, both because the risk of early stroke after stenting was high (14.7%) and because the risk of stroke with aggressive medical therapy alone was lower than expected (5.8%).[19]

3.3 Relevance for clinical practice

Since the SAMMPRIS trial, concerns have emerged that outcomes seen in a clinical trial setting may not be reproducible in non-RCT setting because of demonstrated more optimal surgical outcomes, less complication rates in high-volume centers, and good patient selection. The technical procedural problem rate, including guidewire- or angioplasty-related hemorrhage, could be minimized as more experienced operators overcome the learning curve for mastering the safety precautions of Wingspan stenting for ICAS.[20-22] In the post-SAMMPRIS era, several single or multi-center, registration studies in China,[23-26] suggested lower risks of intracranial stenting for ICAS than those reported for SAMMPRIS.[19]

Second, poor patient selection may increase the peri-operative risks and bias the outcome favoring medical treatment. In the stenting arm of the SAMMPRIS trial, more than 50% (115/224) of patients had a time interval

from qualifying event to randomization of less than 7 days.[19] Short interval or early stenting intervention may confer a higher risk of cerebral vascular event, including thromboembolic events, perforator stroke,[27] or even hemorrhagic transformation. Also, in the SAMMPRIS trial, 22.8% of recruited patients had perforators stroke only, and those patients may not benefit from stenting in addition to medical therapy. Ideally, stenting may be considered for eligible patients based on poor collaterals and medical futility.[28]

Third, intracranial stenting involves a trade-off between a higher short-term perioperative risk in exchange for a lower long-term risk of stroke. In the SAMMPRIS trial the stenting group, mostly due to periprocedural complication, had more disabling or fatal stroke within 30 days than that in medical group (7.1% vs 1.8%), whereas the stenting group had less disabling or fatal stroke beyond 30 days than that in medical group (2.2% vs 6.2%).[19]

The choice for ICAS treatment between medical therapy and stenting remains incompletely settled, at least for certain high-volume centers and for certain patient groups in a Chinese population. Furthermore, the recurrent stroke risk in the real world remains high despite maximal medical therapy.[29] Since the SAMMPRIS trial, an ever-increasing number of PTAS procedures surged beyond guidelines due to increased demand for ICAS treatment in China. The research community has maintained interest in tackling this important cause of stroke. Intracranial stenting with Wingspan is still awaiting a safe landing.[30,31]

3.4 Hypothesis and rationale

It may be hypothesized that the clinical superiority observed in carefully selected patients in high-volume center who received medical therapy had diminished, making stenting a more favorable treatment strategy in comparison. As compared to the design of the SAMMPRIS trial, we thus feel that there is the need for a refined randomized trial reevaluating the role of stenting for ICAS. In the CASSISS trial, patients in both treatment groups have been followed up for 3 more years to establish whether early benefit in the medical group would persist over longer follow-up, or whether the medical group would have a high incidence of late stroke that would eliminate the early efficacy gap between groups.

3.5 Objectives

3.5.1 Primary objective

To determine whether PTAS (using the Gateway PTA balloon catheter and Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical therapy is superior to medical therapy alone for preventing the primary

outcome (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or non-disabling stroke caused by 70% to 99% stenosis of a major intracranial artery).

3.5.2 Secondary objectives

To compare outcomes between groups in terms of:

- Disabling stroke or death beyond 30 days through 3 years;
- Complication rates associated with stenting procedures;
- Restenosis (>50%) related to stenting within a follow-up of 3 years;
- Any stroke, severe TIA, or cardiovascular events within a follow-up of 3 years;
- National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index assessment within a follow-up of 3 years;
- The compliance rate of the patients with regular medical therapy within a follow-up of 3 years;
- Death rate in both arms within a follow-up of 3 years.

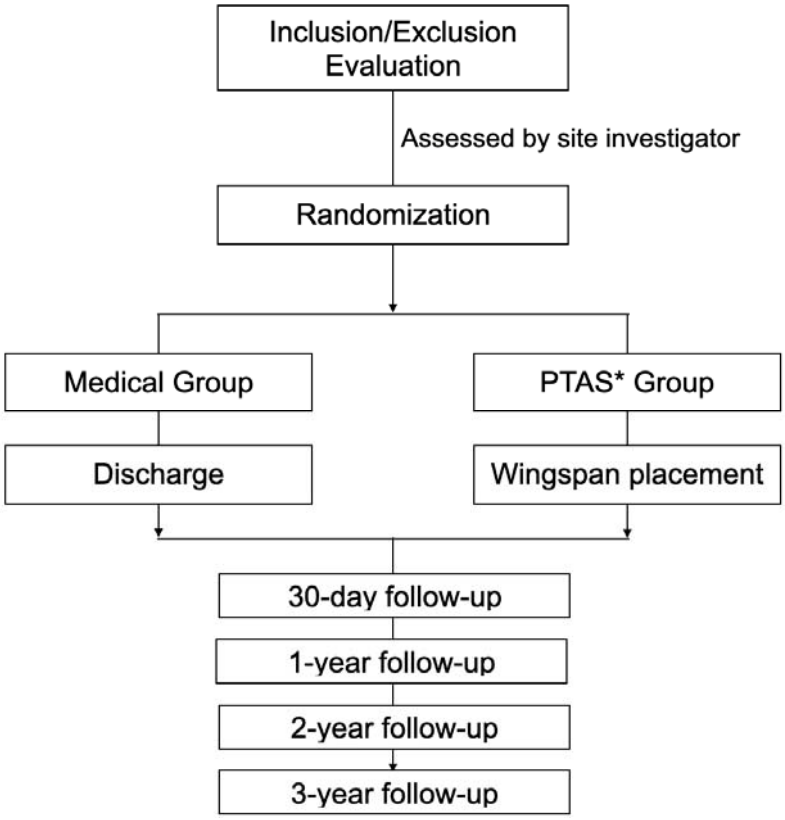
4. STUDY DESIGN

This trial is a prospective, multi-center, open-label, randomized control trial that will be conducted in 8 high-volume centers in China Mainland. Patients who meet inclusion criteria are randomized (1:1) to medical therapy alone or to PTAS plus medical therapy. This trial aims to enroll 380 cases. This sample size is large enough to result in acceptable data about safety and efficacy. At each investigational site, the local treating team will consist of at least a neurologist, a neurosurgeon, a neuroradiologist, and a research coordinator. The local treating team conducted enrollment after they reviewed the qualification of each patient. Patients assigned to the medical group will be discharged without further intervention. They will be administered aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin alone per day thereafter). Medical therapy will be identical in both arms and will be similar to the previously-described risk factor management for the SAMMPRIS trial and AHA/ASA guidelines.[19 32] Patients assigned to the PTAS group will receive PTAS within 3-5 business days after enrollment. All patients will be followed-up in outpatient consultation or by telephone contact with the site investigators at 30-day, 1-year, 2-year, and 3-year marks until the last patient enrolled finishes 3-year follow-up or if patients die before the close-out visit (see flow chart).

Expected enrollment initiation date: March, 2014

Expected enrollment completion date: March, 2017

Expected study end date: March, 2020



Flow Chart

*PTAS, percutaneous transluminal angioplasty and stenting

5. STUDY POPULATION

5.1 Population

Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery. The stenotic degree will be determined on catheter angiogram using the criteria of the Warfarin-Aspirin Symptomatic Intracranial Disease Study [WASID][33]).

5.2 Credentialing of the participating centers and center eligibility

Centers are required to have a team consisting of a neurologist, a neurosurgeon, a neuroradiologist, and a research coordinator. The randomized trial will not begin until the clinical results of the participating centers have been certified. All the centers who are interested in this trial will perform a competitive registration study of recruiting a consecutive 100 PTAS as a pre-clinical trial within a duration of 8 to 10 months. Certification will be achieved by participating centers, whose clinical results are audited by means of a validated selection process. Participating centers meet the following criteria will be included in the randomized trial: 1) the annual volume of the cases treated with intracranial stenting for ICAS over the past three years was more than 30; 2) within the lead-in phase period of eight months, more than five cases will be performed by a single principal operator; 3) less than 15% stroke or death rate within 30 days after the revascularization procedure of the qualifying lesion.

There will be 10 high-volume candidate sites (all tertiary hospitals), involved in a competitive registration study of recruiting a combined total of 100 consecutive patients treated with PTAS:

Table: 10 candidate enrollment sites

#	Sites
1	Xuanwu Hospital, Capital Medical University, Beijing, China
2	The 1st Affiliated Hospital of Harbin Medical University, Harbin, China
3	Henan Provincial People's Hospital, Zhengzhou, China
4	Tangdu Hospital of Air Force Medical University, Xi'an, China
5	Beijing Hospital, Beijing, China
6	Qilu Hospital of Shandong University, Ji'nan, China
7	PLA Strategic support Force Characteristic Medical Center, Beijing,

	China
8	The 2nd affiliated Hospital of Guangzhou Medical University, Guangzhou, China
9	Tianjin Huanhu Hospital, Tianjin, China
10	Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, China

5.3 Inclusion criteria

1. Eligible patients aged between 30 and 80 years; intracranial arterial stenosis related to the following non-atherosclerotic factors will be not be considered: arterial dissection, moya-moya disease; vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with cerebrospinal fluid pleocytosis; radiation-induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; postpartum angiopathy; suspected vasospastic process, and suspected recanalized embolus;
2. Symptomatic intracranial stenosis: presented with transient ischemic stroke (TIA) or stroke within the past 12 months attributed to 70%-99% stenosis of a major intracranial artery (ICA, MCA [M1], vertebral artery, or basilar artery [BA]);
3. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter angiography for enrollment in the trial;
4. Remote infarctions on MRI scan, which can be accounted for by the occlusion of the terminal cortical branches or hemodynamic compromise (perforator occlusion excluded). Infarction due to perforators occlusion is defined as basal ganglia or brainstem/thalamus infarction related with M1 or BA stenosis;
5. Expected ability to deliver the stent to the lesion;
6. All the patients should be performed with stenting beyond a duration of three weeks from the latest ischemic symptom onset;
7. No recent infarctions identified on MRI (indicated as high signals on DWI series) upon enrollment;
8. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage, epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI scan;
9. mRS scale score of <=2;

10. Target vessel reference diameter must be measured to be 2.00 mm to 4.50 mm; target area of stenosis is <=14 mm in length;
11. No childbearing potential or has a negative pregnancy test within the past one week prior to study procedure; female patients had normal menses in the last 18 months;
12. Patient is willing and able to return for all follow-up visits required by the protocol;
13. Patients understand the purpose and requirements of the study and have signed informed consent form.

5.4 Exclusion criteria

1. Refractory to general anesthesia; not able to be overcome by pre-treatment with medical therapy
2. Any condition that precludes proper angiographic assessment
3. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is proximal or distal to the target intracranial lesion
4. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about which lesion is symptomatic (for example, if patient has pon, midbrain, temporal and occipital symptoms)
5. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution within 30 days
6. Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, or plan to perform staged angioplasty followed by stenting of target lesion
7. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement
8. Plan to perform concomitant angioplasty or stenting of an extracranial vessel tandem to an ipsilateral intracranial stenosis
9. Presence of intraluminal thrombus proximal to or at the target lesion
10. Any aneurysm proximal to or distal to intracranial stenotic artery
11. Intracranial tumors or any intracranial vascular malformations
12. Computed tomographic or angiographic evidence of severe calcification at target lesion
13. Thrombolytic therapy within 24 hours before enrollment
14. Evolving stroke or progressive neurologic signs within 24 hours before enrollment

15. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of hemorrhagic transformation during the procedure; hemorrhagic transformation of an ischemic stroke within the past 15 days
16. Previous spontaneous intracerebral (parenchymal) or other intracranial (subarachnoid, subdural, or epidural) hemorrhage within 30 days
17. Untreated chronic subdural hematoma >5 mm in thickness
18. Other cardiac sources of emboli such as left ventricular aneurysms, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, left atrial myxoma
19. Myocardial infarction within previous 30 days
20. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the past six months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation
21. Intolerance or allergic reaction to any of the medical therapy, including aspirin, clopidogrel, heparin, and local or general anesthetics
22. History of life-threatening allergy to contrast medium. If not life threatening and can be effectively pre-treated, patient can be enrolled at physicians' discretion
23. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
24. Active bleeding diathesis or coagulopathy; active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelets count <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia that increases the risk of bleeding, uncontrolled severe hypertension (systolic BP>180mm hg or diastolic BP>115mm hg), severe liver impairment (AST or 25. ALT >3 times normal, cirrhosis), creatinine >265.2 mmol/l (unless on dialysis). Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment
25. Indication for warfarin or heparin beyond enrollment (exceptions allowed for use of systemic heparin during stenting procedure or subcutaneous heparin for deep venous thrombosis prophylaxis while hospitalized)
26. Inability to understand and cooperate with study procedures or sign informed consent
27. Severe dementia or psychiatric problems that prevent the patients from following an outpatient program reliably
28. Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study

29. Actively participating in another drug or device trial that has not completed the required protocol follow-up period

6. Methods

6.1 Primary outcomes

- Stroke or death within 30 days after enrollment;
- Stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year

6.2 Secondary outcomes

- Disabling stroke or death beyond 30 days through 3 years in both arms;
- Complication rates associated with stenting procedures;
- Restenosis (>50%) related to stenting within a follow-up of 3 years;
- Any stroke, severe TIA, or cardiovascular events within a follow-up of 3 years;
- National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index (BI) assessment within a follow-up of 3 years;
- The compliance rate of the patients with regular medical therapy within a follow-up of 3 years;
- Death rate in both arms within a follow-up of 3 years.

6.3 Definitions of outcomes

1. Stroke is defined as the rapid loss of brain functions due to disturbance in the blood supply to the brain that persists beyond 24 hours. Stroke is diagnosed by an independent outcome committee which is composed with experienced neurologists. They will collect additional key neuro-images (CT or MR scans) as adjunct evidence for outcome classification of ischemic or hemorrhagic stroke;
2. Ischemic stroke is defined as a new focal neurological deficit of sudden onset lasting at least 24 hours that is not associated with a hemorrhage on brain CT or MRI. Ischemic strokes are further classified by the neurologic adjudicators as being either in or out of the territory of the qualifying artery;
3. Hemorrhagic stroke is defined as parenchymal, sub-arachnoid, or intra-ventricular hemorrhage detected by CT or MRI that is associated with new neurological signs or symptoms lasting >24 hours or a seizure;
4. Death, any of the following criteria:

a) Procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure.

b) Death to due to cardiac cause, e.g., myocardial infarction, cardiac tamponade, and worsening heart failure

c) Death of other cause (e.g., malignancy, trauma and suicide)

d) Sudden or unwitnessed death

e) Death of unknown cause

5. Disabling stroke is defined by any of the following:

a) a modified Rankin score of 3 or more, on a scale of 0 to 6, with higher scores indicating greater disability;

b) an increase in at least one mRS category from an individual's pre-stroke baseline

c) a score on the composite National Institutes of Health Stroke Scale (NIHSS) of 7 or more, on a scale of 0 to 42, with higher scores indicating more severe deficits;

d) an increase in at least 4 NIHSS scales from pre-stroke baseline.

6. Complication rates associated with stenting procedures: refer perforator occlusion, guidewire perforation, artery-to-artery embolism, stent thrombosis, or reperfusion hemorrhage within 72 hours after PTAS procedures.

7. Restenosis rate: if patients have follow-up vascular imaging, the imaging modality will be recorded, in addition to the percent stenosis of the target lesion. Re-stenosis is defined as 50% narrowing or greater irrespective of symptoms.

8. TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarction;

9. Severe TIA refers to rapidly developed clinical signs of focal or global disturbance of cerebral function lasting longer than 10 minutes but fewer than 24 hours, without apparent nonvascular cause.

10. Cardiovascular events: refer a class of events that is related to stenting or medical therapy, which includes coronary artery diseases (CAD) such as angina and myocardial infarction.

11. BI, mRS and NIHSS: please refer the appendix 12.1, 12.2 and 12.3.

12. Compliance of drug: patients will be contacted at 30-day, 1-year, 2-year and 3-year after enrollment, to gather information regarding the use of anti-platelet drugs, changes in prescribed drugs, medical condition and quality of life.

a) very good, 80% - 120%;

b) good, 60% - 79%;

c) fair, 40% - 59%;

d) poor, < 40%.

6.4 Definitions of other parameters

6.4.1 Major vascular complications

1. Non-neurovascular death: e.g., trauma, suicide, malignancy, or cardiovascular mortality;
2. Major vascular complication: e.g., aortic dissection, aortic rupture, or annulus rupture;
3. Access site of access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or percutaneous closure device failure) leading to death, life-threatening or major bleeding, or neurological impairment;
4. Distal cerebral embolism from a vascular source requiring surgery or endovascular intervention or irreversible neurological damage;
5. Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical examination, and/or decreased or absent blood flow on lower extremity angiogram;
6. surgery for access site-related nerve injury；
7. permanent access site-related nerve injury.

6.4.2 Minor vascular complications

1. Access site of access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, or percutaneous closure device failure) not leading to death, life-threatening or major bleeding, or neurological impairment;
2. Distal cerebral embolism treated with mechanical thrombectomy not resulting in irreversible neurological damage;
3. Any unplanned endovascular stenting or surgical intervention not meeting the criteria for a major vascular complication;
4. Vascular repair: e.g., ultrasound-guided compression or injection embolization, transcatheter embolization or stent-graft;
5. Percutaneous closure device failure.

6.5 Treatment assignment

Eligible patients will be enrolled with their baseline data entered into a web-based database system. Patients will be randomized (1:1) to medical therapy alone or medical therapy plus stenting using Wingspan. There will be no blinding. When a patient is included for participation, site investigator will be informed. The patients will be excluded from the ITT analysis if they sign the ICF while they don't meet the criteria of inclusion and exclusion after central image Corelab adjudication.

A summary will be made of patients who are randomized to PTAS group but do not undergo surgery, and the patients who are randomized to medical therapy but receive surgery. Compliance will be assessed by the investigator at each visit using information provided by the care-giver or patients themselves. This information should be recorded in the source document at each visit.

6.6 Randomization and numbering

A central randomization system, IVRS (Interactive Voice Response System, Clinicalsoft Company Limited, Beijing, China; http://ivr.clinicalsoft.cn) will be used for patient randomization. Each patient has its unique ID number (center number plus screening order number) in this trial. This center number will be assigned to each participating center. Once the patients or their legal representatives sign the informed consent form (ICF) at each center, they will be assigned with a screening order number. At each center, the screening order number will be in order of the patients' enrollment (e.g., 001, 002, 003 and so on).

6.7 Medical group

Patients randomized to medical group will received medical therapy and be discharged without further intervention.

6.7.1 Medical therapy

Medical therapy will be identical in both arms and will be similar to the previously described risk factor management for the SAMMPRIS trial. In brief, it includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg alone per day thereafter) and management of risk factors.

The drugs used in the trial are commercially available in China. Several generic aspirin or clopidogrel are available and allowed to be used. Medical therapy regimen, including DAPT and statin will be purchased by the patients

or their family member, who later received various degrees of reimbursement from the Chinese social security system.

6.7.2 Management of risk factors

Risk factor control is based on the 2011 AHA/ASA guidelines[32] and the SAMMPRIS[19] trial protocol. Medical management of risk factors consists of normalizing low-density lipoprotein (LDL-C) (statins, target LDL-C <2.58 mmol/l [100 mg/dl]), hypertension (systolic pressure <140 mmHg and a diastolic pressure <90 mmHg), glucose disorder (in diabetic patients, hemoglobin A1c [HbA1c] will be checked at enrollment and during each clinical visit with a target level of <6.5%), and lifestyle modification. Intensive management of risk factors is applicable to all the included patients (e.g., hypertension, lipid disorder, diabetes mellitus, overweight, obesity, physical inactivity, and cigarette smoking).

6.7.3 Health education and lifestyle modification

1. Health education and lifestyle modification: quit smoking, moderate-intensity physical exercises (at least 3 times per week for 30 min per session).
2. Obesity: BMI should be maintained below 25 kg/m^2. Weight reduction is associated with a lowering in BP and may thereby reduce stroke risk.

6.8 PTAS group

Patients randomized to PTAS group are to be scheduled for surgery within three to five business days after enrollment. The study protocol requires that the stenting procedure be performed by a qualified operator at each site.

6.8.1 PTAS procedure

Patients randomized to stenting will be placed on DAPT (aspirin, 100 mg daily and clopidogrel 75 mg daily) for 3-5 consecutive days before the procedure. No loading dose will be allowed. The study protocol requires that the PTAS procedure is typically performed under general anesthesia by a credentialed interventionist who should be the primary operator. The procedure is typically performed via a transfemorally placed 6F-long sheath or guiding catheter. The stenotic lesion is primarily crossed with a standard 0.014'' microcatheter microwire system under high magnification fluoroscopic roadmap control. Once across the lesion, the microcatheter is exchanged over a 300-cm,

0.014'' microwire for a Gateway balloon catheter. After angioplasty, the balloon catheter is exchanged for a Wingspan stent delivery system and the self-expanding Wingspan stent is deployed across the stenosis. If the residual stenosis after inserting the Wingspan stent is >50%, the study protocol allows for postdilation with a new balloon catheter. The protocol required frequent measurements of blood pressure during the procedure and at least 1 measurement every half an hour during the next 24 hours while the patient is monitored. The patient will be continued on aspirin, 100 mg daily, and clopidogrel, 75 mg daily, for the next 90 days and subsequently on aspirin alone. Risk factor control should be applied thereafter.

6.8.2 Rescue therapy for PTAS

1. If the residual stenosis is >50% after the primary Wingspan placement, study protocol allows for the postdilation with a new balloon catheter to achieve better angioplasty outcome.
2. If the initial Wingspan stent could not be delivered to the target lesion, the interventionalist can try to deliver a second Wingspan stent.
3. If the second Wingspan stent cannot be delivered to the target lesion, the interventionalist has the following options: a) angioplasty alone with Gateway balloon catheter; b) using non-Wingspan stent; c) procedure aborted.
4. If an ischemic stroke occurs or an intraluminal thrombus develops during the procedure, the interventionalist or stroke neurologist (if available) should administrate appropriate treatment. This may include intravenous or intraarterial use of thrombolytic therapy, e.g., glycoprotein IIb-IIIa Inhibitor (Tirofiban).
5. If a major dissection, other occlusive complication, or stent misplacement occurs that requires placement of a second Wingspan stent, this may be done as a rescue procedure. In the meantime, neuro ICU will provide reservations to deal with patients with serious complications.

6.9 Follow-up schedule

Clinical assessment of patients will be conducted in outpatient consultation or by telephone contact with the site investigators at 30-day, 1-year, 2-year, and 3-year or if the patients died before the close-out visit. At each follow-up visit, patients will be examined by study physicians who also manage the patients' vascular risk factors. Imaging assessment will be achieved by head MRI, CTA, MRA, or DSA at each visit if possible.

Table: follow-up schedule

	In-hospital			Follow-up (Paper-based CRF)			
	Baseline	Procedure	Discharge	30-day	1-year	2-year	3-year
ICF	✓						
In-/Exclusion criteria	✓						
Demographics	✓						
Medical history	✓						
Physical exam	✓			✓	✓	✓	✓
Neurological status							
NIHSS	✓	✓	✓	✓	✓	✓	✓
mRS	✓	✓	✓	✓	✓	✓	✓
Barthel Index	✓	✓	✓	✓	✓	✓	✓
Lab test	✓				✓	✓	✓
Neuro-imaging							
CT/MRI (DWI)	✓				✓	✓	✓
TCD/CTA/MRA	✓				✓	✓	✓
CTP/PWI	✓	✓			✓	✓	✓
DSA	✓	✓			✓	✓	✓
Medication	✓			✓	✓	✓	✓
AE/SAE		✓	✓	✓	✓	✓	✓

6.9.1 Baseline

At baseline, the following parameters should be documented:

I. Date of ICF

II. Demographics

III. Medical history

a. Present history

b. Previous history, e.g., hypertension, diabetes, lipid disorder, coronary and peripheral artery disease, smoking and alcohol abuse, etc.

IV. Clinical status

a. Physical examination

b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature

c. ECG

d. BMI

V. Neurological status

a. NIHSS

b. mRS

c. Barthel Index

VI. Lab test

a. Routine blood test

b. Liver function: e.g., ALT, AST, etc.

c. Renal function: e.g., Cr, BUN, etc.

d. Renal damage: proteinuria (according to site's preference and facilities)

e. FBG and HbA1c

f. Lipid level: LDL, HDL and TC

g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.

h. Inflammation markers: CRP

i. Pregnancy test

VII. Neuro-imaging

a. Cranial CT/MR (DWI)

b. TCD/CTA/MRA

c. CTP/PWI parameters: CBF, CBV, MTT and TTP

d. DSA

6.9.2 Procedure (for PTAS group)

During the procedure, the following parameters should be documented:

I. Date of the procedure

a. delayed procedure: beyond 5 business day after enrollment

b. procedure on time: within 5 business day after enrollment

II. Operator of the procedure

III. Anesthesia: general or local

IV. Morphological characteristics of the lesion on DSA

a. side: right or left

b. size: diameter and length (mm)

c. location: M1, BA, ICA or VA

d. stenotic degree (%) determined using the WASID criterion[33]

e. Mori classification: type A, B or C[34] (Appendix 12.4)

f. TICI perfusion categories[35] (Appendix 12.5)

g. ASITN/SIR collateral flow grading system[35] (Appendix 12.6)

V. Type of procedures
   a. angioplasty plus stent placement
   b. angioplasty alone
   c. none

VI. Angioplasty balloon
   a. size: diameter and length (mm)
   b. type: Gateway or others
   c. number: 1 or more

VII. Stent delivered
   a. size: diameter and length (mm)
   b. type: Wingspan or others
   c. number: 1 or more

VIII. Residual stenosis (%)

IX. Use of post-dilation:
   a. yes or no
   b. if yes, type and size of the balloon used
   c. inflation pressure (atm)
   d. residual stenosis after post-dilation

X. Rescue therapy

XI. Post-PTAS neurological status
   a. NIHSS
   b. mRS
   c. Barthel Index

XII. AE/SAE

6.9.3 Discharge

Before discharge, the following parameters should be documented:

I. Neurological status
   a. NIHSS
   b. mRS
   c. Barthel Index

II. AE/SAE

6.9.4 30-day follow-up

At 30-day follow-up, the following parameters should be documented:

I. Clinical status
   a. Physical examination
   b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
   c. ECG
   d. BMI
II. Neurological status
   a. NIHSS
   b. mRS
   c. Barthel Index
III. Medication
IV. AE/SAE

6.9.5 1-year follow-up

At 1-year follow-up, the following parameters should be documented:

I. Clinical status
   a. Physical examination
   b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
   c. ECG
   d. BMI
II. Neurological status
   a. NIHSS
   b. mRS
   c. Barthel Index
III. Lab test
   a. Routine blood test
   b. Liver function: e.g., ALT, AST, etc.

c. Renal function: e.g., Cr, BUN, etc.
d. Renal damage: proteinuria (according to site's preference and facilities)
e. FBG and HbA1c
f. Lipid level: LDL, HDL and TC
g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
h. Inflammation markers: CRP

IV. Neuro-imaging
a. Cranial CT/MR (DWI)
b. TCD/CTA/MRA
c. CTP/PWI parameters: CBF, CBV, MTT and TTP
d. DSA

V. Medication

VI. AE/SAE

6.9.6 2-year follow-up

At 2-year follow-up, the following parameters should be documented:

I. Clinical status
a. Physical examination
b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
c. ECG
d. BMI

II. Neurological status
a. NIHSS
b. mRS
c. Barthel Index

III. Lab test
a. Routine blood test
b. Liver function: e.g., ALT, AST, etc.
c. Renal function: e.g., Cr, BUN, etc.
d. Renal damage: proteinuria (according to site's preference and facilities)

e. FBG and HbA1c
f. Lipid level: LDL, HDL and TC
g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
h. Inflammation markers: CRP

IV. Neuro-imaging
a. Cranial CT/MR (DWI)
b. TCD/CTA/MRA
c. CTP/PWI parameters: CBF, CBV, MTT and TTP
d. DSA

V. Medication

VI. AE/SAE

6.9.7 3-year follow-up

The following parameters should be documented:

I. Clinical status
a. Physical examination
b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
c. ECG
d. BMI

II. Neurological status
a. NIHSS
b. mRS
c. Barthel Index

III. Lab test
a. Routine blood test
b. Liver function: e.g., ALT, AST, etc.
c. Renal function: e.g., Cr, BUN, etc.
d. Renal damage: proteinuria (according to site's preference and facilities)
e. FBG and HbA1c
f. Lipid level: LDL, HDL and TC

g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
h. Inflammation markers: CRP

IV. Neuro-imaging
a. Cranial CT/MR (DWI)
b. TCD/CTA/MRA
c. CTP/PWI parameters: CBF, CBV, MTT and TTP
d. DSA

V. Medication

VI. AE/SAE

6.10 Consent withdrawal

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Consent withdrawal occurs only when a patient: 1) does not want to participate in the study anymore; 2) or does not want any further visits or assessments; 3) or does not want any further study-related contacts.

When a patient withdraws consent, the investigator is required to determine the primary reason for this decision and record this information. Further attempts to contact the patient are not allowed unless safety efficacy require follow-up. After withdrawal, patients will not be replaced by others and their randomized ID number will not be re-used.

6.11 Follow-up of subjects withdrawn from treatment assignment

Some cases may withdraw from treatment assignment. Since the statistical analysis is planned for ITT principle, they will be analyzed in the group that they were originally allocated to.

6.12 Lost for follow-up

For patients whose status are unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in ICF and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. Lost for follow-up could be accounted by no reply although try to contact the cases three times or more. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

6.13 Study completion and post-study treatment

At the end of the study visit, the investigator should provide follow-up medical care for all patients who are prematurely withdrawn from the study or refer them for appropriate ongoing care. When the patient has completed all scheduled study assessments, the investigator is required to inform to record the patient completion in the EDC system.

6.14 Premature termination of the study

During the trial, AEs or SAEs will be reported to DSMB. The DSMB will monitor SAEs, major safety events, device and procedure failures and any device-related adverse events. In the current trial, SAEs mainly refer disabling stroke, symptomatic intracranial hemorrhage or death within 1 year after enrollment and all-cause death within a follow-up 3 years. The stopping rules will be developed by DSMB and the advices of DSMB will be sent to the executive and steering committee of the study. The Executive and Steering Committee will be responsible for informing the EC whether the advices are fully implemented or not.

6.15 Outcome assessment

This is a multicenter phase IV RCT with open-label treatment and blinded outcome assessment. Outcome assessment will be sent to an independent Outcome Committee. The committee is composed of experienced neurologists who are not involved in the study, will be blinded to the treatment assignment. All the outcome will be adjudicated by the outcome committee, and a consensus will be reached by a third clinician in case of discrepancies.

7. SAFETY MONITORING

7.1 Adverse events (AE)

AE is defined as any unfavorable and unintended sign, symptom or disease that occurs to a subject while enrolled in a clinical investigation, whether or not considered related to the study intervention or device. Medical conditions that exist at study enrollment are not considered an AE unless condition worsens after use of the study intervention or device.

7.2 Serious adverse events (SAE)

7.2.1 Definition of SAE

A SAE is any medical experience regardless of its relationship to the investigational device or study devices that occurs during subject enrollment in this trial that results in any of the following:

- need to be hospitalized or prolonged hospitalization;
- persistent or significant disability/incapacity;
- death of the study subject;
- necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- or causing congenital anomalies/birth defects.

7.2.2 SAE reporting

All SAEs will be recorded in the table of CRF. The details of the SAEs, including starting time, ending time, duration, treatment, outcome, and the relationship with intervention will be recorded as well. Frequency of SAEs will be summarized according to the assignments. All recorded AEs/SAEs will be reported to the investigator. SAEs that result in death or life-threatening stroke will be reported to DSMB/EC within 14 days after the investigator is informed for the first time. In the current trial, SAEs mainly refer disabling stroke, symptomatic intracranial hemorrhage or death within 1 year after enrollment and all-cause death within a follow-up 3 years. For safety analysis, an independent summary will list SAEs related to intervention in PTAS group.

7.2.3 Management and follow-up of AEs/SAEs

Investigators should take appropriate treatment for AEs to ensure the safety of patients and track all AEs/SAEs until they are properly resolved, or the condition is stable. Additional medical procedures and/or referral to a medical

specialist may be required to confirm whether the patients are qualified to continue to participate in the study.

8. DATA MANAGEMENT

8.1 Study Data Collection

Site coordinator records data by filling out the paper-based CRF for each case. The sponsor (Beijing Xuanwu Hospital) provides CRFs to each site. Site investigator is responsible for that all CRFs are completed, reviewed, and approved. Also, site investigator will sign on CRFs and confirm that clinical, imaging and laboratory data entered into the CRFs are true.

Patient ID in CRFs should be recorded in an anonymous form, which are only identified by the patient ID number and Chinese phonetic alphabets (pinyin) initials. CRFs should be filled in with a black ballpen based on the original document. Fill in “not done” for missing data; fill in “not applicable” if not applicable; fill in “unknown” for unknown data.

If the data entered into CRFs needs to be revised, cross out the error with a single line so that it can still be seen clearly, and then fill in the correct data next to it. The revisions should be approved and signed by the site investigator. If necessary, the reason for the revisions should be indicated. Site investigator will review the integrity and accuracy of the CRFs and make further corrections and amendments if necessary. When the trial is finished, site investigator will send the CRFs to Tigermed Data Management Co., Ltd; (https://tigermedgrp.com) for data entry.

The data in the paper-based CRFs will be entered into the database by Tigermed Data Management Co., Ltd, with its completeness and accuracy reviewed. The missing data and questioned data are reported in the data query form, which will be sent back to the site investigator for further verification. Site investigator will send back in the resolved query form with signature and date of signing. Tigermed Data Management shall be responsible for entering the resolved results into the database. After the final confirmation is completed and all queries are resolved, the database is updated and locked. Data is transferred from the database directly to the data file (SAS data set) for statistical analysis. The data can be changed after database is unlocked upon reasonable request.

8.2 Data Processing and Quality Control

The data entry is performed by the staff trained by Tigermed Data Management Co., Ltd. All the input data should go through verification and range check. The staff will be notified of a possible error, depending on the data validation. The staff will not move on unless the error is resolved.

All CRFs will be subject to preliminary inspection for data missing, inconsistency and deviation. Data inconsistency will be completed by electronic tracking and resolved by site coordinators and investigators.

Each data input will receive regular cross-check within forms. Site coordinators will be informed in case of errors identified. Corrections to the data in CRFs will be made by the site coordinators, and approved by the site investigators.

The data editing will continue when all data is cleaned. The site coordinators will supervise the verification of on-site source documents. If further data related to the source file is found during the site visit, additional queries will be generated and processed by the site coordinators.

8.3 Data storage

The investigator will document adequate records during the conduct of the study. Trial data including patient files, CRFs, ICFs, original copies of results, and imaging outcome, will be kept on files by the investigator for a period of 10 years or more.

9. STATISTICAL ANALYSIS

9.1 Analysis data set

Full Analysis Set (FAS): all the subjects who are randomized into groups will be included, and the subjects who do not meet the eligible criteria and who withdraw immediately after randomization without receiving any interventions will be excluded. According to the intention-to-treat (ITT) principle, all randomized patients will be analyzed according to the treatment group assigned to them at the time of randomization. All presenting analyses will be conducted in the FAS population unless otherwise specified

Per-protocol Set (PPS): PPS refers population who are treated according to the study protocol, e.g., fulfilling eligibility criteria, assigned treatment after randomization, medication and follow-up protocol, and completion of the case report form). PPS analysis was conducted on the population who had not crossovers between groups or significant protocol violations. Crossover population from one arm to the other will not impact the ITT analysis. For PTAS group, significant protocol violations include: 1) use of non-Wingspan stents; 2) delayed procedure of PTAS (beyond 5 business days after enrollment; 3) procedure is aborted before lesion is accessed; 4) procedure is aborted due to total occlusion; 5) receive angioplasty only and others. For other details, please refer to the Statistical Analysis Protocol (SAP) in the Appendix.

For other details, please refer to the Statistical Analysis Protocol (SAP) in the Appendix.

9.2 Analysis close date

The analysis close date for each arm is at the completion of 3-year follow-up of the last enrolled patient. The primary outcome is based on the exact 3-year time point for each patient, and event.

9.3 Sample size calculation

For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of ipsilateral stroke risk in medical therapy group WASID study was 18%,[36] which was 7.3% in a study by the Wingspan stent therapy.[23] At a significance level of 5% on both sides, the absolute difference of 10.7% (relative risk reduction 59%), and a power of 80%, within 12 months of follow-up, a total of 302 patients need to be evaluated. Assuming a 20% incidence of loss of follow-up and/or withdrawal, a total of 380 patients, 190 in the stent group and 190 in the medical group, are required to be enrolled in this study.

10. STUDY COMMITTEES

10.1 Executive and Steering Committee

Executive committee is composed of principle and site investigators from the participating centers, which is responsible for making decisions about the direction and strategy of the trial. During the trial period, this committee fulfills the coordination, implementation, organize regular meeting, and report progress. Also, it is required to review main trial publications, analysis plan and publication policy, and consider recommendations of DSMB.

10.2 Ethics Committee

The trial should first obtain the written approval from the Ethics committee of Xuanwu Hospital, Capital Medical University, Beijing, China. The trial will not enroll patient until the study protocol is approved by the local ethics committee (EC) in the other sites. In case of any major amendments to the trial protocol, renewed written approval should be obtained from the ethics committee. Updated ICF after amendments will be sent to patients in the active period of the trial. Minor amendments will not be sent to EC.

10.3 Data and safety Monitoring Board (DSMB)

An independent DSMB that is composed of neurologist, neurosurgeon, neuroradiologist and biostatistics experts who are not involved in the conduct of the trial. DSMB members should not have any scientific or financial conflicts of interest with the sponsor or investigator. DSMB is responsible for study conduct, progress and efficacy. By reviewing safety data, DSMB will advise executive committee to continue, modify or terminate the trial early.

10.4 Clinical outcome committee

Clinical outcome assessment will be sent to an independent Outcome Committee. The committee composed of experienced neurologists who are not involved in the study, will be blinded to the treatment assignment. All the outcome will be adjudicated by the outcome committee, and a consensus will be reached by a third clinician in case of discrepancies. For details, please refer to *2.9 Assessments of clinical outcome* in the *2. Supplementary Methods*.

10.5 Imaging outcome committee:

An independent imaging core-lab, IsCore Image CoreLab (ICIC, http://imagecorelabcn.com/), will be established with the aim of facilitating the central reading by clinicians and integrating medical imaging at the baseline

control and each clinical visit. For details, please refer to *2.10 Assessments of imaging outcome* in the *2. Supplementary Methods*.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1 Regulatory and ethical compliance

The design, implementation and reporting of this trial will follow the principles of the Declaration of Helsinki (World Medical Association: Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects - Version 2008).

11.2 Recruitment and informed consent form

Eligible patients who voluntarily agree to participate in the trial will be required to sign a written informed consent form (ICF). The ICF will be signed by the patients or his/her legal regal representatives prior to randomization. They will be informed shortly by the investigators when the treatment is assigned after central randomization.

11.3 Responsibilities of the investigator

Site investigators will review the eligibility of each candidate patient. If the patient is qualified and interested in this trial, he/she will be given written ICF to participate. Site investigators are responsible for explaining the research background, intervention, protocol, benefits, and risks of participating in the trial. A signed ICF copy will be kept by the patient as part of the study files. The patient is fully entitled to quit at any circumstance.

11.4 Public disclosure and publication policy

As the sponsor of the study, Xuanwu Hospital aims to publicize the primary and secondary outcome results in a high-impact scientific journal. Database of this trial will be locked within 3 months when the last enrolled patient finished the scheduled 3-year follow-up and all the data of the enrolled patients is completed. A manuscript will be submitted for potential publication in a scientific journal within 3 months after database lock. The manuscript will be shared with the financial sponsor(s) 3 months before submission, but the financial sponsor(s) have no influence on its contents. Anonymous data can be provided by principal investigators upon reasonable request.

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13. APPENDIX

13.1 Barthel Index (BI)

The Barthel scale is an ordinal scale used to measure performance in activities of daily living (ADL). Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing ADL and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital.

Category	Scale definition
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
Transfers (bed to	0 = unable, no sitting balance

chair and back)	5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

1198

1199

1200

13.2 Modified Rankin Scale (mRS)

The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The addition of grade 6 indicates dead.

Grade	Disability	Descriptions
0	No symptoms	No symptoms
1	No significant disability	Able to carry out all usual activities, despite some symptoms.
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability	Requires some help, but able to walk unassisted.
4	Moderately severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent.
6	Dead	Dead

13.3 NIH Stroke Scale

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Instructions	Scale definition
1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal	0 = Answers both correctly. 1 = Answers one correctly. 2 = Answers both incorrectly.

cues.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.

3. Visual fields: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Arm motor: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45)

noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm
6. Leg motor: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____

paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided

responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain:_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	

13.4 Mori Classification

The Mori classification, formulated on the basis of DSA, delineates the length and geometry of intracranial stenosis as follows:

Type	Descriptions
A	short (5 mm or less in length) concentric or moderately eccentric lesions less than totally occlusive
B	tubular (5 to 10 mm in length) extremely eccentric or totally occluded lesions, less than 3 months old
C	diffuse lesions (more than 10 mm in length), extremely angulated (>90°) lesions with excessive tortuosity of the proximal segment or totally occluded lesions, 3 months old or older

13.5 TICI perfusion categories

The thrombolysis in cerebral infarction (TICI) grading system was described as a tool for determining the response of thrombolytic therapy for ischemic stroke. In interventional neuroradiology, it is commonly used for patients post endovascular revascularization. Like most therapy response grading systems, it predicts prognosis.

Grade	Descriptions	
0	No Perfusion. No antegrade flow beyond the point of occlusion.	
1	Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.	
2	Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.	
	2a	Only partial filling (<2⁄3) of the entire vascular territory is visualized.
	2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
3	Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.	

13.6 ASITN/SIR collateral flow grading system

ASITN/SIR refers to American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR). The grading system scale is determined on DSA, classifying the cerebral collateral status ranging from grade 0 to 4. Grades 0-1, 2 and 3-4 are usually regarded as poor, moderate and good collateral flow.

Grade	Descriptions
0	No collaterals visible to the ischemic site
1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

CASSISS TRIAL PROTOCOL

THE CASSISS TRIAL

China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial

1264 # The CASSISS Trial

1265

Full Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS)：A prospective, multi-center, randomized controlled trial (RCT)
Short Title	The CASSISS Trial
Version	3.0
Date	May 1st, 2015
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Sponsor	Xuanwu Hospital, Capital Medical University
CRO	Tigermed Data Management Co., Ltd
Funding	Ministry of Health, People's Republic of China; Stryker Neurovascular Inc. (Fremont, CA, USA)

Protocol signature sheet

Name	Signature	Date
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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AHA	American Heart Association
ALT	Alanine transarninase
APTT	Activated Partial Thromboplastin Time
ASA	American Stroke Association
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System
AST	Aspartate aminotransferase
ATM	Atmosphere
BA	Basilar Artery
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
DSMB	Data Safety and Monitoring Board
DWI	Diffusion-weighted Imaging
ECG	Electrocardiogram
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
Cr	Creatine
CRF	Case Report Form
CRP	C-reactive protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DSA	Digital Subtraction Angiography
DAPT	Dural Anti-Platelet Therapy
DWI	Diffusion-Weighted Imaging
EC	Ethics Committee, synonymous to Institutional Review

	Board (IRB) and Independent Ethics Committee (IEC)
EDC	Electronic Data Capture
FAS	Full Analysis Set
FBG	Fasting blood glucose
FIB	Fibrinogen
GCP	Good Clinical Practice
HDL	High-density Lipoprotein
HbA1c	Glycated Hemoglobin
ICA	Internal Carotid Artery
ICAS	IntraCranial Atherosclerotic Stenosis
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LDL	Low-density Lipoprotein
LOCF	Last Observed Carried Forward
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scales
MTT	Mean Transit Time
NIHSS	National Institute of Health Stroke Scale
PI	Principle Investigator
PPS	Per-Protocol Set
PT	Prothrombin Time
PWI	Perfusion Weighted Imaging
RCT	Randomized Control Trial
PTAS	Percutaneous Transluminal Angioplasty and Stenting
SAE	Serious Adverse Event
SIT	Stroke In the Territory of symptomatic intracranial stenosis

Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
TC	Total Cholesterol
TCD	TransCranial Doppler
TIA	Transient Ischemic Attack
TICI	Thrombolysis in Cerebral Infarction
TT	Thrombin Time
TTP	Time-to-Peak
USA	United States of America
VA	Vertebral Artery

1355

1356

2. SUMMARY

Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial
Objectives	To determine whether intracranial angioplasty and stenting with Gateway-Wingspan stent system adds benefit to medical therapy alone for preventing the primary outcomes (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery).
Patient population	Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery.
Sample size	380 (ratio 1:1)
Intervention	Complete randomization will be performed with an Interactive Voice Response System (Clinicalsoft Company, Beijing, China). Eligible patients will be randomized with a 1:1 ratio to medical therapy or medical therapy plus PTAS. Superiority is prospectively defined if the stenting arm has a significantly lower stroke or death rate.
Study design	prospective, multi-center, open-label, outcome-blinded, randomized controlled study.
Main parameters / Outcomes	Primary outcomes: • Stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year Secondary outcomes: • Disabling stroke or death after enrollment through 3 years in both arms; • 2-year rate of the same-territory stroke;

	• 3-year rate of the same-territory stroke; • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years. • Death rate in both arms within a follow-up of 3 years.
Follow-up schedule	Baseline, 30-day, 1-year, 2-year, and 3-year
Statistical analysis plan	• The primary and secondary outcomes including 2-year SIT and 3-year SIT will be compared between the groups using log-rank test by ITT. • For other secondary outcomes and baseline characteristics chi-square or Fisher exact testy will be used for categorical variables, and t-test or Wilcoxon rank test for quantitative variables. • Kaplan-Meier curves will be used to show the incidence of outcomes over time. • All statistical tests will be performed by two-sided test. • A p-value <0.05 is considered statistically significant. • All analyses will be performed with SAS software, version 9.4 (SAS Institute, license: 11202165).

3. INTRODUCTION AND RATIONALE

3.1 Description of the disease

Stroke is one of the leading causes of death in China and confers a large burden and effort upon patients and health professionals.[1-3] In contrast to Western countries, intracranial atherosclerotic stenosis (ICAS) is the most common vascular lesion in patients with cerebrovascular disease, and is an important cause of ischemic stroke and future recurrent events in China.[4-7] Patients with ICAS have long been considered to be at high risk of recurrent stroke, which led to the development and wide use of percutaneous transluminal angioplasty and stenting (PTAS).[8-12]

3.2 Description of the intervention

In 2005, the Wingspan Stent system (Stryker Neurovascular, Fremont, CA, USA) was approved under a Humanitarian Device Exemption by the US Food and Drug Administration (FDA), and had been used to reduce the rate of recurrent ischemic events among patients with severe symptomatic ICAS.[13-17] However, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS trial, ClinicalTrials.gov number, NCT00576693), as the first RCT,[18] demonstrated that aggressive medical management was superior to PTAS with the Wingspan stent among patients with symptomatic severe ICAS, both because the risk of early stroke after stenting was high (14.7%) and because the risk of stroke with aggressive medical therapy alone was lower than expected (5.8%).[19]

3.3 Relevance for clinical practice

Since the SAMMPRIS trial, concerns have emerged that outcomes seen in a clinical trial setting may not be reproducible in non-RCT setting because of demonstrated more optimal surgical outcomes, less complication rates in high-volume centers, and good patient selection. The technical procedural problem rate, including guidewire- or angioplasty-related hemorrhage, could be minimized as more experienced operators overcome the learning curve for mastering the safety precautions of Wingspan stenting for ICAS.[20-22] In the post-SAMMPRIS era, several single or multi-center, registration studies in China,[23-26] suggested lower risks of intracranial stenting for ICAS than those reported for SAMMPRIS.[19]

Second, poor patient selection may increase the peri-operative risks and bias the outcome favoring medical treatment. In the stenting arm of the SAMMPRIS trial, more than 50% (115/224) of patients had a time interval from qualifying event to randomization of less than 7 days.[19] Short interval or early stenting intervention may confer a higher risk of cerebral vascular event, including thromboembolic events,

perforator stroke,[27] or even hemorrhagic transformation. Also, in the SAMMPRIS trial, 22.8% of recruited patients had perforators stroke only, and those patients may not benefit from stenting in addition to medical therapy. Ideally, stenting may be considered for eligible patients based on poor collaterals and medical futility.[28]

Third, intracranial stenting involves a trade-off between a higher short-term perioperative risk in exchange for a lower long-term risk of stroke. In the SAMMPRIS trial the stenting group, mostly due to periprocedural complication, had more disabling or fatal stroke within 30 days than that in medical group (7.1% vs 1.8%), whereas the stenting group had less disabling or fatal stroke beyond 30 days than that in medical group (2.2% vs 6.2%).[19]

The choice for ICAS treatment between medical therapy and stenting remains incompletely settled, at least for certain high-volume centers and for certain patient groups in a Chinese population. Furthermore, the recurrent stroke risk in the real world remains high despite maximal medical therapy.[29] Since the SAMMPRIS trial, an ever-increasing number of PTAS procedures surged beyond guidelines due to increased demand for ICAS treatment in China. The research community has maintained interest in tackling this important cause of stroke. Intracranial stenting with Wingspan is still awaiting a safe landing.[30, 31]

3.4 Hypothesis and rationale

It may be hypothesized that the clinical superiority observed in carefully selected patients in high-volume center who received medical therapy had diminished, making stenting a more favorable treatment strategy in comparison. As compared to the design of the SAMMPRIS trial, we thus feel that there is the need for a refined randomized trial reevaluating the role of stenting for ICAS. In the CASSISS trial, patients in both treatment groups have been followed up for 3 more years to establish whether early benefit in the medical group would persist over longer follow-up, or whether the medical group would have a high incidence of late stroke that would eliminate the early efficacy gap between groups.

3.5 Objectives

3.5.1 Primary objectives

To determine whether PTAS (using the Gateway PTA balloon catheter and Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical therapy is superior to medical therapy alone for preventing the primary outcome (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or non-disabling stroke caused by 70% to 99% stenosis of a major intracranial artery).

3.5.2 Secondary objectives

To compare outcomes between groups in terms of:

- Disabling stroke or death after enrollment through 3 years in both arms;
- 2-year rate of the same-territory stroke;
- 3-year rate of the same-territory stroke;
- Any stroke, TIA, or cardiovascular events within a follow-up of 3 years.
- Death rate in both arms within a follow-up of 3 years.

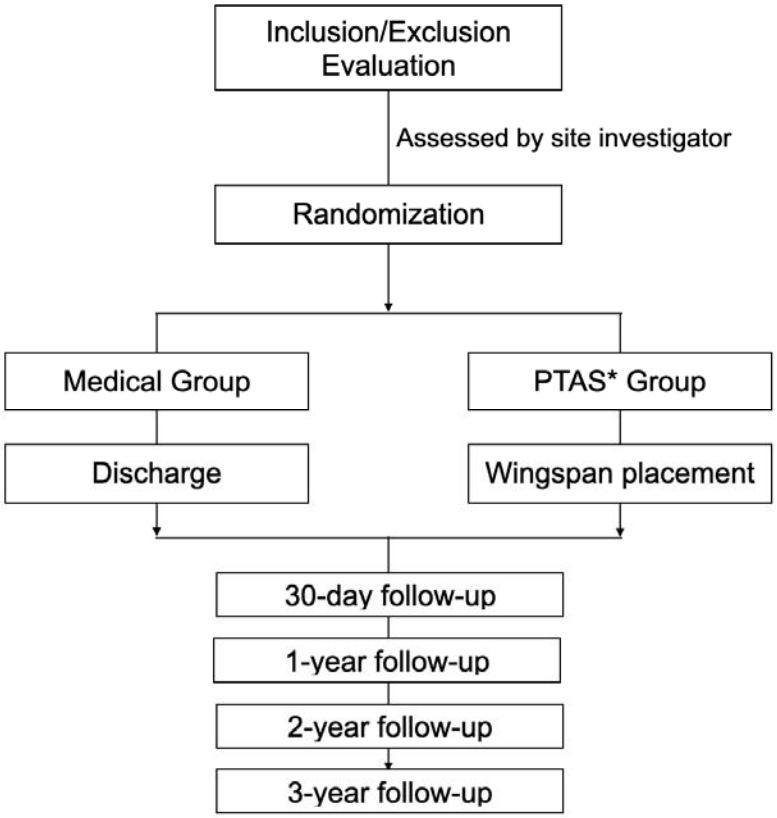
4. STUDY DESIGN

This trial is a prospective, multi-center, open-label, outcome-blinded, randomized control trial that will be conducted in 8 high-volume centers in China Mainland. Patients who meet inclusion criteria are randomized (1:1) to medical therapy alone or to PTAS plus medical therapy. This trial aims to enroll 380 cases. This sample size is large enough to result in acceptable data about safety and efficacy. At each investigational site, the local treating team will consist of at least a neurologist, a neurosurgeon, a neuroradiologist, and a research coordinator. The local treating team conducted enrollment after they reviewed the qualification of each patient. Patients assigned to the medical group will be discharged without further intervention. They will be administered aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin or clopidogrel alone per day thereafter). Medical therapy will be identical in both arms and will be similar to the previously-described risk factor management for the SAMMPRIS trial and AHA/ASA guidelines.[19] [32] Patients assigned to the PTAS group will receive PTAS within 3-5 business days after enrollment. All patients will be followed-up in outpatient consultation or by telephone contact with the site investigators at 30-day, 1-year, 2-year, and 3-year marks until the last patient enrolled finishes 3-year follow-up or if patients die before the close-out visit (see flow chart).

Expected enrollment initiation date: March, 2014

Expected enrollment completion date: March, 2017

Expected study end date: March, 2020



Flow Chart

*PTAS, percutaneous transluminal angioplasty and stenting

5. STUDY POPULATION

5.1 Population

Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery. The stenotic degree will be determined on catheter angiogram using the criteria of the Warfarin-Aspirin Symptomatic Intracranial Disease Study [WASID].[33]

5.2 Credentialing of the participating centers and center eligibility

Centers are required to have a team consisting of a neurologist, a neurosurgeon, a neuroradiologist, and a research coordinator. The randomized trial will not begin until the clinical results of the participating centers have been certified. All the centers who are interested in this trial will perform a competitive registration study of recruiting a consecutive 100 PTAS as a pre-clinical trial within a duration of 8 to 10 months. Certification will be achieved by participating centers, whose clinical results are audited by means of a validated selection process. Participating centers meet the following criteria will be included in the randomized trial: 1) at least five cases were performed by each primary operator during the lead-in phase; 2) annual volume of intracranial PTAS procedures was more than 30 for the past three years with a proven track record; and 3) according to the records of the past three years 30-day rate of stroke or death after PTAS in the territory of the qualifying artery was lower than 15%.

There will be 10 high-volume candidate sites (all tertiary hospitals), involved in a competitive registration study of recruiting a combined total of 100 consecutive patients treated with PTAS:

Table: 10 candidate enrollment sites

#	Sites
1	Xuanwu Hospital, Capital Medical University, Beijing, China
2	The 1st Affiliated Hospital of Harbin Medical University, Harbin, China
3	Henan Provincial People's Hospital, Zhengzhou, China
4	Tangdu Hospital of Air Force Medical University, Xi'an, China
5	Beijing Hospital, Beijing, China
6	Qilu Hospital of Shandong University, Ji'nan, China
7	PLA Strategic support Force Characteristic Medical Center, Beijing,

	China
8	The 2nd affiliated Hospital of Guangzhou Medical University, Guangzhou, China
9	Tianjin Huanhu Hospital, Tianjin, China
10	Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, China

5.3 Inclusion criteria

1. Eligible patients aged between 30 and 80 years; intracranial arterial stenosis related to the following non-atherosclerotic factors will be not be considered: arterial dissection, moya-moya disease; vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with cerebrospinal fluid pleocytosis; radiation-induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; postpartum angiopathy; suspected vasospastic process, and suspected recanalized embolus;
2. Symptomatic intracranial stenosis: presented with transient ischemic stroke (TIA) or stroke within the past 12 months attributed to 70%-99% stenosis of a major intracranial artery (ICA, MCA [M1], vertebral artery, or basilar artery [BA]);
3. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter angiography for enrollment in the trial;
4. Remote infarctions on MRI scan, which can be accounted for by the occlusion of the terminal cortical branches or hemodynamic compromise (perforator occlusion excluded). Infarction due to perforators occlusion is defined as basal ganglia or brainstem/thalamus infarction related with M1 or BA stenosis;
5. Expected ability to deliver the stent to the lesion;
6. All the patients should be performed with stenting beyond a duration of three weeks from the latest ischemic symptom onset;
7. No recent infarctions identified on MRI (indicated as high signals on DWI series) upon enrollment;
8. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage, epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI scan;
9. mRS scale score of <=2;

10. Target vessel reference diameter must be measured to be 2.00 mm to 4.50 mm; target area of stenosis is <=14 mm in length;
11. No childbearing potential or has a negative pregnancy test within the past one week prior to study procedure; female patients had normal menses in the last 18 months;
12. Patient is willing and able to return for all follow-up visits required by the protocol;
13. Patients understand the purpose and requirements of the study and have signed informed consent form.

5.4 Exclusion criteria

1. Refractory to general anesthesia; not able to be overcome by pre-treatment with medical therapy
2. Any condition that precludes proper angiographic assessment
3. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is proximal or distal to the target intracranial lesion
4. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about which lesion is symptomatic (for example, if patient has pon, midbrain, temporal and occipital symptoms)
5. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution within 30 days
6. Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, or plan to perform staged angioplasty followed by stenting of target lesion
7. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement
8. Plan to perform concomitant angioplasty or stenting of an extracranial vessel tandem to an ipsilateral intracranial stenosis
9. Presence of intraluminal thrombus proximal to or at the target lesion
10. Any aneurysm proximal to or distal to intracranial stenotic artery
11. Intracranial tumors or any intracranial vascular malformations
12. Computed tomographic or angiographic evidence of severe calcification at target lesion
13. Thrombolytic therapy within 24 hours before enrollment

14. Evolving stroke or progressive neurologic signs within 24 hours before enrollment
15. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of hemorrhagic transformation during the procedure; hemorrhagic transformation of an ischemic stroke within the past 15 days
16. Previous spontaneous intracerebral (parenchymal) or other intracranial (subarachnoid, subdural, or epidural) hemorrhage within 30 days
17. Untreated chronic subdural hematoma >5 mm in thickness
18. Other cardiac sources of emboli such as left ventricular aneurysms, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, left atrial myxoma
19. Myocardial infarction within previous 30 days
20. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the past six months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation
21. Intolerance or allergic reaction to any of the medical therapy, including aspirin, clopidogrel, heparin, and local or general anesthetics
22. History of life-threatening allergy to contrast medium. If not life threatening and can be effectively pre-treated, patient can be enrolled at physicians' discretion
23. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
24. Active bleeding diathesis or coagulopathy; active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelets count <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia that increases the risk of bleeding, uncontrolled severe hypertension (systolic BP>180mm hg or diastolic BP>115mm hg), severe liver impairment (AST or 25. ALT >3 times normal, cirrhosis), creatinine >265.2 mmol/l (unless on dialysis). Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment
25. Indication for warfarin or heparin beyond enrollment (exceptions allowed for use of systemic heparin during stenting procedure or subcutaneous heparin for deep venous thrombosis prophylaxis while hospitalized)
26. Inability to understand and cooperate with study procedures or sign informed consent

27. Severe dementia or psychiatric problems that prevent the patients from following an outpatient program reliably
28. Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study
29. Actively participating in another drug or device trial that has not completed the required protocol follow-up period

6. Methods

6.1 Primary outcomes

- Stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year

6.2 Secondary outcomes

- Disabling stroke or death after enrollment through 3 years in both arms;
- 2-year rate of the same-territory stroke;
- 3-year rate of the same-territory stroke;
- Any stroke, TIA, or cardiovascular events within a follow-up of 3 years.
- Death rate in both arms within a follow-up of 3 years.

6.3 Definitions of outcomes

1. Stroke is defined as the rapid loss of brain functions due to disturbance in the blood supply to the brain that persists beyond 24 hours. Stroke is diagnosed by an independent outcome committee which is composed with experienced neurologists. They will collect additional key neuro-images (CT or MR scans) as adjunct evidence for outcome classification of ischemic or hemorrhagic stroke;
2. Ischemic stroke is defined as a new focal neurological deficit of sudden onset lasting at least 24 hours that is not associated with a hemorrhage on brain CT or MRI. Ischemic strokes are further classified by the neurologic adjudicators as being either in or out of the territory of the qualifying artery;
3. Hemorrhagic stroke is defined as parenchymal, sub-arachnoid, or intra-ventricular hemorrhage detected by CT or MRI that is associated with new neurological signs or symptoms lasting >24 hours or a seizure;
4. Death, any of the following criteria:
    a) Procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure.
    b) Death to due to cardiac cause, e.g., myocardial infarction, cardiac tamponade, and worsening heart failure
    c) Death of other cause (e.g., malignancy, trauma and suicide)
    d) Sudden or unwitnessed death
    e) Death of unknown cause

5. Disabling stroke is defined by any of the following:
    a) a modified Rankin score of 3 or more, on a scale of 0 to 6, with higher scores indicating greater disability;
    b) an increase in at least one mRS category from an individual's pre-stroke baseline
    c) a score on the composite National Institutes of Health Stroke Scale (NIHSS) of 7 or more, on a scale of 0 to 42, with higher scores indicating more severe deficits;
    d) an increase in at least 4 NIHSS scales from pre-stroke baseline.
6. Complication rates associated with stenting procedures: refer perforator occlusion, guidewire perforation, artery-to-artery embolism, stent thrombosis, or reperfusion hemorrhage within 72 hours after PTAS procedures.
7. Restenosis rate: if patients have follow-up vascular imaging, the imaging modality will be recorded, in addition to the percent stenosis of the target lesion. Re-stenosis is defined as 50% narrowing or greater irrespective of symptoms.
8. TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarction;
9. Cardiovascular events: refer a class of events that is related to stenting or medical therapy, which includes coronary artery diseases (CAD) such as angina and myocardial infarction.
10. BI, mRS and NIHSS: please refer the Appendix 13.1, Appendix 13.2 and Appendix 13.3.
11. Compliance of drug: patients will be contacted at 30-day, 1-year, 2-year and 3-year after enrollment, to gather information regarding the use of anti-platelet drugs, changes in prescribed drugs, medical condition and quality of life.
    a) very good, 80% - 120%;
    b) good, 60% - 79%;
    c) fair, 40% - 59%;
    d) poor, < 40%.

6.4 Definitions of other parameters

6.4.1 Major vascular complications

1. Non-neurovascular death: e.g., trauma, suicide, malignancy, or cardiovascular mortality;
2. Major vascular complication: e.g., aortic dissection, aortic rupture, or annulus rupture;
3. Access site of access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or percutaneous closure device failure) leading to death, life-threatening or major bleeding, or neurological impairment;
4. Distal cerebral embolism from a vascular source requiring surgery or endovascular intervention or irreversible neurological damage;
5. Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical examination, and/or decreased or absent blood flow on lower extremity angiogram;
6. surgery for access site-related nerve injury；
7. permanent access site-related nerve injury.

6.4.2 Minor vascular complications

1. Access site of access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, or percutaneous closure device failure) not leading to death, life-threatening or major bleeding, or neurological impairment;
2. Distal cerebral embolism treated with mechanical thrombectomy not resulting in irreversible neurological damage;
3. Any unplanned endovascular stenting or surgical intervention not meeting the criteria for a major vascular complication;
4. Vascular repair: e.g., ultrasound-guided compression or injection embolization, transcatheter embolization or stent-graft;
5. Percutaneous closure device failure.

6.5 Treatment assignment

Eligible patients will be enrolled with their baseline data entered into a web-based database system. Patients will be randomized (1:1) to medical therapy alone or medical therapy plus stenting using Wingspan. Randomized outcomes will not be blinded to the patients and their family. When a patient is included for participation, site investigator will be informed. The patients will be excluded from the ITT analysis if they sign the ICF while they are not confirmed eligible with central adjudication.

A summary will be made of patients who are randomized to PTAS group but do not undergo surgery, and the patients who are randomized to medical therapy but receive surgery. Compliance will be assessed by the investigator at each visit using information provided by the care-giver or patients themselves. This information should be recorded in the source document at each visit.

6.6 Randomization and numbering

Complete randomization will be performed with an Interactive Voice Response System (Clinicalsoft Company Limited, Beijing, China; http://ivr.clinicalsoft.cn). Eligible patients will be randomized with a 1:1 ratio to medical therapy or medical therapy plus PTAS. Each patient has its unique ID number (center number plus screening order number) in this trial. This center number will be assigned to each participating center. Once the patients or their legal representatives sign the informed consent form (ICF) at each center, they will be assigned with a screening order number. At each center, the screening order number will be in order of the patients' enrollment (e.g., 001, 002, 003 and so on).

6.7 Medical group

Patients randomized to medical group will received medical therapy and be discharged without further intervention.

6.7.1 Medical therapy

Medical therapy will be identical in both arms and will be similar to the previously described risk factor management for the SAMMPRIS trial. In brief, it includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75mg alone per day thereafter) and management of risk factors.

The drugs used in the trial are commercially available in China. Several generic aspirin or clopidogrel are available and allowed to be used. Medical therapy regimen, including DAPT and statin will be purchased by the patients or their family member,

who later received various degrees of reimbursement from the Chinese social security system.

6.7.2 Management of risk factors

Risk factor control is based on the AHA/ASA guidelines[32] and the SAMMPRIS[19] trial protocol. Medical management of risk factors consists of normalizing low-density lipoprotein (LDL-C) (statins, target LDL-C <2.58 mmol/l [100 mg/dl]), hypertension (systolic pressure <140 mmHg and a diastolic pressure <90 mmHg), glucose disorder (in diabetic patients, hemoglobin A1c [HbA1c] will be checked at enrollment and during each clinical visit with a target level of <6.5%), and lifestyle modification. Intensive management of risk factors is applicable to all the included patients (e.g., hypertension, lipid disorder, diabetes mellitus, overweight, obesity, physical inactivity, and cigarette smoking).

6.7.3 Health education and lifestyle modification

1. Health education and lifestyle modification: quit smoking, moderate-intensity physical exercises (at least 3 times per week for 30 min per session).
2. Obesity: BMI should be maintained below 25 kg/m^2. Weight reduction is associated with a lowering in BP and may thereby reduce stroke risk.

6.8 PTAS group

Patients randomized to PTAS group are to be scheduled for surgery within 3-5 business days after enrollment. The study protocol requires that the stenting procedure be performed by a qualified operator at each site.

6.8.1 PTAS procedure

Patients randomized to stenting will be placed on DAPT (aspirin, 100 mg daily and clopidogrel 75 mg daily) for 3-5 consecutive days before the procedure. No loading dose will be allowed. The study protocol requires that the PTAS procedure is typically performed under general anesthesia by a credentialed interventionist who should be the primary operator. The procedure is typically performed via a transfemorally placed 6F-long sheath or guiding catheter. The stenotic lesion is primarily crossed with a standard 0.014'' microcatheter microwire system under high magnification fluoroscopic roadmap control. Once across the lesion, the microcatheter is exchanged over a 300-cm, 0.014'' microwire for a Gateway balloon

catheter. After angioplasty, the balloon catheter is exchanged for a Wingspan stent delivery system and the self-expanding Wingspan stent is deployed across the stenosis. If the residual stenosis after inserting the Wingspan stent is >50%, the study protocol allows for postdilation with a new balloon catheter. The protocol required frequent measurements of blood pressure during the procedure and at least 1 measurement every half an hour during the next 24 hours while the patient is monitored. The patient will be continued on aspirin, 100 mg daily, and clopidogrel, 75 mg daily, for the next 90 days and subsequently on aspirin or clopidogrel alone. Risk factor control should be applied thereafter.

6.8.2 Rescue therapy for PTAS

1. If the residual stenosis is >50% after the primary Wingspan placement, study protocol allows for the postdilation with a new balloon catheter to achieve better angioplasty outcome.
2. If the initial Wingspan stent could not be delivered to the target lesion, the interventionalist can try to deliver a second Wingspan stent.
3. If the second Wingspan stent cannot be delivered to the target lesion, the interventionalist has the following options: a) angioplasty alone; b) using non-study stents; c) procedure aborted.
4. If an ischemic stroke occurs or an intraluminal thrombus develops during the procedure, the interventionalist or stroke neurologist (if available) should administrate appropriate treatment. This may include intravenous or intraarterial use of thrombolytic therapy, e.g., glycoprotein IIb-IIIa Inhibitor (Tirofiban).
5. If a major dissection, other occlusive complication, or stent misplacement occurs that requires placement of a second Wingspan stent, this may be done as a rescue procedure. In the meantime, neuro ICU will provide reservations to deal with patients with serious complications.

6.9 Follow-up schedule

Clinical assessment of patients will be conducted in outpatient consultation or by telephone contact with the site investigators at 30-day, 1-year, 2-year, and 3-year or if the patients died before the close-out visit. At each follow-up visit, patients will be examined by study physicians who also manage the patients' vascular risk factors. Imaging assessment will be achieved by head MRI, CTA, MRA, or DSA at each visit if possible.

Table: follow-up schedule

	In-hospital			Follow-up (Paper-based CRF)			
	Baseline	Procedure	Discharge	30-day	1-year	2-year	3-year
ICF	✓						
In-/Exclusion criteria	✓						
Demographics	✓						
Medical history	✓						
Physical exam	✓			✓	✓	✓	✓
Neurological status							
NIHSS	✓	✓	✓	✓	✓	✓	✓
mRS	✓	✓	✓	✓	✓	✓	✓
Barthel Index	✓	✓	✓	✓	✓	✓	✓
Lab test	✓				✓	✓	✓
Neuro-imaging							
CT/MRI (DWI)	✓				✓	✓	✓
TCD/CTA/MRA	✓				✓	✓	✓
CTP/PWI	✓	✓			✓	✓	✓
DSA	✓	✓			✓	✓	✓
Medication	✓			✓	✓	✓	✓
AE/SAE		✓	✓	✓	✓	✓	✓

6.9.1 Baseline

At baseline, the following parameters should be documented:

I. Date of ICF

II. Demographics

III. Medical history

a. Present history

b. Previous history, e.g., hypertension, diabetes, lipid disorder, coronary and peripheral artery diseases, smoking and alcohol abuse, etc.

IV. Clinical status

a. Physical examination

b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature

c. ECG

d. BMI

V. Neurological status

a. NIHSS

b. mRS

c. Barthel Index

VI. Lab test

a. Routine blood test

b. Liver function: e.g., ALT, AST, etc.

c. Renal function: e.g., Cr, BUN, etc.

d. Renal damage: proteinuria (according to site's preference and facilities)

e. FBG and HbA1c

f. Lipid level: LDL, HDL and TC

g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.

h. Inflammation markers: CRP

i. Pregnancy test

VII. Neuro-imaging

a. Cranial CT/MR (DWI)

b. TCD/CTA/MRA

c. CTP/PWI parameters: CBF, CBV, MTT and TTP

d. DSA

6.9.2 Procedure (for PTAS group)

During the procedure, the following parameters should be documented:

I. Date of the procedure

a. delayed procedure: beyond 5 business day after enrollment

b. procedure on time: within 5 business day after enrollment

II. Operator of the procedure

III. Anesthesia: general or local

IV. Morphological characteristics of the lesion on DSA

a. side: right or left

b. size: diameter and length (mm)

c. location: M1, BA, ICA or VA

d. stenotic degree (%) determined using the WASID criterion[33]

e. Mori classification: type A, B or C[34] (Appendix 13.4)

f. TICI perfusion categories[35] (Appendix 13.5)
g. ASITN/SIR collateral flow grading system[35] (Appendix 13.6)

V. Type of procedures
   a. angioplasty plus stent placement
   b. angioplasty alone
   c. none

VI. Angioplasty balloon
   a. size: diameter and length (mm)
   b. type: Gateway or others
   c. number: 1 or more
   d. inflation pressure (atm)

VII. Stent delivered
   a. size: diameter and length (mm)
   b. type: Wingspan or others
   c. number: 1 or more

VIII. Residual stenosis (%)

IX. Use of post-dilation:
   a. yes or no
   b. if yes, type and size of the balloon used
   c. inflation pressure (atm)
   d. residual stenosis after post-dilation

X. Rescue therapy

XI. Post-PTAS neurological status
   a. NIHSS
   b. mRS
   c. Barthel Index

XII. AE/SAE

6.9.3 Discharge

Before discharge, the following parameters should be documented:

I. Neurological status
    a. NIHSS
    b. mRS
    c. Barthel Index
II. AE/SAE

6.9.4 30-day follow-up

At 30-day follow-up, the following parameters should be documented:

I. Clinical status
    a. Physical examination
    b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
    c. ECG
    d. BMI
II. Neurological status
    a. NIHSS
    b. mRS
    c. Barthel Index
III. Medication
IV. AE/SAE

6.9.5 1-year follow-up

At 1-year follow-up, the following parameters should be documented:

I. Clinical status
    a. Physical examination
    b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
    c. ECG
    d. BMI
II. Neurological status
    a. NIHSS

b. mRS
c. Barthel Index

III. Lab test
a. Routine blood test
b. Liver function: e.g., ALT, AST, etc.
c. Renal function: e.g., Cr, BUN, etc.
d. Renal damage: proteinuria (according to site's preference and facilities)
e. FBG and HbA1c
f. Lipid level: LDL, HDL and TC
g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
h. Inflammation markers: CRP

IV. Neuro-imaging
a. Cranial CT/MR (DWI)
b. TCD/CTA/MRA
c. CTP/PWI parameters: CBF, CBV, MTT and TTP
d. DSA

V. Medication

VI. AE/SAE

6.9.6 2-year follow-up

At 2-year follow-up, the following parameters should be documented:

I. Clinical status
a. Physical examination
b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature
c. ECG
d. BMI

II. Neurological status
a. NIHSS
b. mRS

c. Barthel Index

III. Lab test

a. Routine blood test

b. Liver function: e.g., ALT, AST, etc.

c. Renal function: e.g., Cr, BUN, etc.

d. Renal damage: proteinuria (according to site's preference and facilities)

e. FBG and HbA1c

f. Lipid level: LDL, HDL and TC

g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.

h. Inflammation markers: CRP

IV. Neuro-imaging

a. Cranial CT/MR (DWI)

b. TCD/CTA/MRA

c. CTP/PWI parameters: CBF, CBV, MTT and TTP

d. DSA

V. Medication

VI. AE/SAE

6.9.7 3-year follow-up

The following parameters should be documented:

I. Clinical status

a. Physical examination

b. Vital signs: blood pressure, pulse rate, respiratory rate and body temperature

c. ECG

d. BMI

II. Neurological status

a. NIHSS

b. mRS

c. Barthel Index

III. Lab test
    a. Routine blood test
    b. Liver function: e.g., ALT, AST, etc.
    c. Renal function: e.g., Cr, BUN, etc.
    d. Renal damage: proteinuria (according to site's preference and facilities)
    e. FBG and HbA1c
    f. Lipid level: LDL, HDL and TC
    g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
    h. Inflammation markers: CRP
IV. Neuro-imaging
    a. Cranial CT/MR (DWI)
    b. TCD/CTA/MRA
    c. CTP/PWI parameters: CBF, CBV, MTT and TTP
    d. DSA
V. Medication
VI. AE/SAE

6.10 Consent withdrawal

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Consent withdrawal occurs only when a patient: 1) does not want to participate in the study anymore; 2) or does not want any further visits or assessments; 3) or does not want any further study-related contacts.

When a patient withdraws consent, the investigator is required to determine the primary reason for this decision and record this information. Further attempts to contact the patient are not allowed unless safety efficacy require follow-up. After withdrawal, patients will not be replaced by others and their randomized ID number will not be re-used.

6.11 Follow-up of subjects withdrawn from treatment assignment

Some cases may withdraw from treatment assignment. Since the statistical analysis is planned for ITT principle, they will be analyzed in the group that they were originally allocated to.

6.12 Lost for follow-up

For patients whose status are unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in ICF and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. Lost for follow-up could be accounted by no reply although try to contact the cases three times or more. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

6.13 Study completion and post-study treatment

At the end of the study visit, the investigator should provide follow-up medical care for all patients who are prematurely withdrawn from the study or refer them for appropriate ongoing care. When the patient has completed all scheduled study assessments, the investigator is required to inform to record the patient completion in the EDC system.

6.14 Premature termination of the study

During the trial, AEs or SAEs will be reported to DSMB. The DSMB will monitor SAEs, major safety events, device and procedure failures and any device-related adverse events. In the current trial, SAEs mainly refer disabling stroke, symptomatic intracranial hemorrhage or death within 1 year after enrollment and all-cause death within a follow-up 3 years. The stopping rules will be developed by DSMB and the advices of DSMB will be sent to the executive and steering committee of the study. The Executive and Steering Committee will be responsible for informing the EC whether the advices are fully implemented or not.

6.15 Outcome assessment

This is a multicenter phase IV RCT with open-label treatment and blinded outcome assessment. Outcome assessment will be sent to an independent Outcome Committee. The committee is composed of experienced neurologists who are not involved in the study, will be blinded to the treatment assignment. All the outcome will be adjudicated by the outcome committee, and a consensus will be reached by a third clinician in case of discrepancies.

7. SAFETY MONITORING

7.1 Adverse events (AE)

AE is defined as any unfavorable and unintended sign, symptom or disease that occurs to a subject while enrolled in a clinical investigation, whether or not considered related to the study intervention or device. Medical conditions that exist at study enrollment are not considered an AE unless condition worsens after use of the study intervention or device.

7.2 Serious adverse events (SAE)

7.2.1 Definition of SAE

A SAE is any medical experience regardless of its relationship to the investigational device or study devices that occurs during subject enrollment in this trial that results in any of the following:

- need to be hospitalized or prolonged hospitalization;
- persistent or significant disability/incapacity;
- death of the study subject;
- necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- or causing congenital anomalies/birth defects.

7.2.2 SAE reporting

All SAEs will be recorded in the table of CRF. The details of the SAEs, including starting time, ending time, duration, treatment, outcome, and the relationship with intervention will be recorded as well. Frequency of SAEs will be summarized according to the assignments. All recorded AEs/SAEs will be reported to the investigator. SAEs that result in death or life-threatening stroke will be reported to DSMB/EC within 14 days after the investigator is informed for the first time. In the current trial, SAEs mainly refer disabling stroke, symptomatic intracranial hemorrhage or death within 1 year after enrollment and all-cause death within a follow-up 3 years. For safety analysis, an independent summary will list SAEs related to intervention in PTAS group.

7.2.3 Management and follow-up of AEs/SAEs

Investigators should take appropriate treatment for AEs to ensure the safety of patients and track all AEs/SAEs until they are properly resolved, or the condition is

stable. Additional medical procedures and/or referral to a medical specialist may be required to confirm whether the patients are qualified to continue to participate in the study.

8. DATA MANAGEMENT

8.1 Study Data Collection

Site coordinator records data by filling out the paper-based CRFs for each case. The sponsor (Beijing Xuanwu Hospital) provides CRFs to each site. Site investigator is responsible for that all CRFs are completed, reviewed, and approved. Also, site investigator will sign on CRFs and confirm that clinical, imaging and laboratory data entered into the CRFs are true.

Patient ID in CRFs should be recorded in an anonymous form, which are only identified by the patient ID number and Chinese phonetic alphabets (pinyin) initials. CRFs should be filled in with a black ballpen based on the original document. Fill in “not done” for missing data; fill in “not applicable” if not applicable; fill in “unknown” for unknown data.

If the data entered into CRFs needs to be revised, cross out the error with a single line so that it can still be seen clearly, and then fill in the correct data next to it. The revisions should be approved and signed by the site investigator. If necessary, the reason for the revisions should be indicated. Site investigator will review the integrity and accuracy of the CRFs and make further corrections and amendments if necessary. When the trial is finished, site investigator will send the CRFs to Tigermed Data Management Co., Ltd; (https://tigermedgrp.com) for data entry.

The data in the paper-based CRFs will be entered into the database by Tigermed Data Management Co., Ltd, with its completeness and accuracy reviewed. The missing data and questioned data are reported in the data query form, which will be sent back to the site investigator for further verification. Site investigator will send back in the resolved query form with signature and date of signing. Tigermed Data Management shall be responsible for entering the resolved results into the database. After the final confirmation is completed and all queries are resolved, the database is updated and locked. Data is transferred from the database directly to the data file (SAS data set) for statistical analysis. The data can be changed after database is unlocked upon reasonable request.

8.2 Data Processing and Quality Control

The data entry is performed by the staff trained by Tigermed Data Management Co., Ltd. All the input data should go through verification and range check. The staff will be notified of a possible error, depending on the data validation. The staff will not move on unless the error is resolved.

All CRFs will be subject to preliminary inspection for data missing, inconsistency and deviation. Data inconsistency will be completed by electronic tracking and resolved by site coordinators and investigators.

Each data input will receive regular cross-check within forms. Site coordinators will be informed in case of errors identified. Corrections to the data in CRFs will be made by the site coordinators, and approved by the site investigators.

The data editing will continue when all data is cleaned. The site coordinators will supervise the verification of on-site source documents. If further data related to the source file is found during the site visit, additional queries will be generated and processed by the site coordinators.

8.3 Data storage

The investigator will document adequate records during the conduct of the study. Trial data including patient files, CRFs, ICFs, original copies of results, and imaging outcome, will be kept on files by the investigator for a period of 10 years or more.

9. STATISTICAL ANALYSIS

9.1 Analysis data set

Full Analysis Set (FAS): all the subjects who are randomized into groups will be included. Subjects who do not meet the eligible criteria or who withdraw immediately after randomization without receiving any interventions will be excluded. According to the intention-to-treat (ITT) principle, all randomized patients will be analyzed according to the treatment group assigned to them at the time of randomization. All presenting analyses will be conducted in the FAS population unless otherwise specified

Per-protocol Set (PPS): PPS refers population who are treated according to the study protocol, e.g., fulfilling eligibility criteria, assigned treatment after randomization, medication and follow-up protocol, and completion of the case report form). PPS analysis was conducted on the population who had not crossovers between groups or significant protocol violations. Crossover population from one arm to the other will not impact the ITT analysis. For PTAS group, significant protocol violations include: 1) use of non-study stents; 2) delayed procedure of PTAS (beyond 5 business days after enrollment; 3) procedure is aborted before lesion is accessed; 4) procedure is aborted due to total occlusion; 5) receive angioplasty only and others.

For other details, please refer to the Statistical Analysis Protocol (SAP) in the Appendix.

9.2 Analysis close date

The analysis close date for each arm is at the completion of 3-year follow-up of the last enrolled patient. The primary outcome is based on the exact 3-year time point for each patient, and event.

9.3 Sample size calculation

For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of ipsilateral stroke risk in medical therapy group WASID study was 18%,[36] which was 7.3% in a study by the Wingspan stent therapy.[23] At a significance level of 5% on both sides, the absolute difference of 10.7% (relative risk reduction 59%), and a power of 80%, within 12 months of follow-up, a total of 302 patients need to be evaluated. Assuming a 20% incidence of loss of follow-up and/or withdrawal, a total of 380 patients, 190 in the stent group and 190 in the medical group, are required to be enrolled in this study.

10. STUDY COMMITTEES

10.1 Executive and Steering Committee

Executive committee is composed of principle and site investigators from the participating centers, which is responsible for making decisions about the direction and strategy of the trial. During the trial period, this committee fulfills the coordination, implementation, organize regular meeting, and report progress. Also, it is required to review main trial publications, analysis plan and publication policy, and consider recommendations of DSMB.

10.2 Ethics Committee

The trial should first obtain the written approval from the Ethics committee of Xuanwu Hospital, Capital Medical University, Beijing, China. The trial will not enroll patient until the study protocol is approved by the local ethics committee (EC) in the other sites. In case of any major amendments to the trial protocol, renewed written approval should be obtained from the ethics committee. Updated ICF after amendments will be sent to patients in the active period of the trial. Minor amendments will not be sent to EC.

10.3 Data and safety Monitoring Board (DSMB)

An independent DSMB that is composed of neurologist, neurosurgeon, neuroradiologist and biostatistics experts who are not involved in the conduct of the trial. DSMB members should not have any scientific or financial conflicts of interest with the sponsor or investigator. DSMB is responsible for study conduct, progress and efficacy. By reviewing safety data, DSMB will advise executive committee to continue, modify or terminate the trial early.

10.4 Clinical outcome committee

Clinical outcome assessment will be sent to an independent Outcome Committee. The committee composed of experienced neurologists who are not involved in the study, will be blinded to the treatment assignment. All the outcomes will be adjudicated by the outcome committee, and a consensus will be reached by a third clinician in case of discrepancies. For details, please refer to *2.9 Assessments of clinical outcome* in the *2. Supplementary Methods*.

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2219 **10.5 Imaging outcome committee:**

2220 An independent imaging core-lab, IsCore Image CoreLab (ICIC,
2221 http://imagecorelabcn.com/), will be established with the aim of facilitating the central
2222 reading by clinicians and integrating medical imaging at the baseline control and
2223 each clinical visit. For details, please refer to *2.10 Assessments of imaging outcome*
2224 in the *2. Supplementary Methods*.

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11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1 Regulatory and ethical compliance

The design, implementation and reporting of this trial will follow the principles of the Declaration of Helsinki (World Medical Association: Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects - Version 2008).

11.2 Recruitment and informed consent form

Eligible patients who voluntarily agree to participate in the trial will be required to sign a written informed consent form (ICF). The ICF will be signed by the patients or his/her legal regal representatives prior to randomization. They will be informed shortly by the investigators when the treatment is assigned after central randomization.

11.3 Responsibilities of the investigator

Site investigators will review the eligibility of each candidate patient. If the patient is qualified and interested in this trial, he/she will be given written ICF to participate. Site investigators are responsible for explaining the research background, intervention, protocol, benefits, and risks of participating in the trial. A signed ICF copy will be kept by the patient as part of the study files. The patient is fully entitled to quit at any circumstance.

11.4 Public disclosure and publication policy

As the sponsor of the study, Xuanwu Hospital aims to publicize the primary and secondary outcome results in a high-impact scientific journal. Database of this trial will be locked within 3 months when the last enrolled patient finished the scheduled 3-year follow-up and all the data of the enrolled patients is completed. A manuscript will be submitted for potential publication in a scientific journal within 3 months after database lock. The manuscript will be shared with the financial sponsor(s) 3 months before submission, but the financial sponsor(s) have no influence on its contents. Anonymous data can be provided by principal investigators upon reasonable request.

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13. APPENDIX

13.1 Barthel Index (BI)

The Barthel scale is an ordinal scale used to measure performance in activities of daily living (ADL). Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing ADL and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital.

Category	Scale definition
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)

Transfers (bed to chair and back)	0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

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13.2 Modified Rankin Scale (mRS)

The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The addition of grade 6 indicates dead.

Grade	Disability	Descriptions
0	No symptoms	No symptoms
1	No significant disability	Able to carry out all usual activities, despite some symptoms.
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability	Requires some help, but able to walk unassisted.
4	Moderately severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent.
6	Dead	Dead

13.3 NIH Stroke Scale

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Instructions	Scale definition
1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded	0 = Answers both correctly. 1 = Answers one correctly. 2 = Answers both incorrectly.

and that the examiner not "help" the patient with verbal or non-verbal cues.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.

contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	
3. Visual fields: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Arm motor: The limb is placed in	0 = No drift; limb holds 90 (or 45) degrees

the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm
6. Leg motor: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg
7. Limb ataxia: This item is aimed at finding evidence of a unilateral	0 = Absent.

cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.

9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain:_____ ___

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

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13.4 Mori Classification

The Mori classification, formulated on the basis of DSA, delineates the length and geometry of intracranial stenosis as follows:

Type	Descriptions
A	short (5 mm or less in length) concentric or moderately eccentric lesions less than totally occlusive
B	tubular (5 to 10 mm in length) extremely eccentric or totally occluded lesions, less than 3 months old
C	diffuse lesions (more than 10 mm in length), extremely angulated (>90°) lesions with excessive tortuosity of the proximal segment or totally occluded lesions, 3 months old or older

13.5 TICI perfusion categories

The thrombolysis in cerebral infarction (TICI) grading system was described as a tool for determining the response of thrombolytic therapy for ischemic stroke. In interventional neuroradiology, it is commonly used for patients post endovascular revascularization. Like most therapy response grading systems, it predicts prognosis.

Grade	Descriptions	
0	No Perfusion. No antegrade flow beyond the point of occlusion.	
1	Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.	
2	Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.	
	2a	Only partial filling (<2⁄3) of the entire vascular territory is visualized.
	2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
3	Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.	

13.6 ASITN/SIR collateral flow grading system

ASITN/SIR refers to American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR). The grading system scale is determined on DSA, classifying the cerebral collateral status ranging from grade 0 to 4. Grades 0-1, 2 and 3-4 are usually regarded as poor, moderate and good collateral flow.

Grade	Descriptions
0	No collaterals visible to the ischemic site
1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

CASSISS Study Protocol: Summary of Changes (Version 1.0 ⇒ Version 3.0)

CASSISS Study: **C**hina **A**ngioplasty & **S**tenting for **S**ymptomatic **I**ntracranial **S**evere **S**tenosis

Prepared: May 1st, 2015

#	Item	Page	Description of change(s)		Reasons for change
			Before change (Version 1.0, date prepared: March 4th, 2013)	After change (Version 3.0, date prepared: May 1st, 2015)	
1	Secondary outcome	2. Summary (Page 9-10) 3.5.2 Secondary objectives (Page 13) 6.2 Secondary endpoints (Page 21)	Secondary outcome: • Disabling stroke or death beyond 30 days through 3 years in both arms; • Complication rates associated with stenting procedures; • Restenosis (>50%) related to stenting within a follow-up of 3 years; • Any stroke, severe TIA, or cardiovascular events within a follow-up of 3 years; • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index assessment within a follow-up of 3 years; • The compliance rate of the patients with regular medical therapy within a follow-up of 3	Secondary outcome: • Disabling stroke or death after enrollment through 3 years in both arms; • 2-year rate of the same-territory stroke; • 3-year rate of the same-territory stroke; • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years. • Death rate in both arms within a follow-up of 3 years.	Due to content revisions

			years; • Death rate in both arms within a follow-up of 3 years.		
2	Medical therapy	4. Study design (Page 14) 6.7.1 Medical therapy (Page 24) 6.8.1 PTAS procedure (Page 26)	Medical therapy includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg alone per day thereafter) and management of risk factors.	Medical therapy includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75mg alone per day thereafter) and management of risk factors.	Due to content revisions
3	Severe TIA	6.3 Definitions of endpoints (Page 22)	• Severe TIA refers to rapidly developed clinical signs of focal or global disturbance of cerebral function lasting longer than 10 minutes but fewer than 24 hours, without apparent nonvascular cause.	Deleted	Due to content revisions

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