China **A**ngioplasty **& St**enting for **S**ymptomatic **In**tracranial **S**evere **S**tenosis **(CASSISS)**

A prospective multi-center, randomized controlled trial (RCT)

Statistical Analysis Plan

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1. Abbreviations

ALT	Serum alanine aminotransferase
AST	Serum glutamic-oxalacetic transaminase
APTT	Activated partial thromboplastin time
BUN	Urea nitrogen (blood)
BMI	Body mass index
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CTA	Computed tomography angiography
CTP	CT perfusion scan
DSA	Digital subtraction angiography
DSMB	Data Safety Monitoring Board
DWI	Magnetic resonance diffusion weighted imaging
EC	Ethics committee
ECG	Electrocardiogram
FAS	Full analysis set
FBS	Fasting plasma glucose
HDL-C	High density lipoprotein cholesterol
ICF	Informed consent
INR	International standard ratio
ITT	Intention to treat
LDL-C	Low density lipoprotein cholesterol
LOCF	The last observation was carried forward
MCA	Middle cerebral artery
MedDRA	Dictionary of medical terms used for drug registration

MRA	Nuclear magnetic angiography
mRS	Modified Rankin Scale
MTT	Mean transit time
NIHSS	National Institutes of Health Stroke Assessment Scale
PET	Positron emission tomography
PPS	Per-protocol set
PT	Prothrombin time
PWI	Perfusion-weighted imaging
RCT	Randomized controlled trial
SFDA	State Food and Drug Administration
TCD	Transcranial Doppler scan
TIA	Transient ischemic attack
XeCT	Xenon enhanced computed tomography

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2. Protocol Abstract

2.1 Study purpose

Main purpose: 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).

Secondary purpose: 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;
- mRS, NIHSS scores of patients.

2.2 Study design

This study is a multicenter, randomized, open-label, outcome-blinded trial comparing medical therapy alone or medical therapy plus stenting with the use of the Wingspan Stent system in patients with transient ischemic attack (TIA) or non-disabling ischemic stroke caused by 70%-99% stenosis of a major intracranial artery.

2.3 Sample size

For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of ipsilateral stroke risk in medical therapy group WASID study was 18%, which was

7.3% in a study by the Wingspan stent therapy (Wei-jian Jiang, etc.). 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 needs to be evaluated. Assuming a 20% incidence of loss of follow-up and/or withdrawal, a total of 380 patients, 190 per group, are required to be enrolled in this study.

2.4 Blinding and randomization

Complete randomization methodology will be used. Once the patient meets the inclusion criteria after signing the informed consent form, the researcher will immediately make a phone call to the research group, and the answering staff will assign the patient a random number according to the patient number, and the random number will associate the patient with the corresponding treatment group. Patients will be given medical therapy alone or Wingspan stent plus medical therapy, depending on the treatment group randomly assigned. Patients randomly assigned to the medical treatment group will be discharged after DSA examination.

This study is an open, outcome-blinded study.

2.5 Interventions

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, asprin 100 mg plus clopigdorel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75 mg alone per day thereafter) and management of risk factors. Medical management of risk factors consists of control of low-density lipoprotein (LDL-C) (target: LDL-C<2.58mmol/L (100 mg/dL) with statins, and hypertension (systolic pressure <140 mmHg [<130mmHg in the case of patients with diabetes] and diastolic pressure <90 mmHg) based on 2014 AHA/ASA guidelines.

Stenting:

Patients randomized to stenting will be scheduled for intervention within three to five business days. The study protocol requires that the stenting procedure be performed under general anesthesia by a qualified operator at each site. Intensive management of risk factors will be applied thereafter.

2.6 Study population and diagnostic criteria

This trial aims to recruit patients who have had a TIA or ischemic stroke (mRS≤2) and advanced ICAS (70%–99% on angiogram). Catheter angiography is required to confirm 70%–99% stenosis by the WASID criterion for a patient to qualify. Patients who have an ischemic stroke within the last three weeks will not be included because of concern for hemorrhagic transformation.

2.6.1 Inclusion criteria

Detailed inclusion criteria were as follows:

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.

2.6.2 Exclusion criteria

Detailed exclusion criteria were as follows:

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

3. Assessment of Outcome evaluation

3.1 Outcome evaluation

3.1.1 Primary Outcome

Stroke or death within 30 days after enrollment or stroke in the territory of qualifying artery (SIT) beyond 30 days through 1 year.

3.1.2 Secondary Outcomes

- Disabling stroke or death within 3 years after randomization;
- 2-year rate of SIT;
- 3-year rate of SIT;
- Death rate within 3 years;
- Any stroke, TIA, or cardiovascular events within 3 years.

Note

Stroke is defined as the rapid loss of brain function due to disturbance in the blood supply to the brain that persists beyond 24 hours. This can be due to ischemia or hemorrhage.

TIA is defined as rapidly developed clinical signs of focal or global disturbance of cerebral function lasting longer than 10 minutes but fewer than 24 hours, with no apparent nonvascular cause.

3.2 Safety outcomes

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.

4. Data Safety Monitoring Board (DSMB)

An independent data safety monitoring committee composed of experts in neurosurgery, internal medicine, neuroradiology, and biostatistics who are not involved in the study is responsible for the following:

1. All potential outcome events including TIA, stroke, and death will be reviewed and confirmed. Clinical records and imaging results related to any outcomes are required to be emailed to the outcome committee, and the outcome committee's decision will be the final decision.
2. Efficacy and safety data, as well as balance of patient benefits and risks will be reviewed regularly. Timely recommendations will be given to the executive committee on whether to continue, modify, or discontinue the study.

5. Analysis data set

Full Analysis Set (FAS): all the subjects who are randomized into groups will be included, except the subjects who do not meet the inclusion and exclusion criteria and who are withdrawn immediately after randomization without receiving any intervention 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.

Per-protocol Set (PPS): All patients who are treated according to the study protocol (the eligibility criteri, the assigned treatment after randomization, additional medication protocol, the follow-up protocol, and completion of the case report form).

Safety Analysis Set (SAS): Randomized patients who receive at least one dose of antiplatelet therapy with a documented safety outcome.

Efficacy analysis will be carried out based on the FAS and the PPS, and the conclusions will be made based on the FAS. All baseline demographic data analyses will be performed on the basis of the FAS and safety assessments will be performed on the SAS.

6. Processing of missing data

For patients who die or are lost to follow-up within 36 months after randomization, the 30-day, 12-month, and 36-month NIHSS and mRS score will be filled using the last observed value (LOCF) method. For other missing data, no filling or other processing will be conducted. For survival analysis, missing data will be considered as censored.

7. Statistical analysis method

7.1 General principles of statistical analysis

Prior to database locking, the statistician is responsible for developing a statistical analysis plan in consultation with the principal investigator. SAS 9.4 statistical software will be used. The efficacy evaluation includes the analysis of PPS and FAS sets, and the conclusion will be based on the FAS set. SAS set analysis will be used for safety evaluation.

All statistical tests will be conducted using a two-sided test, and a p-value of 0.05 or less will be considered statistically significant (unless otherwise specified).
For patients who cross groups, that is, the actual group is not consistent with the randomly assigned group, efficacy will be analyzed according to the ITT principle based on the FAS, and safety will be analyzed according to the SAS.

7.2 Analysis plan

After the study protocol is finalized, the statistician will develop the statistical analysis plan in consultation with the principal investigator. All the analyses will be performed with the use of SAS software, version 9.4 (SAS Institute, license number: 11202165).

Numerical variables will be presented with mean, standard deviation (normally distributed), or median (interquartile interval). Categorical and hierarchicalvariables will be presented with the number of cases and percentages.

Appropriate method for comparison of baseline between two groups will be adopted according to the types of variables, and the comparison of numerical variables will be tested with t-test (normal distribution) or Wilcoxon rank test according to the data distribution, categorical variables with chi-square test or the exact probability method

(if a chi-square test is not applicable), hierarchical data with Wilcoxon rank test or CMH.

7.3 Completion

The number of patients enrolled in each center, the number of patients who complete the trial and the number of patients withdrawn from the trial will be summarized, and the list of patients not included in the FAS/PPS set and the reasons for exclusion will be listed. The number of cases in each group FAS/PPS dataset, the distribution of cases in each center, and a detailed list of incomplete causes will be listed.

7.4 Demographic data and baseline characteristics

Baseline data such as patient demographic characteristics (age and gender), vital signs, past medical history, treatment history and current medical history will be described, and baseline data such as age, gender and BMI of the two groups will be compared to measure the comparability of the two groups.

7.5 Efficacy analysis

FAS and PPS will be used for efficacy analysis.

7.5.1 Main Efficacy index

Stroke or death within 30 days after randomization; And stroke in the territory of qualifying artery (SIT) beyond 30 days through 12 months after randomization.

The incidence of stroke or death at 12 months will be compared between the medical therapy group and the stent group, and a 95% confidence interval will be calculated for the difference between the two groups. CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If the impact of other

factors is adjusted, Logistics regression model can be considered for inter-group comparison.

The Log Rank test will be used to analyze the primary efficacy outcomes, and the center information will be stratified as covariates. The Cox proportional risk model will be used to calculate HR and its 95% confidence interval (CI) to estimate efficacy. The model included the same covariates as the Log Rank test for fitting. Kaplan-Meier curves will be plotted by treatment group.

For comparison of patient demographic characteristics (age, gender), vital signs, medical history, history of treatment and the medical records of baseline data between groups, if there are important significant differences for baseline data, the Cox proportional hazards model will be used for adjustment of these baseline variables, which will be included as a sensitivity analysis.

7.5.2 Secodary Efficacy index

Disabling stroke or death after enrollment within 3 years in both arms; 2) 2-year rate of SIT; 3) 3-year rate of SIT; 4) any stroke, TIA, or cardiovascular events within 3 years; 5) survival rate within 3 years. All above will be analyzed using the same method as the primary efficacy outcomes. The incidence of each outcome and the 95% confidence interval will be described by groups.

7.5.3 Others

Mixed effects model will be used to compare the changes of neurological function indexes between groups. At the same time, the dichotomous variables will be transformed by selecting clinically significant cut-off points for inter-group comparison. For mRS, 0-2 versus 3-6 will be used. For NIHSS, an increase of 4 points or more from baseline to 12 months will be considered to have deteriorated neurological function. CMH Chi-square test considering multicenter design will be

adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.

7.6 Safety analysis

The safety evaluation will be analyzed on the SAS dataset.

The number of adverse events of the two groups, as well as the incidence of adverse events, serious adverse events will be described in tables. The changes of laboratory and ECG will be described in tables. Procedure-related complications within 30 days after operation in the stent group will be analyzed. Chi-square test/Fisher exact test will be used to compare the incidence of adverse events and the incidence of serious adverse events between the two groups.

8. Statistical analysis results

8.1 Distribution of included patients

Table 1 Population distribution of each center1

	FAS			PPS			SS (Actual Group)		
Center	PTAS group	Medical group	Total	PTAS group	Medical group	Total	PTAS group	Medical group	Total
Total number									

422 Table 2 List of patients not included in the FAS/PPS set2

				Included in analysis dataset		
Center	Patient ID	Time of enrollment	Reason of exclusion	PPS	FAS	SS

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424 Table 3 Data sets of enrolled patients and safety and efficacy analysis sets.3

	Items	PTAS group	Medical group	Total
The whole data set				
	Randomly enrollment			
Not included in the FAS set				
	Failure to meet inclusion/exclusion criteria			
	Exit after randomization			
Suspension during study				
	Upon requests from subjects or subject's legal authorized representatives.			
	lost of follow-up			
	Crossover			
	Failure to follow the plan			
	Other			
Safey analysis set				
	SS (Actual Group)			
Efficacy analysis set				

	FAS			
	PPS			

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8.2 Demographic data and baseline characteristics

Table 4 Demographic data4

Items	Indicatiors	Total	PTAS group	Medical group	P
Age (years)	Mean (SD)				
Gender	Male, n (%)				
	Female, n (%)				
Ethnicity	Han, n (%)				
	Other, n (%)				

Table 5 Baseline information5

Items	Indicatiors	Total	PTAS group	Medical group	P
Systolic blood pressure (mmHg)	Mean (SD)				
Diastolic blood pressure (mmHg)	Mean (SD)				
Heart rate (times per minute)	Mean (SD)				
BMI (kg/m2)	Mean (SD)				
Smoking history	None n (%)				

Items	Indicatiors	Total	PTAS group	Medical group	P
	Previous n (%)				
	Current n (%)				
Alcohol use	No n (%)				
	Previous n (%)				
	Current n (%)				
Family history of cerebrovascular disease	No n (%)				
	Yes n (%)				
Family history of cardiovascular disease	No n (%)				
	Yes n (%)				
High density lipoprotein cholesterol	Mean (SD)				
Low density lipoprotein cholesterol	Mean (SD)				
Total cholesterol	Mean (SD)				
triglycerides	Mean (SD)				
C-reactive protein	Mean (SD)				
HbA1c	Mean (SD)				

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434 Table 6 Past medical history6

Items	Indicatiors	Total	PTAS group	Medical group	P
Hypertension	No n (%)				
	Yes n (%)				
Diabetes	No n (%)				
	Yes n (%)				
Hyperlipidemia	No n (%)				
	Yes n (%)				
Coronary heart disease (CHD)	No n (%)				
	Yes n (%)				
Myocardial infarction	No n (%)				
	Yes n (%)				
Atrial fibrillation	No n (%)				
	Yes n (%)				
Peripheral vascular disease	No n (%)				
	Yes n (%)				
Alimentary ulcer	No n (%)				
	Yes n (%)				

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437 Table 7 History of previous and current medical therapy for cerebrovascular diseases7

Items	Indicatiors	Total	PTAS group	Medical group	P
Antiplatelet agent	No n (%)				
	Yes n (%)				
Anticoagulant drugs	No n (%)				
	Yes n (%)				
History of radiotherapy for cerebrovascular disease	No n (%)				
	Yes n (%)				
History of surgical treatment of cerebrovascular disease	No n (%)				
	Yes n (%)				

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440 Table 8 Medical records of the present ischemic attack.8

Items	Indicatiors	Total	PTAS group	Medical group	P

Items	Indicatiors	Total	PTAS group	Medical group	P
Ischemia-cerebrovascular disease occurred within 12 months	Cerebral infarction n (%)				
	TIA n (%)				
Time from symptom onset to randomization	Median (IntQ)				
Artery stenosis	Intracranial segment of internal carotid artery N (%)				
	Middle cerebral artery N (%)				
	Intracranial segment of vertebral artery N (%)				
	Basilar artery N (%)				
	Others n (%)				
Stenosis degree	Median (IntQ)				
	70-79% n (%)				
	80-89% n (%)				
	90-99% n (%)				
Mori classification	Short of n (%)				

Items	Indicatiors	Total	PTAS group	Medical group	P
	Tubular n (%)				
	Dispersion of n (%)				
mRS score	Median (IntQ)				
NIHSS score	Median (IntQ)				

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8.3 Efficacy evaluation

8.3.1 Primary efficacy outcome

Table 9 Incidence of primary outcome (stroke or death) 12 months after randomization9

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Stroke or death	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95% CI				
	Testing statistic (CMH)				
	P value				
	Outcome Event (%)				
	Loss (%)				
	Incidence				
	95%CI				
	Log - rank test				
	P values				

Items	Indicatiors	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Cox regression	Hazard Ratio				
	95% CI				
	P values				
Cox regression (sensitivity analysis)	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 1 Incidence of primary outcome (stroke or death) within 12 months after randomization (KM curve) (FAS)1

Figure 2 Incidence of primary end point (stroke or death) within 12 months after randomization (KM curve) (PPS)2

8.3.2 Secondary efficacy outcomes

Table 10 Incidence of disabling stroke or death within 36 months after randomization10

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Disabling stroke or death	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

457 Figure 3 Disabling stroke or death within 36 months after randomization (KM curve) (FAS)3

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459 Figure 4 Disabling stroke or death within 36 months after randomization (KM curve) (PPS)4

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463 Table 11 2-year rate of the same-territory stroke11

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 5 2-year rate of the same-territory stroke (KM curve) (FAS)5

Figure 6 2-year rate of the same-territory stroke (KM curve) (PPS)6

Table 12 3-year rate of the same-territory stroke 12

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Mortality				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 7 3-year rate of the same-territory stroke (KM curve) (FAS)7

Figure 8 3-year rate of the same-territory stroke (KM curve) (PPS)8

477 Table 13 Changes of neurological function evaluation (mRS and NIHSS score)13

Items	Follow-up time	Indicatiors	Total	Experimental group	Control group	P
NIHSS	Baseline	Median (IntQ)				
	1 day after randomization	Median (IntQ)				
	7 days after randomization	Median (IntQ)				
	1 month after randomization	Median (IntQ)				
	12 months after randomization	Median (IntQ)				
	24 months after randomization	Median (IntQ)				
	36 months after randomization	Median (IntQ)				
NIHSS	1 day after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	7 days after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	1 month after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				

Items	Follow-up time	Indicatiors	Total	Experimental group	Control group	P
	12 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	24 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	36 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
mRS	Baseline	Median (IntQ)				
	7 days after randomization	Median (IntQ)				
	1 month after randomization	Median (IntQ)				
	12 months after randomization	Median (IntQ)				
	24 months after randomization	Median (IntQ)				
	36 months after randomization	Median (IntQ)				
mRS	7 days after randomization	0-2 n (%)				
		3-6 n (%)				

Items	Follow-up time	Indicatiors	Total	Experimental group	Control group	P
		P values				
	1 month after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	12 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	24 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	36 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				

478

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480 Table 14 any stroke, severe TIA, cardiovascular events related to stenting or medical therapy within a follow-up of 3 years14

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Any stroke, severe TIA, cardiovascular events related to stenting or medical therapy	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test Statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

481 Note: Cox regression adjusted for variables

482

8.4 Safety analysis

8.4.1 Adverse events

Table 15 Summary of adverse events15

Items	PTAS group cases	total	percentage	Medical group cases	total	percentage	P values
Adverse events							
Adverse events related to interventions							
Serious Adverse Events							
Serious adverse events associated with interventions							
Adverse events leading to shedding							

Note: Adverse reactions associated with experimental drugs are defined as likely, likely, and definitely related.

Table 16 Summary of the severity of adverse events16

	PTAS group			Medical group			
Items	cases	total	percentage	cases	total	percentage	P values
Mild Adverse Events							
Moderate Adverse Events							
Major Adverse Events							

China **A**ngioplasty **& St**enting for **S**ymptomatic **In**tracranial **S**evere **S**tenosis **(CASSISS)**

A prospective multi-center, randomized controlled trial (RCT)

Statistical Analysis Plan

Ver. 2.0

Version date: December 19, 2020

Type of research:	Investigator-initiated Phase IV clinical trial
Organizer:	Xuanwu Hospital Capital Medical University
Statistical analysis:	Clinical Research Institute Peking University

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1. Abbreviations

ALT	Serum alanine aminotransferase
AST	Serum glutamic-oxalacetic transaminase
APTT	Activated partial thromboplastin time
BUN	Urea nitrogen (blood)
BMI	Body mass index
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CTA	Computed tomography angiography
CTP	CT perfusion scan
DSA	Digital subtraction angiography
DSMB	Data Safety Monitoring Board
DWI	Magnetic resonance diffusion weighted imaging
EC	Ethics committee
ECG	Electrocardiogram
FAS	Full analysis set
FBS	Fasting plasma glucose
HDL-C	High density lipoprotein cholesterol
ICF	Informed consent
INR	International standard ratio
ITT	Intention to treat
LDL-C	Low density lipoprotein cholesterol
LOCF	The last observation was carried forward
MCA	Middle cerebral artery
MedDRA	Dictionary of medical terms used for drug registration

MRA	Nuclear magnetic angiography
mRS	Modified Rankin Scale
MTT	Mean transit time
NIHSS	National Institutes of Health Stroke Assessment Scale
PET	Positron emission tomography
PPS	Per-protocol set
PT	Prothrombin time
PWI	Perfusion-weighted imaging
RCT	Randomized controlled trial
SFDA	State Food and Drug Administration
TCD	Transcranial Doppler scan
TIA	Transient ischemic attack
XeCT	Xenon enhanced computed tomography

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2. Protocol Abstract

2.1 Study purpose

Main purpose: 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).

Secondary purpose: 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.

2.2 Study design

This study is a multicenter, randomized, open-label, outcome-blinded trial comparing medical therapy alone or medical therapy plus stenting with the use of the Wingspan Stent system in patients with transient ischemic attack (TIA) or non-disabling ischemic stroke caused by 70%-99% stenosis of a major intracranial artery.

2.3 Sample size

For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of ipsilateral stroke risk in medical therapy group WASID study was 18%, which was 7.3% in a study by the Wingspan stent therapy (Wei-jian Jiang, etc.). 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 needs to be evaluated. Assuming a 20% incidence of loss of follow-up and/or withdrawal, a total of 380 patients, 190 per group, are required to be enrolled in this study.

2.4 Blinding and randomization

Complete randomization methodology will be used. Once the patient meets the inclusion criteria after signing the informed consent form, the researcher will immediately make a phone call to the research group, and the answering staff will assign the patient a random number according to the patient number, and the random number will associate the patient with the corresponding treatment group. Patients will be given medical therapy alone or Wingspan stent plus medical therapy, depending on the treatment group randomly assigned. Patients randomly assigned to the medical treatment group will be discharged after DSA examination.

This study is an open, outcome-blinded study.

2.5 Interventions

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, asprin 100 mg plus clopigdorel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75 mg alone per day thereafter) and management of risk factors. Medical management of risk factors consists of control of low-density lipoprotein (LDL-C) (target: LDL-C<2.58mmol/L (100 mg/dL) with statins, and hypertension (systolic pressure <140 mmHg [<130mmHg in the case of patients with diabetes] and diastolic pressure <90 mmHg) based on 2014 AHA/ASA guidelines.

Stenting:

Patients randomized to stenting will be scheduled for intervention within three to five business days. The study protocol requires that the stenting procedure be performed under general anesthesia by a qualified operator at each site. Intensive management of risk factors will be applied thereafter.

2.6 Study population and diagnostic criteria

This trial aims to recruit patients who have had a TIA or ischemic stroke (mRS≤2) and advanced ICAS (70%–99% on angiogram). Catheter angiography is required to confirm 70%–99% stenosis by the WASID criterion for a patient to qualify. Patients who have an ischemic stroke within the last three weeks will not be included because of concern for hemorrhagic transformation.

2.6.1 Inclusion criteria

Detailed inclusion criteria were as follows:

14. 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;

15. 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]);

16. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter angiography for enrollment in the trial;
17. 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;
18. Expected ability to deliver the stent to the lesion;
19. All the patients should be performed with stenting beyond a duration of three weeks from the latest ischemic symptom onset;
20. No recent infarctions identified on MRI (indicated as high signals on DWI series) upon enrollment;
21. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage, epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI scan;
22. mRS scale score of <=2;
23. 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;
24. 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;
25. Patient is willing and able to return for all follow-up visits required by the protocol;
26. Patients understand the purpose and requirements of the study and have signed informed consent form.

2.6.2 Exclusion criteria

Detailed exclusion criteria were as follows:

30. Refractory to general anesthesia; not able to be overcome by pre-treatment with medical therapy
31. Any condition that precludes proper angiographic assessment
32. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is proximal or distal to the target intracranial lesion
33. 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)
34. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution within 30 days
35. 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
36. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement
37. Plan to perform concomitant angioplasty or stenting of an extracranial vessel tandem to an ipsilateral intracranial stenosis
38. Presence of intraluminal thrombus proximal to or at the target lesion
39. Any aneurysm proximal to or distal to intracranial stenotic artery
40. Intracranial tumors or any intracranial vascular malformations
41. Computed tomographic or angiographic evidence of severe calcification at target lesion
42. Thrombolytic therapy within 24 hours before enrollment
43. Evolving stroke or progressive neurologic signs within 24 hours before enrollment
44. 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

45. Previous spontaneous intracerebral (parenchymal) or other intracranial (subarachnoid, subdural, or epidural) hemorrhage within 30 days
46. Untreated chronic subdural hematoma >5 mm in thickness
47. 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
48. Myocardial infarction within previous 30 days
49. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the past six months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation
50. Intolerance or allergic reaction to any of the medical therapy, including aspirin, clopidogrel, heparin, and local or general anesthetics
51. 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
52. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
53. 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
54. 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)

55. Inability to understand and cooperate with study procedures or sign informed consent

56. Severe dementia or psychiatric problems that prevent the patients from following an outpatient program reliably

57. Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study

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

3. Assessment of Outcome evaluation

3.1 Outcome evaluation

3.1.1 Primary Outcome

Stroke or death within 30 days after enrollment or stroke in the territory of qualifying artery (SIT) beyond 30 days through 1 year.

3.1.2 Secondary Outcomes

- Disabling stroke or death within 3 years after randomization;
- 2-year rate of SIT;
- 3-year rate of SIT;
- Death rate within 3 years;
- Any stroke, TIA, or cardiovascular events within 3 years.

Note

Stroke is defined as the rapid loss of brain function due to disturbance in the blood supply to the brain that persists beyond 24 hours. This can be due to ischemia or hemorrhage.

TIA is defined as rapidly developed clinical signs of focal or global disturbance of cerebral function lasting longer than 10 minutes but fewer than 24 hours, with no apparent nonvascular cause.

3.2 Safety outcomes

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

772 required to confirm whether the patients are qualified to continue to participate in the
773 study.

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4. Data Safety Monitoring Board (DSMB)

An independent data safety monitoring committee composed of experts in neurosurgery, internal medicine, neuroradiology, and biostatistics who are not involved in the study is responsible for the following:

1. All potential outcome events including TIA, stroke, and death will be reviewed and confirmed. Clinical records and imaging results related to any outcomes are required to be emailed to the outcome committee, and the outcome committee's decision will be the final decision.
2. Efficacy and safety data, as well as balance of patient benefits and risks will be reviewed regularly. Timely recommendations will be given to the executive committee on whether to continue, modify, or discontinue the study.

5. Analysis data set

Full Analysis Set (FAS): all the subjects who are randomized into groups will be included, except the subjects who do not meet the inclusion and exclusion criteria and who are withdrawn immediately after randomization without receiving any intervention 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.

Per-protocol Set (PPS): All patients who are treated according to the study protocol (the eligibility criteri, the assigned treatment after randomization, additional medication protocol, the follow-up protocol, and completion of the case report form).

Safety Analysis Set (SAS): Randomized patients who receive at least one dose of antiplatelet therapy with a documented safety outcome.

Efficacy analysis will be carried out based on the FAS and the PPS, and the conclusions will be made based on the FAS. All baseline demographic data analyses will be performed on the basis of the FAS and safety assessments will be performed on the SAS.

6. Processing of missing data

For patients who die or are lost to follow-up within 36 months after randomization, the 30-day, 12-month, and 36-month NIHSS and mRS score will be filled using the last observed value (LOCF) method. For other missing data, no filling or other processing will be conducted. For survival analysis, missing data will be considered as censored.

7. Statistical analysis method

7.1 General principles of statistical analysis

Prior to database locking, the statistician is responsible for developing a statistical analysis plan in consultation with the principal investigator. SAS 9.4 statistical software will be used. The efficacy evaluation includes the analysis of PPS and FAS sets, and the conclusion will be based on the FAS set. SAS set analysis will be used for safety evaluation.

All statistical tests will be conducted using a two-sided test, and a p-value of 0.05 or less will be considered statistically significant (unless otherwise specified).
For patients who cross groups, that is, the actual group is not consistent with the randomly assigned group, efficacy will be analyzed according to the ITT principle based on the FAS, and safety will be analyzed according to the SAS.

7.2 Analysis plan

After the study protocol is finalized, the statistician will develop the statistical analysis plan in consultation with the principal investigator. All the analyses will be performed with the use of SAS software, version 9.4 (SAS Institute, license number: 11202165).

Numerical variables will be presented with mean, standard deviation (normally distributed), or median (interquartile interval). Categorical and hierarchicalvariables will be presented with the number of cases and percentages.

Appropriate method for comparison of baseline between two groups will be adopted according to the types of variables, and the comparison of numerical variables will be tested with t-test (normal distribution) or Wilcoxon rank test according to the data distribution, categorical variables with chi-square test or the exact probability method

(if a chi-square test is not applicable), hierarchical data with Wilcoxon rank test or CMH.

7.3 Completion

The number of patients enrolled in each center, the number of patients who complete the trial and the number of patients withdrawn from the trial will be summarized, and the list of patients not included in the FAS/PPS set and the reasons for exclusion will be listed. The number of cases in each group FAS/PPS dataset, the distribution of cases in each center, and a detailed list of incomplete causes will be listed.

7.4 Demographic data and baseline characteristics

Baseline data such as patient demographic characteristics (age and gender), vital signs, past medical history, treatment history and current medical history will be described, and baseline data such as age, gender and BMI of the two groups will be compared to measure the comparability of the two groups.

7.5 Efficacy analysis

FAS and PPS will be used for efficacy analysis.

7.5.1 Main Efficacy index

Stroke or death within 30 days after randomization; And stroke in the territory of qualifying artery (SIT) beyond 30 days through 12 months after randomization.

The incidence of stroke or death at 12 months will be compared between the medical therapy group and the stent group, and a 95% confidence interval will be calculated for the difference between the two groups. CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If the impact of other

factors is adjusted, Logistics regression model can be considered for inter-group comparison.

The Log Rank test will be used to analyze the primary efficacy outcomes, and the center information will be stratified as covariates. The Cox proportional risk model will be used to calculate HR and its 95% confidence interval (CI) to estimate efficacy. The model included the same covariates as the Log Rank test for fitting. Kaplan-Meier curves will be plotted by treatment group.

For comparison of patient demographic characteristics (age, gender), vital signs, medical history, history of treatment and the medical records of baseline data between groups, if there are important significant differences for baseline data, the Cox proportional hazards model will be used for adjustment of these baseline variables, which will be included as a sensitivity analysis.

7.5.2 Secodary Efficacy index

Disabling stroke or death after enrollment within 3 years in both arms; 2) 2-year rate of SIT; 3) 3-year rate of SIT; 4) any stroke, TIA, or cardiovascular events within 3 years; 5) survival rate within 3 years. All above will be analyzed using the same method as the primary efficacy outcomes. The incidence of each outcome and the 95% confidence interval will be described by groups.

7.5.3 Others

At the same time, the dichotomous variables will be transformed by selecting clinically significant cut-off points for inter-group comparison. CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.

7.6 Safety analysis

The safety evaluation will be analyzed on the SAS dataset.

The number of adverse events of the two groups, as well as the incidence of adverse events, serious adverse events will be described in tables. The changes of laboratory and ECG will be described in tables. Procedure-related complications within 30 days after operation in the stent group will be analyzed. Chi-square test/Fisher exact test will be used to compare the incidence of adverse events and the incidence of serious adverse events between the two groups.

8. Statistical analysis results

8.1 Distribution of included patients

Table 1 Population distribution of each center17

	FAS			PPS			SS (Actual Group)		
Center	PTAS group	Medical group	Total	PTAS group	Medical group	Total	PTAS group	Medical group	Total
Total number									

908 Table 2 List of patients not included in the FAS/PPS set18

				Included in analysis dataset		
Center	Patient ID	Time of enrollment	Reason of exclusion	PPS	FAS	SS

909

910 Table 3 Data sets of enrolled patients and safety and efficacy analysis sets.19

	Items	PTAS group	Medical group	Total
The whole data set				
	Randomly enrollment			
Not included in the FAS set				
	Failure to meet inclusion/exclusion criteria			
	Exit after randomization			
Suspension during study				
	Upon requests from subjects or subject's legal authorized representatives.			
	lost of follow-up			
	Crossover			
	Failure to follow the plan			
	Other			
Safey analysis set				
	SS (Actual Group)			
Efficacy analysis set				

	FAS			
	PPS			

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912

8.2 Demographic data and baseline characteristics

Table 4 Demographic data20

Items	Indicatiors	Total	PTAS group	Medical group	P
Age (years)	Mean (SD)				
Gender	Male, n (%)				
	Female, n (%)				
Ethnicity	Han, n (%)				
	Other, n (%)				

Table 5 Baseline information21

Items	Indicatiors	Total	PTAS group	Medical group	P
Systolic blood pressure (mmHg)	Mean (SD)				
Diastolic blood pressure (mmHg)	Mean (SD)				
Heart rate (times per minute)	Mean (SD)				
BMI (kg/m2)	Mean (SD)				
Smoking history	None n (%)				

Items	Indicatiors	Total	PTAS group	Medical group	P
	Previous n (%)				
	Current n (%)				
Alcohol use	No n (%)				
	Previous n (%)				
	Current n (%)				
Family history of cerebrovascular disease	No n (%)				
	Yes n (%)				
Family history of cardiovascular disease	No n (%)				
	Yes n (%)				
High density lipoprotein cholesterol	Mean (SD)				
Low density lipoprotein cholesterol	Mean (SD)				
Total cholesterol	Mean (SD)				
triglycerides	Mean (SD)				
C-reactive protein	Mean (SD)				
HbA1c	Mean (SD)				

Table 6 Past medical history22

Items	Indicatiors	Total	PTAS group	Medical group	P
Hypertension	No n (%)				
	Yes n (%)				
Diabetes	No n (%)				
	Yes n (%)				
Hyperlipidemia	No n (%)				
	Yes n (%)				
Coronary heart disease (CHD)	No n (%)				
	Yes n (%)				
Myocardial infarction	No n (%)				
	Yes n (%)				
Atrial fibrillation	No n (%)				
	Yes n (%)				
Peripheral vascular disease	No n (%)				
	Yes n (%)				
Alimentary ulcer	No n (%)				
	Yes n (%)				

922

923 Table 7 History of previous and current medical therapy for cerebrovascular diseases23

Items	Indicatiors	Total	PTAS group	Medical group	P
Antiplatelet agent	No n (%)				
	Yes n (%)				
Anticoagulant drugs	No n (%)				
	Yes n (%)				
History of radiotherapy for cerebrovascular disease	No n (%)				
	Yes n (%)				
History of surgical treatment of cerebrovascular disease	No n (%)				
	Yes n (%)				

924

925

926 Table 8 Medical records of the present ischemic attack.24

Items	Indicatiors	Total	PTAS group	Medical group	P

Items	Indicatiors	Total	PTAS group	Medical group	P
Ischemia-cerebrovascular disease occurred within 12 months	Cerebral infarction n (%)				
	TIA n (%)				
Time from symptom onset to randomization	Median (IntQ)				
Artery stenosis	Intracranial segment of internal carotid artery N (%)				
	Middle cerebral artery N (%)				
	Intracranial segment of vertebral artery N (%)				
	Basilar artery N (%)				
	Others n (%)				
Stenosis degree	Median (IntQ)				
	70-79% n (%)				
	80-89% n (%)				
	90-99% n (%)				
Mori classification	Short of n (%)				

Items	Indicatiors	Total	PTAS group	Medical group	P
	Tubular n (%)				
	Dispersion of n (%)				
mRS score	Median (IntQ)				
NIHSS score	Median (IntQ)				

927

928

8.3 Efficacy evaluation

8.3.1 Primary efficacy outcome

Table 9 Incidence of primary outcome (stroke or death) 12 months after randomization25

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Stroke or death	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95% CI				
	Testing statistic (CMH)				
	P value				
	Outcome Event (%)				
	Loss (%)				
	Incidence				
	95%CI				
	Log - rank test				
	P values				

Items	Indicatiors	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Cox regression	Hazard Ratio				
	95% CI				
	P values				
Cox regression (sensitivity analysis)	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 1 Incidence of primary outcome (stroke or death) within 12 months after randomization (KM curve) (FAS)9

Figure 2 Incidence of primary end point (stroke or death) within 12 months after randomization (KM curve) (PPS)10

8.3.2 Secondary efficacy outcomes

Table 10 Incidence of disabling stroke or death within 36 months after randomization26

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Disabling stroke or death	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

941 Note: Cox regression adjusted for variables

942

943 Figure 3 Disabling stroke or death within 36 months after randomization (KM curve) (FAS)11

944

945 Figure 4 Disabling stroke or death within 36 months after randomization (KM curve) (PPS)12

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949 Table 11 2-year rate of the same-territory stroke27

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 5 2-year rate of the same-territory stroke (KM curve) (FAS)13

Figure 6 2-year rate of the same-territory stroke (KM curve) (PPS)14

Table 12 3-year rate of the same-territory stroke 28

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				

Items	Indicatiors	FAS PTAS group	FAS Medical group	PPS PTAS group	PPS Medical group
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Mortality				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

Note: Cox regression adjusted for variables

Figure 7 3-year rate of the same-territory stroke (KM curve) (FAS)15

Figure 8 3-year rate of the same-territory stroke (KM curve) (PPS)16

963

964 Table 13 any stroke, severe TIA, cardiovascular events related to stenting or medical therapy within a follow-up of 3 years29

		FAS		PPS	
Items	Indicatiors	PTAS group	Medical group	PTAS group	Medical group
Any stroke, severe TIA, cardiovascular events related to stenting or medical therapy	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test Statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				

Items	Indicatiors	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
	P values				

Note: Cox regression adjusted for variables

8.4 Safety analysis

8.4.1 Adverse events

Table 14 Summary of adverse events30

	PTAS group			Medical group			
Items	cases	total	percentage	cases	total	percentage	P values
Adverse events							
Adverse events related to interventions							
Serious Adverse Events							
Serious adverse events associated with interventions							
Adverse events leading to shedding							

Note: Adverse reactions associated with experimental drugs are defined as likely, likely, and definitely related.

Table 15 Summary of the severity of adverse events31

	PTAS group			Medical group			
Items	cases	total	percentage	cases	total	percentage	P values
Mild Adverse Events							
Moderate Adverse Events							
Major Adverse Events							

CASSISS Study

Statistical Analysis Plan (SAP):

Summary of Changes (Ver.1.0 ⇒ Ver.2.0)

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

Prepared: Dec 19, 2020

#	Page	Item	Description of change(s)		Reasons for change
			Before change (Ver. 1.0 Date prepared: May 10, 2015)	After change (Ver. 2.0 Date prepared: Dec 19, 2020)	
1	14	3.1.2 Secondary Endpoints	• Disabling stroke or death within 3 years after randomization; • 2-year rate of SIT; • 3-year rate of SIT; • Any stroke, TIA, or cardiovascular events related to therapy within 3 years; • Death rate within 3 years; • mRS, NIHSS scores of patients.	• Disabling stroke or death within 3 years after randomization; • 2-year rate of SIT; • 3-year rate of SIT; • Any stroke, TIA, or cardiovascular events related to therapy within 3 years; • Death rate within 3 years;	Due to protocol revisions
2	20-22	7.5	(3) **Mixed effects model will be used to**	At the same time, the dichotomous variables	Due to

		Efficacy analysis	**compare the changes of neurological function indexes between groups.** At the same time, the dichotomous variables will be transformed by selecting clinically significant cut-off points for inter-group comparison. **For mRS, 0-2 versus 3-6 will be used. For NIHSS, an increase of 4 points or more from baseline to 12 months will be considered to have deteriorated neurological function.** CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.	will be transformed by selecting clinically significant cut-off points for inter-group comparison. CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.	revision No.1

3	38	Table 13	Table 13 Changes of neurological function evaluation (mRS and NIHSS score)	Omit this table	Due to revision No.1

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