Endovascular Treatment With or Without Intravenous Thrombolysis in Acute Ischemic Stroke Due to Basilar Artery Occlusion: A Multicentre, Prospective, Randomized Controlled Trial (The BEST-BAO trial)

Protocol

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Contract Research Organization: JetMed (Beijing) Co., Ltd.

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Contents

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Protocol Signature Page

Name	**Signature**	**Date**
Sponsor: Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital		

I have carefully read the trial protocol and acknowledge that it sufficiently covers all the necessary aspects for conducting the trial. I agree to conduct the study in accordance with the protocol and will ensure that the study is completed within the specified time-frame.

I will assist all personnel involved in this study by providing copies of the research protocol and all relevant materials. I will also collaborate with them to discuss these materials to ensure they fully understand the investigational drug and how to conduct the trial.

Name	**Signature**	**Date**
Principal investigator:		

List of abbreviations

Abbreviation	Full Term
AIS	Acute ischemic stroke
AIS-LVO	Acute ischemic stroke with large vessel occlusion
BAO	Basilar artery occlusion
AIS-BAO	Acute ischemic stroke due to basilar artery occlusion
IVT	Intravenous thrombolysis
RCT	Randomized controlled trial
EVT	Endovascular therapy
sICH	Symptomatic intracranial hemorrhage
mRS	Modified rankin scale
PCS	Posterior circulation stroke
ACS	Anterior circulation stroke
DTP	Door-to-puncture
NIHSS	National institutes of health stroke scale
DSMB	Data and safety monitoring board
DNT	Door-to-needle
NMPA	National medical products administration
CTA	Computed tomography angiography
MRA	Magnetic resonance angiography
DSA	Digital subtraction angiography
CT	Computed tomography
MRI	Magnetic resonance imaging
AHA	American heart association
ASA	American stroke association
ICH	Intracranial hemorrhage
INR	International normalized ratio
APTT	Activated partial thromboplastin time
rtPA	Recombinant tissue plasminogen activator
SC	Steering committee
eTICI	Expanded thrombolysis in cerebral infarction
GCS	Glasgow coma scale
BI	Barthel index
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
mAOL	Modified arterial occlusive lesion score
PC-ASPECTS	Posterior circulation alberta stroke program early CT score
PMI	Pon-midbrain index

PC-CS	Posterior circulation collateral score
BATMAN	Basilar artery on CT angiography score
EC	Ethics committee
AE	Adverse event
SAE	Serious adverse event
ITT	Intention-to-treat
m-ITT	Modified intention-to-treat
ATS	Acute treatment study
PPS	Per-protocol set
SAP	Statistical analysis plan
EDC	Electronic data capture
CRF	Case report form
CRC	Clinical research coordinator
CRA	Clinical research associate

Protocol Summary

Study title: Endovascular treatment with or without intravenous thrombolysis in acute ischemic stroke due to basilar artery occlusion: A multicentre, prospective, randomized controlled trial.

Rationale: It is well-established that both intravenous thrombolysis (IVT) and endovascular treatment (EVT), including stent retrievers and aspiration thrombectomy, are safe and effective in treating acute ischemic stroke (AIS) caused by basilar artery occlusion (BAO) within 4.5 hours of symptom onset in selected patients. Currently, both IVT followed by EVT and EVT alone are widely used for the treatment of AIS-BAO, but no direct comparison of their efficacy and safety was reported. Only a limited number of cohort and registry studies have preliminarily compared the two strategies in the treatment of AIS-BAO, with results generally indicating that IVT followed by EVT was slightly superior to EVT alone. However, these findings are generally limited by small sample sizes, heterogeneous inclusion and exclusion criteria, different endpoint definitions, and distinct study designs, leading to inconsistent conclusions.

Objective: To assess the efficacy and safety of IVT followed by EVT and EVT alone in the treatment of patients with AIS-BAO who are eligible for both treatment strategies within 4.5 hours of symptom onset.

Study design: This is a multicentre, prospective, open-label, blinded endpoint evaluation, randomized controlled trial (PROBE design). Based on previous observational studies, this trial primarily aims to validate the superiority of IVT followed by EVT over EVT alone. However, given the limited prior data and evidence from the anterior circulation, this trial will also investigate the non-inferiority of EVT alone comparing with IVT followed by EVT in case the two strategies demonstrate similar efficacy. An interim analysis will be conducted when 1/3 of the sample size (114 patients) has completed primary endpoint follow-up. The interim analysis will focus on sample size re-estimation based on conditional power calculated by the data and safety monitoring board (DSMB), which will provide recommendations on whether to adjust the sample size.

Inclusion criteria:

1. A clinical diagnosis of AIS.
2. Caused by BAO confirmed by CTA, MRA, or DSA. (BAO is defined as the absence of visualization of the basilar artery on CTA, MRA or DSA. Bilateral vertebral artery occlusions or occlusion of a unilateral vertebral artery that is the sole supplier of the basilar artery, even in the presence of patent basilar artery, will be considered de facto BAO.)
3. CT or MRI ruling out intracranial hemorrhage,
4. Eligible for IVT and EVT (within 4.5 hours of symptom onset). (Symptoms onset is defined as point in time the patient was last seen well [at baseline] if patients are unable to provide a reliable history or the point in time when symptoms have started if patients can provide a reliable history. Symptoms onset includes diplopia, midline ataxia, visual loss, sensory or motor deficits, and conscious disturbance. Isolated vertigo [not accompanied by dysarthria, motor weakness, sensory symptoms, double vision, depressed level of consciousness] is not considered onset of symptoms.)
5. NIHSS score ≥ 6.
6. Age ≥ 18 years.
7. Signed informed consent by the patient or legal representative.

Exclusion criteria:

1. mRS score > 2 before this stroke.
2. Any contraindication to IVT as per the 2019 AHA/ASA guidelines for early management of AIS:

(1) Blood pressure > 185/110 mmHg and cannot be controlled by standard medication,

(2) Blood glucose < 50mg/dL (2.8 mmol/L) or > 400mg/dL (22.2 mmol/L),

(3) Had a cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging,

(4) Severe head trauma in the previous 3 months,

(5) Major surgery or severe trauma in the previous 2 weeks,

(6) Gastrointestinal or urinary bleeding in the previous 3 weeks,

(7) previous intracranial hemorrhage,

(8) Using anticoagulants and INR > 1.7,

(9) Known platelet count < 100×10^9/L,

(10) treatment with direct thrombin or factor X inhibitors,

(11) Heparin treatment in the previous 48 hours with the APTT exceeding the upper limit of normal.

3. Pregnancy, breastfeeding, or intention to conceive during the study period.
4. Other conditions deemed unsuitable by the investigator.

Intervention: In accordance with the 2019 AHA/ASA guidelines for early management of AIS and recommendations from the steering committee (SC): In EVT alone group, EVT will be performed as quickly as possible. In IVT followed by EVT group, patients will receive IVT with alteplase (0.9 mg/kg, maximum 90 mg in one hour) before EVT. Efforts will be made to minimize delays in EVT initiation due to IVT administration. EVT techniques include retrievable stent thrombectomy, thrombus aspiration, balloon angioplasty, stent implantation, or combinations thereof. The specific EVT approach will be at the discretion of the treatment team.

Primary endpoint: The primary endpoint of the study is the proportion of patients achieving mRS $\leqslant$ 2 at 90±14 days after stroke onset. The proportion of patients achieving the primary endpoint will be calculated for each group, along with the rate difference (RD) and its 95% confidence interval (CI). A log-binomial model with a log-link function will be used to adjust the rate difference for multiple covariates, including age, pre-stroke mRS, time from onset to randomization, stroke severity (baseline NIHSS), and collateral circulation status (baseline PC-CS). The adjusted RD and its 95% CI will be reported.

Secondary endpoints:

1. Proportions of patients with mRS = 0 or 1 and mRS = 0–3, and mRS score at 90±14 days after stroke onset.
2. NIHSS score at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.
3. Proportions of patients with a NIHSS score = 0 or 1, a NIHSS score = 0–2, a NIHSS score improvement ≥ 4 points, and a NIHSS score improvement ≥ 8 points. at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset.
4. GCS score at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.
5. BI score and the proportion with BI = 95–100 at 30±7 and 90±14 days after stroke onset.
6. EQ-5D-5L score at 90±14 days after stroke onset.
7. eTICI score and successful reperfusion rates before and after EVT.
8. mAOL score and recanalization rates at 24–72 hours after procedure.
9. PC-ASPECTS score at 24–72 hours after procedure.
10. Lesion volume based on quantitative imaging detection at 24–72 hours after procedure and 5–7 days after stroke onset.

Safety endpoints:

1. All-cause mortality within 7, 30±7 and 90±14 days after stroke onset.
2. Proportions of patients with intracranial hemorrhage and symptomatic intracranial hemorrhage at 24–72 hours after procedure and 5–7 days after stroke onset.
3. Proportions of patients with embolization to new territory during EVT.
4. Proportions of patients with new cerebral infarction at 24–72 hours after procedure and 5–7 days after stroke onset.
5. EVT procedure-related complications within 90±14 days after stroke onset.
6. Other serious adverse events within 90±14 days after stroke onset.

Sample size and statistical methods: Currently, no large-scale randomized controlled trials (RCTs) exist in this field. Therefore, the calculation of the sample size for this study will be based on the results of the RESCUE-RE registry study conducted in the Chinese population. According to the study, the proportion of patients achieving a mRS score ≤ 2 at 90±14 days post-procedure was 42.03% in the IVT followed by EVT group and 26.14% in the EVT alone group. Based on a superiority hypothesis, this study aims to verify whether the favorable outcome rate in the IVT followed by EVT group is superior to that in the EVT alone group. Assuming a one-sided type I error rate of 0.025 and a statistical power of 80%, with equal allocation between the two groups (1:1), each group will require 136 patients (a total of 272 patients). Considering an anticipated dropout rate of approximately 20%, the final sample size will be adjusted to 340 patients, with 170 patients per group.

This study hypothesizes that IVT followed by EVT is superior to alone EVT. However, given limited reference data and evidence suggesting the non-inferiority of EVT alone in the anterior circulation, an interim analysis will be conducted after one-third (114) of patients have completed follow-up for the primary endpoint. At this stage, the Data and Safety Monitoring Board (DSMB) will perform a sample size re-estimation based on the efficacy data obtained from both groups. Using the available data, the DSMB will calculate the conditional power and provide recommendations to the BEST-BAO research team regarding sample size adjustments or potential modifications to the study hypothesis.

If the efficacy advantage of the IVT followed by EVT group over the EVT alone group is less than anticipated, the sample size may be expanded appropriately, with an upper limit of no more than 20% of the original sample size. If the efficacy of the two groups appears to be similar, the study design will shift to a non-inferiority framework, evaluating whether EVT alone is non-inferior to IVT followed by EVT. Assuming similar efficacy (with both groups achieving a 90-day mRS score ≤ 2 in 42.03% of patients), the current sample size of 170 patients per group provides 80% power to test non-inferiority, with a one-sided type I error rate of 0.025 and a non-inferiority margin of -15% in rate difference. The interim analysis and sample size re-estimation will be conducted under the strict control of the DSMB to ensure that the type I error rate is not inflated.

The primary analysis of this study will follow the intention-to-treat (ITT) principle. The main analysis will be conducted on the modified intention-to-treat (m-ITT) population, defined as all randomized patients who received treatment, analyzed according to their original randomization group. Additional populations, such as the As-Treated Set (ATS) and the Per-Protocol Set (PPS), will be used for sensitivity analyses. Except for the primary efficacy endpoint, which will be tested using a one-sided significance level of 0.025 for superiority or non-inferiority evaluation, all other statistical tests will be conducted using a two-sided significance level. A P-value < 0.05 will be considered statistically significant for these comparisons.

1. Introduction and background

Stroke is a leading cause of death and disability in China, with acute ischemic stroke (AIS) accounting for approximately 85% of all acute strokes. Among these, large vessel occlusion-related AIS (AIS-LVO) represents about 20% of cases[1]. Posterior circulation infarction, which occur in the vertebrobasilar artery territory, comprise 20–25% of all ischemic strokes. Although less common than anterior circulation ischemic strokes, posterior circulation infarctions—particularly AIS caused by basilar artery occlusion (AIS-BAO)—often present with severe symptoms and poor outcomes. Due to the heterogeneity of initial symptoms and diagnostic challenges, AIS-BAO frequently results in poor prognoses, posing significant challenges in clinical diagnosis and treatment.

The safety and efficacy of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) within 4.5 hours of symptom onset in AIS have been confirmed by numerous randomized controlled trials (RCTs). However, the heterogeneous presentation of posterior circulation AIS, the difficulty in clinical recognition compared to anterior circulation AIS, and the severe neurological deficits—especially the high mortality rate of AIS-BAO—pose various limitations on IVT. Endovascular treatment (EVT), including thrombectomy techniques, has substantially reduced the mortality and disability rates of patients with AIS-LVO. The key to treating AIS-BAO is recanalizing the acutely occluded basilar artery and rescuing the ischemic penumbra. Large RCTs have demonstrated that early EVT achieves better clinical outcomes in anterior circulation AIS-LVO patients eligible for mechanical thrombectomy compared to IVT alone[2-8].

In recent years, while multiple large RCTs have confirmed the efficacy of EVT for anterior circulation AIS-LVO, evidence for EVT in posterior circulation AIS-LVO remains limited. The BEST trial enrolled AIS patients with vertebrobasilar artery occlusion within 8 hours of symptom onset to compare EVT plus standard medical treatment versus medical treatment alone. The results showed that the combination group achieved better outcomes at 90 days, with no significant difference in mortality or symptomatic intracranial hemorrhage (sICH) rates compared to the medical treatment-only group[9]. Similarly, the BASICS trial, an international multicenter RCT, enrolled 300 AIS-BAO patients within 6 hours of symptom onset and compared EVT combined with standard medical treatment to standard medical treatment alone. This study found no significant differences between the two groups in good functional outcomes, sICH, or mortality[10].

Recently, two studies focusing on thrombectomy for AIS-BAO reported promising results. The BAOCHE study[11] randomized AIS-BAO patients who presented 6–24 hours after symptom onset into a thrombectomy plus standard medical treatment group or a standard medical treatment-only group. The primary endpoint was the proportion of patients with modified Rankin Scale (mRS) scores of 0–3 at 90 days. A total of 217 patients (110 in the combination group, 107 in the medical treatment group) were enrolled, and the results demonstrated that thrombectomy performed within 6–24 hours led to better functional outcomes at 90 days. The ATTENTION study[12], another RCT conducted across 36 stroke centers in China, enrolled AIS-BAO patients within 12 hours of symptom onset. Patients were randomized 2:1 to thrombectomy plus optimal medical treatment or optimal medical treatment alone. The primary outcome was the proportion of patients achieving an mRS score of 0–3 at 90 days, and 340 patients (226 in the combination group, 114 in the medical treatment group) were enrolled. The results showed that thrombectomy within 12 hours significantly improved functional outcomes. Both studies demonstrated that thrombectomy combined with medical treatment yielded better outcomes than medical treatment alone for AIS-BAO. However, questions remain regarding the optimal timing, treatment modalities, bridging strategies, and anesthesia options for EVT in posterior circulation AIS. Further exploration is required to rapidly identify posterior circulation strokes and select appropriate EVT strategies based on clinical indications.

Clinically, the morbidity and mortality of posterior circulation AIS-LVO exceed 80%. AIS-BAO, in particular, is a neurological emergency with extremely high mortality if untreated, significantly affecting patients' quality of life and imposing substantial medical and financial burdens on families and society. IVT remains the most effective

ultra-early treatment for AIS within 6 hours of onset. However, the adoption of IVT for posterior circulation AIS is lower than that for anterior circulation AIS, potentially due to delays in diagnosis or missed diagnoses caused by the heterogeneity of AIS-BAO symptoms. Among AIS patients receiving IVT, posterior circulation strokes (PCS) account for about 5–19%. Studies comparing the efficacy and safety of IVT in PCS and anterior circulation strokes (ACS) have found that while the risk of hemorrhagic complications is halved for PCS, functional outcomes are similar, but mortality is higher[13]. Clinically, IVT can be used as standalone therapy for AIS-BAO or as a prelude to EVT. Which approach better improves AIS-BAO outcomes remains uncertain.

To date, most studies on IVT with EVT have focused on anterior circulation AIS. Both IVT and EVT are time-dependent treatments for AIS, with EVT success hinging on prompt initiation and optimization of processes to reduce door-to-puncture time (DTP). The SKIP trial found no significant difference in the time from randomization to femoral artery puncture between only EVT and IVT with EVT[14]。Similarly, the DEVT trial, conducted in China, also reported no difference in this time interval between the two groups[15]. A meta-analysis of 38 observational studies including 11,798 AIS-LVO patients (56% of whom underwent IVT with EVT) also confirmed no significant difference in EVT procedural time between the two groups[16]. For anterior circulation AIS-LVO, four recent RCTs showed mixed results. DIRECT-MT and DEVT demonstrated that only EVT was non-inferior to IVT with EVT in terms of good functional outcomes at 90 days, while SKIP and MR CLEAN-IV did not confirm non-inferiority. Thus, EVT alone requires further robust evidence[17, 18]. Regarding safety, all four RCTs confirmed that IVT with EVT does not increase sICH rates[14, 15, 17, 18]. Additionally, the aforementioned meta-analysis[16] confirmed that IVT with EVT does not increase sICH risk. SKIP, DIRECT-MT, and DEVT further showed no significant difference in mortality between the two groups[14, 15, 17]. However, the meta-analysis[16] suggested that IVT with EVT significantly reduces 90-day mortality compared to only EVT. A real-world study[19] also found that IVT with EVT was independently associated with lower 90-day mortality compared to only EVT.

Does IVT before EVT achieve higher recanalization rates? A retrospective study[20] including 93 AIS patients with middle cerebral artery occlusion showed that IVT with EVT resulted in a higher proportion of reperfusion within 1 hour of femoral artery puncture compared to only EVT. Moreover, IVT with EVT achieved significantly higher rates of successful reperfusion (mTICI ≥ 2b). The DIRECT-MT study[17] found that IVT with EVT caused fewer new infarctions from thrombus fragmentation than only EVT. Similarly, post-hoc analyses of the ESCAPE trial[21] demonstrated that IVT with EVT significantly reduced new infarct risk compared to only EVT. Another study of 57 patients with M1 segment occlusions[22] reported that IVT with EVT often required fewer thrombectomy passes to achieve recanalization compared to only EVT.

Combination therapy combines the rapidity of IVT with the high recanalization rates of EVT, theoretically offering better outcomes than only EVT. However, most of these studies focus on anterior circulation stroke treatment. To date, no large-scale RCTs have specifically evaluated EVT with or without prior IVT for AIS-BAO. Therefore, we plan to conduct a multicenter, prospective, randomized controlled study to assess the impact of different EVT strategies on outcomes in AIS-BAO.

2. Study objectives

The primary objective of this trial is to compare the efficacy and safety of IVT followed by EVT versus EVT alone in patients with AIS caused by BAO who are eligible for both treatment strategies within 4.5 hours after symptom onset.

The secondary objectives include assessing the effects of the two treatment strategies on neurological function (assessed by National Institutes of Health Stroke Scale [NIHSS] score), activities of daily living (assessed by Barthel Index [BI] score), quality of life (assessed by EQ-5D-5L score), cerebrovascular reperfusion (assessed by

eTICI), cerebrovascular recanalization (assessed by mAOL), infarct size (assessed by PC-ASPECTS and quantitative imaging detection), mortality, and the incidence of symptomatic intracranial hemorrhage (sICH).

3. Study design

This is a multicentre, prospective, open-label, blinded endpoint evaluation, randomized controlled clinical trial (PROBE design). Based on published observational studies, this trial will first validate the superiority of IVT followed by EVT compared with EVT alone. However, given the limited prior evidence and the current findings from anterior circulation stroke studies, this trial will also validate the non-inferiority of EVT compared with IVT followed by EVT alone if the efficacy of the two treatment strategies is found to be comparable.

An interim analysis is scheduled after one-third of the sample size completes follow-up for the primary endpoint. The primary purpose of the interim analysis is to allow for sample size re-estimation. The data and safety monitoring board (DSMB) will calculate the conditional power based on the current data and provide recommendations to the BEST-BAO research team regarding potential sample size adjustments.

The trial will be conducted at nationally recognized stroke centers and is expected to last for 3 years.

4. Study population

4.1 Population

According to the latest epidemiological survey of stroke in China in 2020, the standardized prevalence of stroke in China is 2.6%, with an incidence rate of 505.2 per 100,000 person-years and a mortality rate of 343.4 per 100,000 person-years[23]. Among individuals aged 40 years and older, there are approximately 17.8 million prevalent stroke cases, 3.4 million new cases, and 2.3 million stroke-related deaths annually[23]. From 1990 to 2019, while the incidence and mortality rates of stroke have shown a gradual decline in Western countries, the overall burden of stroke in China has significantly increased[24]. During this period, the prevalence of stroke in China grew by 106%, reflecting that stroke has become a major public health challenge in the country.

4.2 Participating center and center qualification

A eligible participating center must meet the following minimum qualifications:

(1) Tertiary hospital in their respective region.

(2) Previous experience as a leader or participant in AIS clinical trials.

(3) Capability to perform both IVT and EVT, with at least 30 AIS cases with EVT conducted annually.

(4) Median door-to-needle time (DNT) < 60 minutes and door-to-puncture time (DTP) < 90 minutes.

* The previous experience indicates that the interventional team has the experience in endovascular procedures for cerebrovascular diseases (e.g., EVT, vertebral artery or basilar atery stenting, aneurysm coiling), peripheral arterial diseases, or coronary arterial diseases. The stroke team (including neurologists and interventionalists should have expertise in intra-anterial treatment. The intervention team is proficient in using one or more devices approved by the National Medical Products Administration (NMPA). At least one team member has the experience of using specific interventional devices.

Note: A patient can only be enrolled in the trial after being evaluated by an intervention team which must include at least one intervention specialist with EVT experience.

4.3 Inclusion criteria

Participants must meet all of the following criteria to be eligible for enrollment:

(1) A clinical diagnosis of AIS.

(2) Caused by BAO confirmed by CTA, MRA, or DSA. (BAO is defined as the absence of visualization of the basilar artery on CTA, MRA or DSA. Bilateral vertebral artery occlusions or occlusion of a unilateral vertebral artery that is the sole supplier of the basilar artery, even in the presence of patent basilar artery, will be considered de facto BAO.)

(3) CT or MRI ruling out intracranial hemorrhage,

(4) Eligible for IVT and EVT (within 4.5 hours of symptom onset). (Symptoms onset is defined as point in time the patient was last seen well [at baseline] if patients are unable to provide a reliable history or the point in time when symptoms have started if patients can provide a reliable history. Symptoms onset includes diplopia, midline ataxia, visual loss, sensory or motor deficits, and conscious disturbance. Isolated vertigo [not accompanied by dysarthria, motor weakness, sensory symptoms, double vision, depressed level of consciousness] is not considered onset of symptoms.)

(5) NIHSS score ≥ 6.

(6) Age ≥ 18 years.

(7) Signed informed consent by the patient or legal representative.

4.4 Exclusion criteria

Potential participants will be excluded from the study if they meet any of the following criteria:

(1) mRS score > 2 before this stroke.

(2) Any contraindication to IVT as per the 2019 AHA/ASA guidelines for early management of AIS:

1) Blood pressure > 185/110 mmHg and cannot be controlled by standard medication,

2) Blood glucose < 50mg/dL (2.8 mmol/L) or > 400mg/dL (22.2 mmol/L),

3) Had a cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging,

4) Severe head trauma in the previous 3 months,

5) Major surgery or severe trauma in the previous 2 weeks,

6) Gastrointestinal or urinary bleeding in the previous 3 weeks,

7) previous intracranial hemorrhage,

8) Using anticoagulants and International normalized ratio (INR) > 1.7,

9) Known platelet count < 100×10^9/L,

10) treatment with direct thrombin or factor X inhibitors,

11) Heparin treatment in the previous 48 hours with the activated partial thromboplastin time (APTT) exceeding the upper limit of normal.

(3) Pregnancy, breastfeeding, or intention to conceive during the study period.

(4) Other conditions deemed unsuitable by the investigator.

4.5 Sample size

Currently, no large-scale RCTs exist in this field. The sample size calculation for this study is based on the findings of the RESCUE-RE registry study conducted in the Chinese population[25]. According to the study, the proportion of patients achieving a mRS score ≤ 2 at 90±14 days post-procedure was 42.03% in the IVT followed by EVT group and 26.14% in the EVT alone group.Based on a superiority hypothesis, this study aims to determine whether the good outcome rate (90-day mRS ≤ 2) in the IVT followed by EVT group is superior to that of the EVT alone group. Assuming a one-sided type I error rate of 0.025 and 80% statistical power, and using a 1:1 randomization ratio, a total of 272 patients (136 per group) is required. Accounting for an anticipated dropout rate of approximately 20%, the final sample size is adjusted to 340 patients, with 170 patients per group.

This study hypothesizes that IVT followed by EVT is superior to EVT alone. However, given the limited

reference data and clinical evidence in the anterior circulation indicating that EVT alone may be non-inferior to IVT followed by EVT, an interim analysis is planned after one-third (114) of patients complete follow-up for the primary endpoint. During this interim analysis, the Data and Safety Monitoring Board (DSMB) will evaluate the efficacy data from both groups and conduct a sample size re-estimation based on the calculated conditional power. Based on the available data, the DSMB will provide recommendations to the BEST-BAO research team on whether to adjust the sample size or modify the study hypothesis.

If the efficacy advantage of the IVT followed by EVT group over the EVT alone group is less than anticipated, the sample size may be expanded appropriately, with an upper limit of no more than 20% of the original sample size. If the efficacy of the two groups appears to be similar, the study design will shift to a non-inferiority framework, evaluating whether EVT alone is non-inferior to IVT followed by EVT. Assuming similar efficacy (with both groups achieving a 90-day mRS score ≤ 2 in 42.03% of patients), the current sample size of 170 patients per group provides 80% power to test non-inferiority, with a one-sided type I error rate of 0.025 and a non-inferiority margin of -15% in rate differece. The interim analysis and sample size re-estimation will be conducted under the strict control of the DSMB to ensure that the type I error rate is not inflated.

5. Intervention

5.1 Study treatment

Patients in the IVT followed by EVT group will receive IVT with rtPA (0.9 mg/kg, maximum 90 mg in one hour), which is followed by EVT. Patients in the EVT alone group will not receive IVT and will undergo EVT alone.

Note: The efforts should be made to minimize delays in EVT initiation caused by IVT procedure in the IVT followed by EVT group. For patients undergoing screening evaluation by CTA or MRA, the time from randomization to femoral artery puncture should be as short as possible, with all patients aiming to achieve a median time of 60 minutes or less from randomization to groin puncture and prompt completion of the guiding catheter inserting into the vascular puncture sheath. For patients undergoing screening evaluation by DSA, the guiding catheter insertion into the vascular puncture sheath should be completed as quickly as possible after randomization according to the assigned treatment strategy. We will record and compare the time from onset to door, from onset to screening imaging, from last non-invasive imaging to groin puncture in the DSA randomized patients, from onset to randomization, from hospital admission to IVT, from hospital admission to groin puncture, from hospital admission to guiding catheter inserted into vascular puncture sheath, from randomization to IVT, from randomization to groin puncture, from randomization to guiding catheter inserted into vascular puncture sheath, and from randomization to cerebrovascular reperfusion/recanalization between the two groups

In this trial, the initiation time of EVT procedure is defined as the moment the guiding catheter is inserted into the vascular puncture sheath in preparation for subsequent therapeutic procedures which may include retrievable stent thrombectomy, thrombus aspiration, balloon angioplasty, stent implantation, or combinations thereof. The end time of EVT procedure is defined as the moment all devices in the vascular puncture sheath are removed (regardless of whether the vascular puncture sheath is retained for a short period of time). The specific EVT approach for each patient will be determined by the treatment team based on the individual's clinical condition. Vascular imaging processes conducted before EVT initiation, including CTA, MRA, and DSA, are all considered vascular screening procedures during the screening phase.

5.2 Concomitant treatments

The steering committee (SC) does not recommend any standardized concomitant drug regimen. All additional treatments, aside from IVT and EVT, must adhere to "China Stroke Prevention and Treatment Guidelines (2021 Edition)" and "Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018". According to both AHA/ASA and Chinese guidelines, antiplatelet or antithrombotic therapy is typically initiated 24 hours after EVT procedure. In case of stent placement, the patient should be administered clopidogrel (300mg) orally or tirofiban intravenously as soon as possible, followed by daily oral doses of clopidogrel (75mg) and aspirin (100mg) for 3 months.

5.3 Rescue medications

If deemed necessary by the interventionalist, the use of local (intra-arterial) rtPA is permitted for all patients enrolled in BEST-BAO. The SC recommends that rtPA be given as a 5 mg bolus at a 5−10 min interval (maximum 40 mg) and that vascular patency be checked after each bolus. Patients who have already received IVT should not be administered more than 30 mg of intra-arterial rtPA during the EVT.

For patients in the EVT alone group who do not achieve successful reperfusion (defined as eTICI 2b–3) within the 4.5-hour time window and do not achieve the maximum rtPA dose, they may subsequently receive IVT with rtPA at a dose of 0.9 mg/kg. The total amount of rtPA for IVT received before and after EVT should not exceed the dose specified in the guidelines.

6. Investigational products

6.1 Name and description of the investigational products

The IVT drug used in this trial is rtPA (Alteplase), a thrombolytic agent composed of a glycoprotein with 526 amino acids. It binds to fibrin via lysine residues and activates fibrin-bound plasminogen, converting it into plasmin. Clinically, it is primarily indicated for the treatment of acute myocardial infarction, pulmonary embolism, acute ischemic stroke, deep vein thrombosis, and other vascular diseases.

6.2 Summary of clinical research findings

Currently, there are no RCTs comparing IVT followed by EVT with EVT alone in posterior circulation AIS patients. The IST-3 trial, which evaluated the efficacy of IVT in posterior circulation AIS, found that its benefits in this population were similar to those observed in anterior circulation AIS[26]. A meta-analysis of 13 studies demonstrated that posterior circulation AIS patients treated with rtPA had better functional outcomes than those with anterior circulation AIS, while the risk of symptomatic intracranial hemorrhage was approximately half[13]. These findings suggest that IVT with rtPA is similarly effective in posterior circulation AIS compared to anterior circulation AIS, with a lower bleeding risk.

6.3 Summary of known and potential risks and benefits

The known potential adverse effects of rtPA can be found in its product information leaflet.

6.4 Description and justification of route of administration and dosage

The route of administration and dosage are determined based on the 2019 AHA/ASA guidelines for early management of AIS.

7. Non-investigational products

7.1 Name and description of non-investigational products

In this trial, EVT procedures include retrievable stent thrombectomy, thrombus aspiration, balloon angioplasty, stent implantation, or combinations thereof (excluding DSA during the screening phase). The specific EVT approach for each patient will be determined by the treatment team based on the patient's condition. Endovascular devices approved by the NMPA will be used as the preferred devices during EVT.

7.2 Summary of other clinical research findings

To date, four RCTs have evaluated EVT for AIS-BAO. The first-generation thrombectomy trials, BEST and BASICS, failed to demonstrate the superiority of EVT[9, 10]. However, more recent trials with improved designs and higher quality, such as ATTENTION and BAOCHE, confirmed that EVT significantly improves functional outcomes in AIS-BAO patients within 24 hours of symptom onset compared to standard treatment. These studies showed an approximately 22–23% increase in the proportion of patients achieving disability-free outcomes at 3 months. Standard treatment typically includes intravenous rtPA. Interestingly, a subgroup analysis of the ATTENTION trial suggested that patients who did not receive IVT might benefit more from EVT, leaving the efficacy and safety of IVT followed by EVT versus EVT alone in posterior circulation stroke unresolved.

7.3 Summary of known and potential risks and benefits

Potential risks include intracranial and extracranial hemorrhage, hemorrhagic transformation of the infarct, procedural risks such as dissection, perforation, and embolization in other vascular territories, as well as post-procedural risks such as infection. Previous studies on anterior circulation AIS indicated that the risk of hemorrhagic events and hemorrhagic transformation are comparable between IVT followed by EVT and EVT alone. Post-procedural complications, such as pneumonia and other infections, are similarly infrequent, and procedural complications are rare.

Both retrievable stent thrombectomy and thrombus aspiration, as primary EVT methods for AIS-BAO, are NMPA-approved for recanalization of occluded large intracranial vessels. Numerous studies have demonstrated that vascular recanalization significantly improves clinical outcomes in these patients. While EVT carries inherent risks, the ATTENTION and BAOCHE trials both have confirmed that EVT combined with standard medical therapy significantly increases the proportion of good functional outcomes at 90±14 days compared with standard medical therapy alone for AIS-BAO[11, 12]. Thus, participation in this trial ensures that enrolled patients receive evidence-based treatment, with individual patients benefiting from either of the assigned treatment strategies. Additionally, this trial will improve understanding of both treatment strategies, ultimately benefiting the broader patient population. Retrievable stent thrombectomy and thrombus aspiration techniques have been in use for several years, and only cerebrovascular disease interventionalists who are well-trained and experienced are permitted to participate in this trial. Therefore, patients receiving EVT are not exposed to additional risks in this trial. The risks and benefits associated with the procedures are described below.

7.3.1 Risks of EVT

EVT related risks are diverse. Potential complications include, but are not limited to: air embolism, hematoma or bleeding at the puncture site, infection, distal embolization, vasospasm, thrombosis, dissection or perforation, embolus fragmentation, acute vessel closure, ischemia, intracranial hemorrhage, pseudoaneurysm formation, neurological deficits including stroke, and death.

7.3.2 Benefits of EVT

Participants should understand that the treatments offered in this study are currently recognized as effective and beneficial. However, based on prior research, it remains unclear which of the two commonly used clinical strategies—IVT followed by EVT or EVT alone—achieves better vascular recanalization rates and clinical outcomes.

7.3.3 Potential risks and benefits to participants

Participants in the IVT followed by EVT group will receive standard medical therapy available at their healthcare facilities. Intravenous rtPA is an approved and evidence-based treatment for posterior circulation stroke, and some patients in this trial may receive intravenous rtPA. Due to the more detailed follow-up plan of BEST-BAO compared to the current guidelines, participants in this trial may need to undergo more follow-up imaging or neurological examinations (such as 24–72 hour imaging, 90±14 day mRS scores, etc.) than those who are not enrolled. The risks associated with these imaging and neurological function tests are acceptable, and participants may benefit more from these additional examinations.

7.3.4 Risk-benefit ratio

The primary aim of this trial is to determine the efficacy and safety of IVT followed by EVT versus EVT alone for AIS-BAO. Previous non-randomized studies, including retrospective and cohort analyses, have shown inconsistent conclusions. Due to limitations in their designs, the differences in efficacy and safety between these two treatment strategies remain unclear. Regardless of which treatment strategy is ultimately proven superior, this trial will represent a significant benefit for all patients with AIS-BAO. Even if the two strategies are proven to be equivalent in efficacy and safety, this finding will guide clinical practice by emphasizing the focus on EVT itself, simplifying emergency workflows, increasing the proportion of patients receiving timely treatment, reducing the burden on healthcare systems, and ultimately benefiting a greater number of patients.

8. Methods

8.1 Study endpoints

8.1.1 Primary endpoint

The primary endpoint of this trial is the proportion of patients achieving a mRS score ≤ 2 at 90±14 days after stroke onset. The mRS is the preferred parameter for assessing disability in stroke-related clinical trials. It is an ordinal scale with 7 levels, ranging from 0 to 6, where a score of 6 indicates death **(Appendix 1)**. Using the standardized reports, mRS assessments will be conducted by trained and independent investigators and evaluators who are blinded to the assigned groups and the actual treatments received.

8.1.2 Secondary endpoints

The secondary endpoints are as following:

(1) Proportions of patients with mRS = 0 or 1 at 90±14 days after stroke onset.

(2) Proportions of patients with mRS = 0–3 at 90±14 days after stroke onset.

(3) mRS score at 90±14 days after stroke onset.

(4) NIHSS score **(Appendix 2)** at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(5) Proportion of patients with a NIHSS score = 0 or 1, a NIHSS score = 0–2, a NIHSS score improvement ≥ 4 points, and a NIHSS score improvement ≥ 8 points. at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset.

(6) Glasgow coma scale score (GCS; **Appendix 3**) at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(7) Barthel Index score (BI; **Appendix 4**) and the proportion with BI = 95–100 at 30±7 and 90±14 days after stroke onset.

(8) EQ-5D-5L score **(Appendix 5)** at 90±14 days after stroke onset.

(9) eTICI score **(Appendix 6)** and successful reperfusion rates before and after EVT.

(10) mAOL score **(Appendix 7)** and recanalization rates at 24–72 hours after procedure.

(11) PC-ASPECTS score **(Appendix 8)** at 24–72 hours after procedure and 5–7 days after stroke onset.

(12) Lesion volume based on quantitative imaging detection at 24–72 hours after procedure and 5–7 days after stroke onset.

8.1.3 Safety endpoints

The safety endpoints include:

(1) All-cause mortality within 7, 30±7, and 90±14 days after stroke onset.

(2) Proportions of patients with intracranial hemorrhage and symptomatic intracranial hemorrhage **(Appendices 9–11)** at 24–72 hours after procedure and 5–7 days after stroke onset.

(3) Proportions of patients with new regional cerebral embolisms during EVT **(Appendix 12)**.

(4) Proportions of patients with new cerebral infarction at 24–72 hours after procedure and 5–7 days after stroke onset.

(5) EVT procedure-related complications within 90±14 days after stroke onset.

(6) Other serious adverse events within 90±14 days after stroke onset.

8.1.4 Additional study parameters

Baseline parameters to be recorded include demographic data such as age, sex, ethnicity, and body mass index, as well as clinical histories, including prior stroke, comorbidities (e.g., hypertension, diabetes, atrial fibrillation, and myocardial infarction), smoking, alcohol consumption, prior medications (e.g., antiplatelets and anticoagulants), and vital signs (e.g., blood pressure, temperature, pulse, and respiration rate). Neurological assessments include pre-stroke mRS, NIHSS, and GCS scores. Clinical laboratory tests include INR, APTT, platelet count, and blood glucose levels. Imaging results will include PC-ASPECTS, PMI (Pons-midbrain index; **Appendix 13**), PC-CS (Posterior circulation collateral score; **Appendix 14**), and BATMAN (Basilar artery on CT angiography; **Appendix 15**) scores.

We will document the actual dose, type, route, and administration time of IVT medications. Additionally, we will record the time intervals from symptom onset to emergency department arrival, CT/MR/DSA imaging, randomization, IVT initiation, EVT procedure initiation, reperfusion, and EVT procedure completion. Details of endovascular devices, including model, specifications, quantity, and usage sequence, as well as type of anesthesia and sedatives (if used), will also be recorded.

Patients included in this trial are recruited from two main pathways: (1) direct referrals from external healthcare facilities and (2) direct admissions to the comprehensive stroke center (Mothership model). This recruitment strategy reflects typical clinical practice and ensures the inclusion of a diverse patient population.

8.1.5 Assessments of Clinical Outcomes

Using a standardized questionnaire, assessment of the mRS score at 30 ± 7 and 90 ± 14 days is performed by local trained investigators who are not aware of treatment allocation based on a standardized process of telephone or in-person interview. If a patient is unavailable or unable to answer the questions, a proxy or healthcare provider will be interviewed. These assessment processes must be recorded, either through audio or video. Written reports and the corresponding audio and video of the interviews will be sent to the independent endpoint adjudication committee who are also blinded for treatment allocation. The mRS score will be determined after review of these reports. If there is disagreement between the two observers, a third independent observer, who is also blinded, will resolve differences in interpretation.

Assessment of the EQ5D-5L and BI scores at 30 ± 7 and 90 ± 14 days is performed by local trained investigators who are not aware of treatment allocation based on a standardized process of telephone or in-person interview.

These assessment processes must be recorded, either through audio or video.

Assessment of the mRS, NIHSS, GCS scores at 18-24 hours, 24-72 hours, and 5-7 days is performed by local trained investigators who are not aware of treatment allocation based on a standardized process of in-person interview. These assessment processes must be recorded through video.

Video recording of the processes of assessing mRS, NIHSS, GCS at baseline is required. Video recording of the patients' baseline neurological assessment is obtained in order to allow for an independent team of investigators to confirm the satisfactory fulfillment of all inclusion/exclusion criteria.

To ensure the data quality, an independent CRO will perform 100% data verification for all centers, investigator meetings will be organized frequently to provide feedback and to discuss potential avenues for improvement, and all local trained investigators are required to receive both on-site and web-based video training.

8.1.6 Assessments of Radiological Imaging

All radiological imaging will be assessed by an independent imaging adjudication committee blinded to treatment allocation. All independent imaging adjudication committee members are required to be trained and tested before the official reading in order to reduce reader variability and increase reliability. The independent imaging adjudication committee is consisted of a CT/CTA team, MRI/MRA team and DSA team. All imaging will be read by two independent readers and a consensus reading will be performed by a senior reader of each team in case of discrepancies.

PC-ASPECTS score, infarction in new territory, and cerebral hemorrhages are determined by means of CT or MRI-DWI. PC-CS, BATMAN, and mAOL scores are determined by means of CTA, MRA, or DSA. Embolization to new territory and eTICI score are determined by means of the angiograms during EVT procedures. Lesion volume is assessed by an automated, validated algorithm. Cause of stroke is determined according to assessments of the angiograms in combination with medical records. In addition, the DSA team will review all series and images captured during EVT to determine the procedure related complication

8.2 Randomization, blinding, and treatment allocation

The randomization process will use a web-based randomization system. Patients can be randomized **(Appendix 16)** when AIS-BAO is confirmed by CTA, MRA, or DSA.

Before a patient is registered in the study database, assigned groups and treatment allocation will remain inaccessible, and patients cannot be excluded from the study after the allocation is revealed. Both patients and treating physicians will be aware of the assigned treatment group. However, trained investigators, who are blinded to assigned groups and treatment allocation, will record endpoint-related information using standardized forms and procedures, and details of the interviews. These trained evaluators will assess mRS outcomes and evaluate neuroimaging results in a blinded manner. Information related to assigned groups and treatment allocation will be maintained separately from the study database. The SC will not be informed of interim analysis results on the efficacy and safety. Independent trial statisticians will combine treatment allocation data with study database for reporting to the DSMB.

8.3 Study procedures

Patients will undergo evaluations of vital signs, mRS, NIHSS, and GCS at baseline, 18–24 hours after procedure, 24–72 hours after procedure, and 5–7 days after stroke onset. These evaluations are also routine clinical practices and will be conducted by certified investigators.

At baseline, patients will undergo CT/CTA, MRI/MRA, or CT/DSA tests to assess infarct size, vascular lesion location and extent, and collateral circulation. During the EVT procedure, vascular recanalization, reperfusion, and new regional embolism will be evaluated, along with documentation of procedural details. At 24–72 hours after procedure, patients will undergo CT/CTA or MRI/MRA tests to evaluate infarct size, vascular recanalization, and

intracranial hemorrhage. At 5–7 days after stroke onset, patients will undergo a CT or MRI test to assess infarct size and intracranial hemorrhage.

Additionally, patients will undergo evaluations of mRS, BI, and EQ-5D-5L at 30±7 days and 90±14 days after stroke onset.

Detailed trial flowcharts and visit schedules are presented in **Appendices 16 and 17**.

8.4 Withdrawal of individual participants

Participants can withdraw from the trial at any time and for any reason without any consequence. Investigators can also decide to withdraw a participant due to urgent medical reasons. Data from patients who do not provide consent for further participation will be anonymized and used for baseline analysis to better describe the study population. Missing data, including the final mRS score, will be addressed using statistical methods during analysis. Critical parts of personal data will be removed.

8.5 Premature termination of the trial

The study will only be prematurely terminated if recommended by the DSMB or required by the Ethics Committee (EC), NMPA, or other regulatory authorities. If the study is terminated early, the database will be locked after the last enrolled patient completes their 90-day follow-up, and study results will be reported.

9. Safety reporting

9.1 Temporary suspension for participant safety

If there is sufficient evidence that continuing the study may harm participants' health or safety, the sponsor will suspend the trial. The sponsor will inform the EC of any delays caused by the suspension, including the reasons for taking such action. The trial will remain suspended until further review by the EC. Investigators must notify all participants accordingly.

9.2 Definitions

9.2.1 Definition of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore, an AE may be: A new illness; The worsening of a concomitant illness; An effect of vaccination, including the comparator; A combination of the above.

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-randomization.

9.2.2 Definition of serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose: Result in death; Are life-threatening; Require or prolong inpatient hospitalization; Result in persistent or significant disability/incapacity, or; Are a congenital/birth defect.

A SAE can also be an important medical event that may not result in death, be life-threatening, or require

hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. For example, any new diagnosis of cancer (made after study enrollment) is considered an important medical event. Because our primary safety endpoints for the trial are also SAEs by definition, they will be reported dually as SAEs and as endpoints. SAEs should be managed according to the best current standard of care.

All deaths occurring during the follow up to day 90±14 will be reported as an SAE. When reporting a death, the event or condition that caused or contributed to the fatal outcome should be reported as a single medical concept.

AE occurring within 30±7 days of randomization and all SAEs will be reported in the Case Report Form (CRF). Severity and relationship definitions are presented below.

9.2.3 Definitions of AE-Related Terms

AE Severity:

Mild: Awareness of sign or symptom but easily tolerated.

Moderate: Discomfort sufficient to cause interference with normal activities.

Severe: Incapacitating, with inability to perform normal activities.

AE Relationship:

Related: A clinical event, including laboratory test abnormality, where there is a "reasonable possibility" that the SAE was caused by the study drug, meaning that there is evidence or arguments to suggest a causal relationship.

Probably: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.

Possibly: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unrelated: This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

9.3 Clinical management of adverse events

9.3.1 Identification of adverse events by the investigator

AE monitoring and reporting will be followed-up until day 30±7. SAEs will be followed through the final study exit visit (day 90±14 visit or death or end of study whichever is sooner) or until the subject is deemed "lost to follow-up".

AE identification while the subject is admitted to the acute stroke hospital will be collected via acute stroke hospital patient records and verbal histories from the subject or legally authorized representative (LAR). For follow up visits after discharge from the acute stroke hospital the subject (or LAR if the subject is not able to respond to the questions) will be asked about the occurrence of AEs since the last contact, and if available, from records at the acute stroke hospital. AEs that were ongoing at the last contact will be updated with a stop date or confirmed as ongoing. AE collection will continue until day 30±7, and SAE to day 90±14 or the final contact.

A consistent methodology of eliciting AEs at all subject evaluation timepoints will be used. Non-directive questions include: How have you felt since your last clinical visit/hospital discharge? Have you had any new or changed health problems since you were last here? Have you had any unusual or unexpected worsening of your underlying medical condition or overall health? Have there been any changes in the medicines you take since your last clinical visit/hospital discharge?

Diagnosis versus signs and symptoms for the purpose of AE reporting: if known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis it is acceptable to report the information that is ultimately available.

9.3.2 Reporting of adverse events

AEs should be reported as they occur on the electronic CRF (e-CRF). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the investigator, action taken and outcome.

9.3.3 Reporting of serious adverse events

In order to comply with current regulations on SAE reporting to health authorities, the investigator must document all SAEs regardless of causal relationship and notify the sponsor. The investigator will give access and provide the sponsor with all necessary information to allow the sponsor to conduct a detailed analysis of the safety of the investigational product. It is the responsibility of the investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed into the e-SAE form.

9.3.4 Reporting by the investigator

All SAEs must be reported to the sponsor within 24 hours of the local investigator's first awareness of its occurrence. SAEs will be reviewed by the trial medical monitor. The investigator will report the SAEs using the e-SAE form in the e-CRF, which will send an immediate alert to the sponsor. If the e-CRF system is not available, a paper SAE form should be directed within 24 hours.

9.3.5 Reporting SAEs to the health authorities and ethics committees

The sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the sponsor's standard operating procedures.

SAEs that are assessed by the sponsor to be unexpected and related to study drug (expedited reporting SAEs) will be reported to the regulatory agencies as per country requirements. All other SAEs will be reported to regulatory agencies based upon local reporting requirements.

The sponsor's medical monitor or designee will notify the investigators in writing of the occurrence of any reportable SAEs. The sponsor or delegate will be responsible for reporting suspected unexpected serious adverse reaction to any Central EC in compliance with local current legislation. The investigators will be responsible for informing their local EC of any reportable SAEs as per their local requirements.

9.4 Data and safety monitoring board

To ensure the safety of the interventional procedures, an independent DSMB will monitor the trial. The independent DSMB will be composed of an experienced neurologist, an interventionalist, and a biostatistician, which are not involved in the trial. The DSMB will meet at least once a year, and is provided with structured unmasked reports, prepared by the trial statistician, for their reference only. DSMB is responsible for recommendations to the executive committee regarding stopping or extending the trial. In addition, the DSMB will review the occurrence of SAEs and make recommendations to the executive committee regarding safety of the trial.

In addition, interim analysis results, including mortality and other primary outcome data (e.g., SAEs attributed to treatment), will be confidentially shared with the DSMB chair. The DSMB will also review all accumulated safety data and conduct a single interim analysis when one-third (114 patients) of the primary endpoint follow-ups are completed. Based on the interim analysis, the DSMB may provide the BEST-BAO research team with recommendations for sample size adjustments, changes to the study design, or early termination of the trial if

necessary. These recommendations will be conveyed to the sponsor through the SC chair. If the sponsor decides not to fully implement the DSMB's recommendations, a rationale will be provided to the EC for review. Further details on DSMB procedures are outlined in the DSMB charter.

10. Statistical analysis

10.1 Sample size calculation

Currently, no large-scale RCTs exist in this field. The sample size calculation for this study is based on the results of the RESCUE-RE registry study in the Chinese population[25], which reported that the proportion of patients achieving a mRS score ≤ 2 at 90±14 days post-procedure was 42.03% in the IVT followed by EVT group and 26.14% in the EVT alone group. Based on the superiority hypothesis, the study aims to determine whether the favorable outcome rate (90-day mRS ≤ 2) in the IVT followed by EVT group is superior to that in the EVT alone group. Assuming a one-sided type I error rate of 0.025 and 80% statistical power, and using a 1:1 randomization ratio, the required sample size is 136 patients per group (a total of 272 patients). Considering an anticipated dropout rate of approximately 20%, the final sample size is adjusted to 340 patients, with 170 patients per group.

This study hypothesizes that IVT followed by EVT is superior to EVT alone. However, given the limited reference data and clinical evidence in the anterior circulation indicating that EVT alone may be non-inferior to IVT followed by EVT, an interim analysis is planned after one-third (114) of the patients have completed follow-up for the primary endpoint. During the interim analysis, the DSMB will evaluate the efficacy data from both groups and conduct a sample size re-estimation based on the conditional power calculated from the available data. The DSMB will provide recommendations to the BEST-BAO research team on adjustments to the sample size or modifications to the study hypothesis.

If the efficacy advantage of the IVT followed by EVT group over the EVT alone group is less than anticipated, the sample size may be expanded appropriately, with an upper limit of no more than 20% of the original sample size. If the efficacy of the two groups appears to be similar, the study design will shift to a non-inferiority framework, evaluating whether EVT alone is non-inferior to IVT followed by EVT. Assuming similar efficacy (with both groups achieving a 90-day mRS score ≤ 2 in 42.03% of patients), the current sample size of 170 patients per group provides 80% power to test non-inferiority, with a one-sided type I error rate of 0.025 and a non-inferiority margin of -15%. The interim analysis and sample size re-estimation will be conducted under the strict control of the DSMB to ensure that the type I error rate is not inflated.

10.2 Statistical analysis

The primary endpoint of the study is the proportion of patients achieving mRS ≤ 2 at 90±14 days after stroke onset. The proportion of patients achieving the primary endpoint will be calculated for each group, along with the rate difference (RD) and its 95% confidence interval (CI). A log-binomial model with a log-link function will be used to adjust the rate difference for multiple covariates, including age, pre-stroke mRS, time from onset to randomization, stroke severity (baseline NIHSS), and collateral circulation status (baseline PC-CS). The adjusted RD and its 95% CI will be reported.

For the shift analysis of mRS scores, a logistic ordinal regression model will be applied to calculate the common odds ratio (cOR) and its corresponding 95% CI.

The primary analysis will follow the intention-to-treat (ITT) principle. The main analysis will be based on a modified ITT population (m-ITT), defined as patients who were randomized and received treatment. Analyses will be conducted according to the original randomization group. Other populations, such as the as-treated set (ATS) and per-protocol set (PPS), will be used for sensitivity analyses. Details of the specific analytical methods and

population definitions can be found in the Statistical Analysis Plan (SAP).

10.3 Subgroup analyses

Subgroup analyses of the primary endpoint will be conducted based on the following variables:

(1) Age
(2) Sex
(3) Medication history
(4) Pre-stroke mRS score
(5) Baseline stroke severity (NIHSS score)
(6) Blood glucose level at admission
(7) Baseline infarct size (PC-ASPECTS score and quantitative measurement)
(8) Baseline collateral circulation status (PC-CS and BATMAN scores)
(9) Stroke etiology
(10) Location of basilar artery occlusion
(11) Time from symptom onset to randomization
(12) Time from randomization to groin puncture
(13) Time from randomization to guiding catheter insertion into the vascular puncture sheath
(14) Time from randomization to cerebrovascular reperfusion

10.4 Interim analysis

An interim analysis will be conducted after one-third (114) of the patients have completed follow-up for the primary endpoint, with the primary objective of reassessing the sample size. The DSMB will calculate the conditional power based on the available data and provide recommendations to the research team regarding any potential adjustments to the sample size. If the efficacy advantage of the IVT followed by EVT group over the EVT alone group is less than anticipated, the sample size may be expanded appropriately, with an upper limit of no more than 20% of the original sample size. If the efficacy of the two groups appears to be similar, the study design will shift to a non-inferiority framework, evaluating whether EVT alone is non-inferior to IVT followed by EVT.

The study does not include predefined conditions for early termination, except in cases where the DSMB recommends stopping the trial for safety reasons. Otherwise, enrollment will continue until the target sample size is achieved.

11. Quality control and quality assurance

11.1 Quality control

11.1.1 Requirements for study personnel

Personnel participating in this trial must have the necessary professional expertise, qualifications, and research capabilities. They are required to thoroughly study and discuss the clinical trial protocol and study manual, and their participation must be approved after qualification review. Once approved, the personnel involved should remain relatively consistent throughout the trial. Tasks such as record management, drug or device usage, and calibration of relevant testing equipment must be managed by qualified individuals dedicated to those responsibilities.

To ensure all procedures are performed by experienced neurointerventionists, the neurointerventionists must meet specific requirements. Each interventionlist must have a minimum of three years of experience in cerebrovascular interventions and have independently completed at least 30 cases of retrievable stent

thrombectomy and thrombus aspiration.

11.1.2 Training of study personnel

Before the trial begins, all study personnel will undergo training to ensure a full understanding of the trial protocol and the specific meanings of each parameter. Descriptions of subjective symptoms must be objective and free from any suggestion or prompting. Objective indicators should be assessed according to the protocol's specified time, location, and methods. Special attention must be paid to the observation and follow-up of AEs.

11.1.3 Quality control measures for clinical laboratories

The criteria for determining abnormal results in clinical laboratory tests will follow the normal reference ranges established by each participating center.

11.2 Quality assurance

11.2.1 Establishment of the BEST-BAO committees

To ensure the quality of the study, BEST-BAO has established the following committees: the SC, the DSMB, the Independent Endpoint Adjudication Committee, the Independent Adverse Event Assessment Committee, and the Independent Imaging Assessment Committee **(Appendix 18)**.

11.2.2 Independent imaging assessment committee

The imaging data of all participants will be uploaded via storage media and online platforms for evaluation by the Independent Imaging Assessment Committee. The committee will assess baseline infarct size as well as infarct size at 24–72 hours and 5–7 days using CT and MRI. It will also evaluate vessel occlusion, recanalization, and reperfusion at baseline and 24–72 hours using CTA, MRA, or DSA, as well as new cerebral embolisms during the EVT procedure. Additionally, intracranial hemorrhage (ICH) and symptomatic ICH (sICH) at 24–72 hours and 5–7 days will be evaluated based on CT, and new areas of cerebral infarction will be assessed using CT and MRI during the same timeframes.

Before participant enrollment, imaging data, including CT, CTA, MRA, and DSA, will be interpreted by at least two neurointerventional or radiology specialists at each participating center. These specialists will not be directly involved in the execution of the trial.

12. Ethical considerations

12.1 Regulatory statement

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki (October 2013) [27].

12.2 Informed consent

In compliance with article 28 of the quality management standards for clinical trials of medical devices (effective May 1, 2022), researchers must provide participants or their legal representatives (guardians) with detailed information about the clinical trial before it begins. This includes the nature and purpose of the trial, potential benefits and risks, available alternative treatments, and the rights and obligations of participants as defined by the declaration of Helsinki.

After thorough and detailed explanation, the participant or their legal representative must sign and date the informed consent form, and the researcher must also sign and date the form before the trial begins. Each participant must provide contact information, and the researcher must share their own contact details with the participant to ensure availability in case of any changes in the participant’s condition. This also allows the researcher to stay

informed about the participant's condition throughout the study.

12.3 Issues regarding minors or incapacitated participants

Minors (patients under 18 years of age) will not be enrolled in this trial. Approximately 50% of participants in the trial are expected to have language impairments due to stroke, and about one-fourth may experience some degree of anosognosia (lack of awareness of their illness). In these cases, following Article 28 of the quality management standards for clinical trials of medical devices (effective May 1, 2022), incapacitated participants may be included in the trial if the Ethics Committee agrees in principle and the researcher determines that participation is in the participant's best interest. In such cases, the legal representative (guardian) of the participant must fully understand the study details and provide their signature and date on the informed consent form before the trial begins.

12.4 Benefits and risks assessment, group relatedness

According to published studies, all participants are expected to benefit from the treatment methods used in this trial (IVT followed by EVT or EVT alone). While EVT carries inherent risks, this trial does not involve investigational drugs or devices undergoing pre-approval evaluation. All approved treatment methods, drugs, and interventional devices are consistent with current clinical practice and have been authorized by national regulatory agencies.

Additionally, the trial will provide all participants with other standard medical care as recommended by ASA/AHA and Chinese guidelines, including secondary prevention of cerebrovascular disease and management of stroke-related complications.

12.5 Compensation for injury

All participating centers have obtained liability insurance that covers compensation for potential injuries or death caused during the trial.

13. Data management, monitoring, and publication

13.1 Data and document processing and storage

All data will be entered into the electronic data capture (EDC) database by local research staff. Participants will be recorded and coded using unique study identifiers. A list linking the codes to participant names will be kept by local researchers. The only file containing identifying information will be stored separately from the study database in a secure digital system and organized by study ID. Only the clinical research coordinator (CRC) have access to the information.

13.2 Monitoring and quality assurance

Clinical research associates (CRAs) will arrange site visits based on the enrollment rate at each center and any deviations previously identified. In principle, monitoring visits will be scheduled within five working days after a site begins enrolling participants. CRAs will verify informed consent and source data for all participants. Data to be monitored includes, but is not limited to, inpatient records, outpatient records, follow-up records, imaging data, and assessment forms. Additionally, CRAs will verify the completeness and consistency of data entered into the EDC system.

13.3 Revisions

Amendments refer to any changes made to the study protocol after a favorable opinion has been obtained from the Ethics Committee (EC). All amendments will be reported to the EC that provided the favorable opinion.

13.4 Annual progress reports

The sponsor/researchers will submit an annual summary of the trial's progress to the EC. The report will include information such as the date of the first participant's enrollment, the number of participants enrolled and completed, details of SAEs, serious adverse reactions, other issues, and any amendments.

13.5 Suspension and early study termination reports

The researchers/sponsor will notify the EC of study completion within eight weeks. Study completion is defined as the last visit of the last participant enrolled. If the study is suspended, the sponsor will immediately inform the EC, including the reasons for the suspension. In the case of early termination, the sponsor will notify the EC within 15 days, providing the reasons for the termination. The sponsor/researchers will submit a final study report, including all publications/abstracts related to the study, to the EC and regulatory authorities within one year after the study ends.

13.6 Public disclosure and publication policy

The trial has been registered on ClinicalTrials.gov with the registration number NCT05631847 and with the Chinese Clinical Trial Registry (https://www.chictr.org.cn) under registration number ChiCTR2300070584.

The study database will be locked one month after the last follow-up visit of the last enrolled participant. A manuscript describing the study and addressing the primary research questions will be submitted to a major clinical research journal within three months of database closure. The manuscript will be shared with the sponsor one month prior to submission, though the sponsor will not intervene in its content.

Detailed anonymized data, including the purpose and methods for using the data, can be requested from the principal investigator. Data will be made available for at least 18 months following the publication of the primary report, provided they are used for legitimate purposes. Data may also be shared with non-commercial organizations for scientific purposes or with commercial entities for regulatory purposes. These purposes will be specifically outlined in the informed consent form provided to participants.

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Appendix 1. Modified Rankin Scale (mRS)

The mRS is an ordinal scale ranging from 0 to 6, where higher scores indicate a greater degree of disability. *(**Source:** Stroke. 1988 May;19(5):604-7.)*

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

Appendix 2. NIH Stroke Scale

The NIH Stroke Scale (NIHSS) is an ordinal scale used to assess the severity of stroke by evaluating the patient's physical condition. Scores range from 0 to 42, with higher scores indicating greater severity of ischemia. The stroke scale items should be performed sequentially as listed. After each subscale assessment, record the patient's performance in each category. Scores should not be revisited or modified. Follow the provided instructions for performing each assessment technique. The score should reflect the patient's actual performance rather than what the clinician believes the patient is capable of. Responses should be documented during the examination, and the process should be conducted promptly. Unless otherwise specified, patients should not be prompted or encouraged (e.g., repeatedly asked to make a special effort). *(**Source:** Stroke. 1989 Jul;20(7):864-70.)*

Instructions	**Scale definition**
1a. Level of consciousness (LOC): 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; required 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 are flexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Phasic 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 examiners not "help" the patient with verbal or non-verbal clues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
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 hand 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 a 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, preexisting 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: 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 finger 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 in this case. If there is extinction, the 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 response 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. Motor arm: 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 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.	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) 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. Motor leg: 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 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.	0 = Absent. 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. Ascore 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; patients 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 laced 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 conservation 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 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 by 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.

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.

Appendix 3. Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is widely used to assess the level of consciousness in stroke patients, postoperative patients with brain injuries, and those with varying degrees of coma due to other causes. ***(Source:*** *Lancet. 1974 Jul 13;2(7872):81-4.)*

Category	**Response**	**Score**
Eye Opening Response	Spontaneous: Normal spontaneous eye opening	4
	Speech: Eye opening in response to verbal command or shouting	3
	Pain: Eye opening in response to painful stimulus	2
	None: No eye opening to any stimulus	1
Verbal Response	Oriented: Correctly answers questions about time, place, and person	5
	Confused: Can speak, but cannot correctly answer questions about time, place, or person	4
	Inappropriate words: Incoherent responses, but recognizable words	3
	Incomprehensible sounds: Unintelligible sounds or moaning	2
	None: No verbal response to any stimulus	1
Motor Response	Obeys commands: Performs simple actions as instructed	6
	Localizes pain: Moves purposefully in response to pain	5
	Withdraws: Withdraws from pain with flexion	4
	Abnormal flexion: Flexes limbs abnormally in response to pain (decorticate posture)	3
	Abnormal extension: Extends limbs in response to pain (decerebrate posture)	2
	None: No motor response to pain	1

Appendix 4. Barthel Index

The Barthel Index (BI) is an ordinal scale used to measure performance in 10 activities of daily living. Scores range from 0 to 100, with higher scores indicating better performance in these activities. *(**Source:** Md State Med J. 1965 Feb;14:61-5.)*

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

Guidelines:

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important.

However, direct testing is not needed.

5. Usually the patient's performance over the preceding 24–48 hours is important, but occasionally longer periods will be relevant.

6. Middle categories imply that the patient supplies over 50 per cent of the effort.

7. Use of aids to be independent is allowed.

Appendix 5. EUROQOL 5D-5L

The EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire is a standardized instrument for measuring health outcomes and is widely used in stroke patients. *(**Source:** Health Policy. 1990 Dec;16(3):199-208.)*

Category	**Scale definition**
Mobility	□ I have no problems in walking about □ I have slight problems in walking about □ I have moderate problems in walking about □ I have severe problems in walking about □ I am unable to walk about
Self-care	□ I have no problems washing or dressing myself □ I have slight problems washing or dressing myself □ I have moderate problems washing or dressing myself □ I have severe problems washing or dressing myself □ I am unable to wash or dress myself
Usual activities (e.g. work, study, housework, family or leisure activities)	□ I have no problems doing my usual activities □ I have slight problems doing my usual activities □ I have moderate problems doing my usual activities □ I have severe problems doing my usual activities □ I am unable to do my usual activities
Pain/discomfort	□ I have no pain or discomfort □ I have slight pain or discomfort □ I have moderate pain or discomfort □ I have severe pain or discomfort □ I have extreme pain or discomfort
Anxiety/depression	□ I am not anxious or depressed □ I am slightly anxious or depressed □ I am moderately anxious or depressed □ I am severely anxious or depressed □ I am extremely anxious or depressed

Appendix 6. eTICI

The Expanded Thrombolysis in Cerebral Infarction (eTICI) scale is a standardized method for assessing the degree of vascular reperfusion after endovascular treatment in patients with acute ischemic stroke. It is widely used in clinical research and practice for acute ischemic stroke. *(**Source:** J Neurointerv Surg. 2014 Mar;6(2):83-6.)*

Score	Definition
0	No perfusion or anterograde flow beyond site of occlusion.
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory.
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed butrate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories.
2a	Some perfusion with distal branch filling of < 50% of territory visualized.
2b	Substantial perfusion with distal branch filling of > 50% of territory visualized.
2c	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli.
3	Complete perfusion with normal filling of all distal branches.

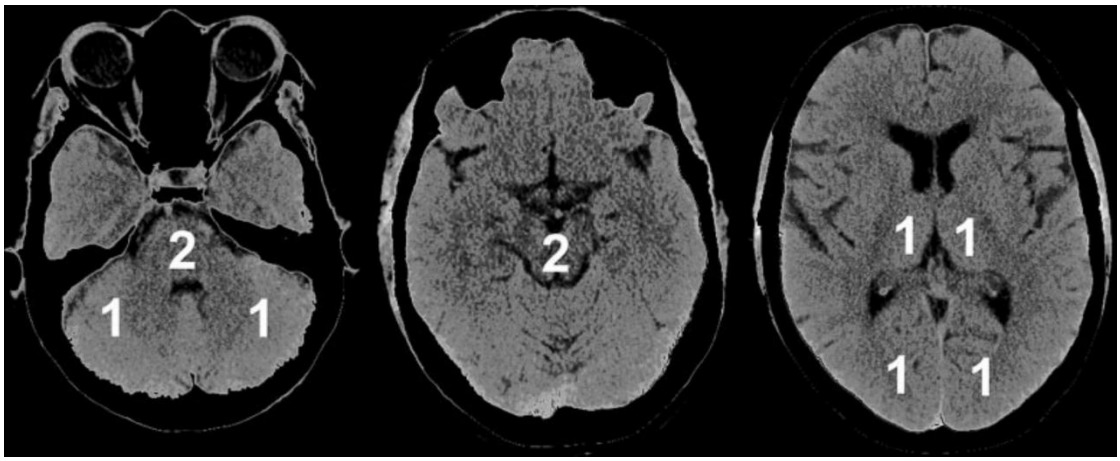
Appendix 7. mAOL

The modified Arterial Occlusive Lesion (mAOL) scale is a standardized method used to evaluate arterial recanalization in acute ischemic stroke patients following endovascular treatment. It assesses the degree of reopening in the previously occluded artery, providing critical insights into the success of the intervention. ***(Source:*** *Stroke. 2013 Sep;44(9):2650-63.)*

Grades	**Definitions**
Grade 0	Complete occlusion of the target artery.
Grade 1	Incomplete occlusion or partial local recanalization at the target artery with no distal flow.
Grade 2	Incomplete occlusion or partial local recanalization at the target artery with any distal flow.
Grade 3	Complete recanalization and restoration of the target artery with any distal flow.

Appendix 8. PC-ASPECTS

The Posterior Circulation Alberta Stroke Program Early CT Score (PC-ASPECTS) is a standardized tool used to evaluate early ischemic changes in the posterior circulation territory. *(**Source:** Stroke. 2008 Sep;39(9):2485-90.)*



Region	Initial Points	Ischemic/Hypodense Changes Present	Subtracted Points
Left Thalamus	1	Yes	-1
Right Thalamus	1	Yes	-1
Left Cerebellum	1	Yes	-1
Right Cerebellum	1	Yes	-1
Left PCA Territory	1	Yes	-1
Right PCA Territory	1	Yes	-1
Midbrain (any part)	2	Yes	-2
Pons (any part)	2	Yes	-2

Notes:

1. Initial score is 10.
2. Subtract the specified points for each region if early ischemic changes or hypodensity are detected.
3. PC-ASPECTS = 10 indicates a normal scan (no abnormalities).
4. PC-ASPECTS = 0 indicates ischemic changes or hypodensity in all the above regions.

Appendix 9. Heidelberg Bleeding Classification (HBC)

*(**Source:** Stroke. 2015 Oct;46(10):2981-6.)*

Class	Type	Description
1 Hemorrhagic transformation of infarcted brain tissue		
1a	HI1	Scattered small petechiae within infarcted brain tissue, no mass effect.
1b	HI2	Confluent petechiae within the infarct area, no mass effect.
1c	PH1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect.
2 Intracerebral hemorrhage within and beyond infarcted brain tissue		
	PH2	Hematoma occupying ≥30% of the infarcted tissue, extending within and beyond the infarcted area, with obvious mass effect.
3 Intracerebral hemorrhage outside the infarcted brain tissue orintracranial-extracerebral hemorrhage		
3a	Parenchymal hematoma remote from infarcted brain tissue	
3b	Intraventricular hemorrhage	
3c	Subarachnoid hemorrhage	
3d	Subdural hemorrhage	

Abbreviations: HBC, Heidelberg bleeding classification; HI, hemorrhagic infarction; PH, parenchymatous hematoma.

Notes:

1. Symptomatic intracranial hemorrhage: new intracranial hemorrhage detected by brain imaging associated with any of the item below:

1.1 ≥ 4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status

1.2 ≥ 2 points in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of ≥ 4 points on the NIHSS score.

1.3 Leading to intubation/hemicraniectomy/external ventricular drain placement or other major medical/surgical intervention.

1.4 Absence of alternative explanation for deterioration 4b.

2. Asymptomatic intracranial hemorrhage: new hemorrhage that has no implications for prognosis or change in management, and there is no substantive change in the patient's neurological status.

Appendix 10. SITS-MOST Criteria

*(**Source:**Lancet. 2007 Jan 27;369(9558):275-82.)*

Evaluation Dimension	**Scoring Criteria**
Imaging Evidence	Intracranial hemorrhage detected on CT or MRI post-treatment.
Hematoma Type	PH 2: hematoma occupies ≥30% of the infarcted area with significant mass effect.
Neurological Deterioration	NIHSS score increased by ≥ 4 points compared to baseline or the lowest value within 24 hours, or led to death.
Overall Assessment	If all the above criteria are met, classify as symptomatic intracerebral hemorrhage.

Notes: PH 2, parenchymal haemorrhage 2.

Appendix 11. ECASS II Classification

*(**Source:** Lancet. 1998 Oct 17;352(9136):1245-51.)*

Category	Definition
HI1	Small petechiae along the margins of the infarct.
HI2	Confluent petechiae within the infarcted area but no space-occupying effect.
PH1	Blood clots in 30% or less of the infarcted area with some slight space-occupying effect.
PH2	Blood clots in more than 30% of the infarcted area with substantial space-occupying effect.
Overall Assessment	Symptomatic Intracerebral Hemorrhage is classified if: blood at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator), documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (e.g., drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points.

Notes: HI 1, haemorrhagic infarction 1; HI 2, haemorrhagic infarction 2; PH 1, parenchymal haemorrhage 1; PH 2, parenchymal haemorrhage 2; sICH, symptomatic Intracranial haemorrhage.

Appendix 12. Embolization to new territory assessment

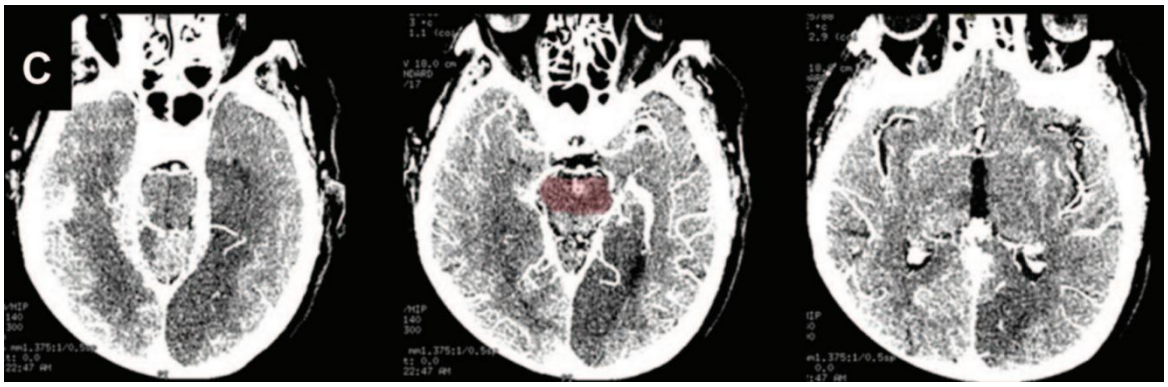
*(**Source:** J Neurointerv Surg. 2017 May;9(5):449-450.)*

<table>
<tr><th colspan="2">Classification based on size</th><th>Classification based on catheter manipulation across territory ostium</th></tr>
<tr><td>Type I</td><td>≤ 2 mm diffusion lesion (unidentifiable on NCCT)</td><td rowspan="3">Type A: Catheter was manipulated past the ostium of the new territory (e.g. large ACA infarct in a patient with an initial M1 occlusion): greater likelihood that infarct is related to the procedure.

Type B: Catheter was not manipulated past the ostium of the new territory (e.g. left PICA infarct in a patient with an initial right M1 occlusion): lower likelihood that infarct is related to procedure</td></tr>
<tr><td>Type II</td><td>> 2 mm to ≤ 20 mm lesion (potentially difficult to identify on CT scan)</td></tr>
<tr><td>Type III</td><td>Large (> 20 mm) infarct</td></tr>
</table>

Appendix 13. PMI

*(**Source:** Stroke. 2008 Nov;39(11):3107-9.)*



Location	**Scoring Method**
Left Half-Pons	0 = No hypoattenuation; 1 = Hypoattenuation area < 50%; 2 = Hypoattenuation area > 50%
Right Half-Pons	0 = No hypoattenuation; 1 = Hypoattenuation area < 50%; 2 = Hypoattenuation area > 50%
Left Half-Midbrain	0 = No hypoattenuation; 1 = Hypoattenuation area < 50%; 2 = Hypoattenuation area > 50%
Right Half-Midbrain	0 = No hypoattenuation; 1 = Hypoattenuation area < 50%; 2 = Hypoattenuation area > 50%

Notes:

(1) The initial PMI score is 0.

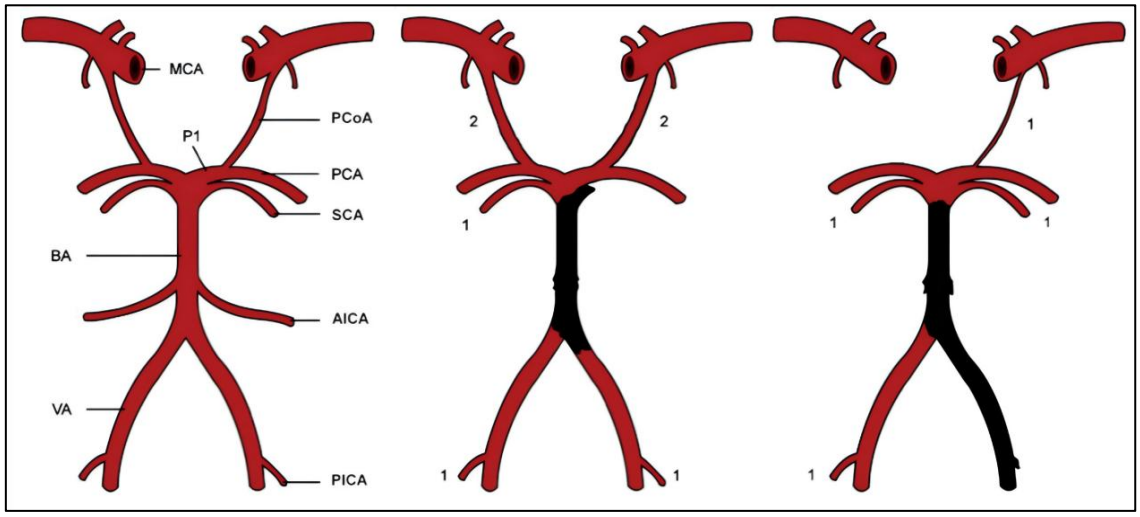
(2) Add points for each region with hypoattenuation observed.

(3) The minimum PMI score of 0 indicates no ischemic damage in all regions.

(4) The maximum PMI score of 8 indicates severe ischemic changes in all regions.

Appendix 14. PC-CS

*(**Source:** Int J Stroke. 2016 Oct;11(7):768-75.)*

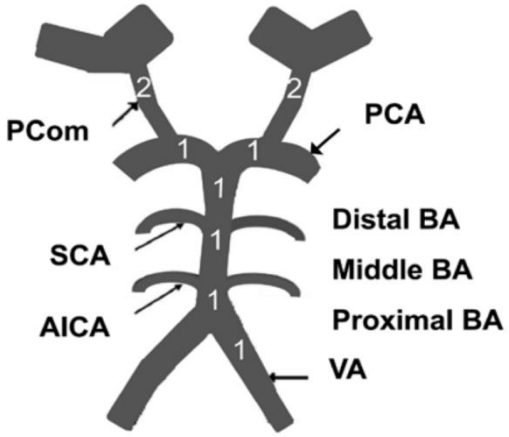


Artery	Scoring Criteria	Points
PCoA	Diameter ≥ ipsilateral P1 segment	2 points (each side)
	Diameter < ipsilateral P1 segment (hypoplastic)	1 point (each side)
PICA	Patent artery visible on CTA	1 point (each side)
AICA	Patent artery visible on CTA	1 point (each side)
SCA	Patent artery visible on CTA	1 point (each side)

Notes: PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery； SCA, superior cerebellar artery.

Appendix 15. BATMAN

*(**Source:** Stroke. 2017 Mar;48(3):631-637.)*



Segment	**Point Allocation**
Patent intracranial vertebral artery	1 point
Basilar artery segments	
Proximal (from vertebrobasilar junction to AICAs origin)	1 point
Middle (from AICAs origin to SCAs origin)	1 point
Distal (from SCAs origin to basilar artery's rostral end)	1 point
Posterior cerebral artery (PCA) P1 segment (each side)	1 point per side
Posterior communicating artery (PCom)	
Patent PCom (≥ 1 mm in diameter)	2 points per side
Hypoplastic PCom (< 1 mm but in continuity with P1 segment)	1 point per side
Fetal PCom (absent P1 segment with flow through PCom)	3 points per side

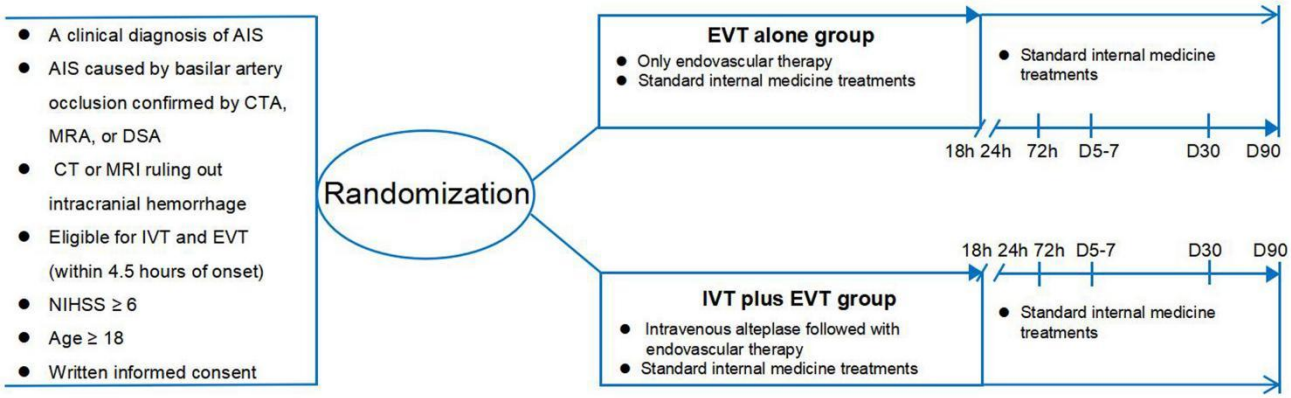
Notes:

(1) The total possible score is 10 points.

(2) Points are deducted for occlusion or absence in the above segments.

(3) Higher scores indicate better collateral circulation and lower clot burden.

Appendix 16. Study flowchart



Appendix 17. Visit Schedule

Assessment/Step	Baseline	Treatment/ Intervention	Follow-up period[1]				
			18–24 hrs after procedure	24–72 hrs after procedure	5–7 days after stroke onset	30±7 days after stroke onset	90±14 days after stroke onset
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Randomization	X						
Demographics[2]	X						
Medical History	X						
Vital Signs[3]	X	X	X	X	X		
Clinical Lab Tests[4]	X			X	X		
CT/CTA or MRI/MRA or CT/DSA	X			X[5]			
CT/MRI (Head)					X		
mRS Score	X		X	X	X	X	X
NIHSS Score	X		X	X	X		
GCS Score	X		X	X	X		
IVT/EVT[6]		X					
Vascular Recanalization		X		X			

eTICI Score		X					
mAOL Score	X			X			
PC-ASPECTS Score	X			X			
PMI Score	X						
PC-CS Score	X						
BATMAN Score	X						
BI Score						X	X
EQ-5D-5L Score						X	X
Concomitant Medications	X	X	X	X	X	X	X
Death		X	X	X	X	X	X
ICH/sICH		X		X	X		
Procedure-Related Complications		X	X	X	X	X	X
New Territory Embolization		X					
New Infarction				X	X		
AE/SAE		X	X	X	X	X	X

Abbreviations: h, hours; CT, Computed tomography; CTA, Computed tomographic angiography; MRI, Magnetic resonance imaging; MRA, Magnetic resonance angiography; DSA, Digital subtraction angiography; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale;

EVT, Endovascular treatment; IVT, Intravenous thrombolysis; eTICI, Extended thrombolysis in cerebral infarction score; mAOL, Modified arterial occlusion lesion score; PC-ASPECTS, Posterior circulation acute stroke prognosis early CT score; PMI, Pons-midbrain index; PC-CS, Posterior circulation collateral score; BATMAN, Basilar artery on CTA score; BI, Barthel index; EQ-5D-5L, EuroQoL five dimensions five levels health questionnaire; ICH, Intracranial hemorrhage; sICH, Symptomatic intracranial hemorrhage; AE, Adverse event; SAE, Serious adverse event.

Notes:

(1) Follow-Up: At 30±7 days and 90±14 days, follow-ups are conducted through telephone, video calls, or in-person visits.

(2) Demographics: Includes basic patient information such as sex, age, BMI, etc.

(3) Vital Signs: Covers temperature, heart rate, respiratory rate, and blood pressure.

(4) Clinical Laboratory Tests: Encompasses blood biochemistry, complete blood count, and coagulation parameters.

(5) Imaging Follow-Up: Investigators are required to complete imaging evaluations at 24–72 hours after EVT procedure. If clinical deterioration necessitates earlier imaging, assessments can be conducted within 24 hours. In such cases, angiography (CTA or MRA) should be completed as synchronously as possible. In addition, given logistical constraints such as insurance policies and patient safety during transportation, the 24–72-hour imaging requirement for these cases can be waived.

(6) IVT/EVT: Includes thrombolytic drug details (type, dose, timing, and route), time intervals from symptom onset to various procedural steps, and specifics of devices and sedation/anesthesia used during the procedure.

Appendix 18. BEST-BAO research committees

1. Steering committee

Chair: Professor Fuqiang Guo (Department of Neurology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital).

Members: Professor Wouter J. Schonewille (Department of Neurology, Sint Antonius Hospital, Nieuwegein, NL), Professor Aquilla S. Turk (Department of Neurosurgery, Prisma Health Upstate, Greenville, SC, USA), Professor Nengwei Yu (Department of Neurology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Professor Yang Xiang (Department of Neurology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Dr. Shu Yang (Department of Neurology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital).

2. Data and safety monitoring board

Chair: Professor Qingwu Yang (Department of Neurology, Xinqiao Hospital, Army Medical University).

Members: Professor Yuxiu Liu (Department of Medical Statistics, Eastern Theater General Hospital), Dr. Guang-Ming Zhu (Banner University Medical Center Tucson, AZ, USA).

3. Independent endpoint adjudication committee

Chair: Professor Yanjiang Wang (Department of Neurology, Army Specialty Medical Center)

Members: Professor Ju Han (Department of Neurology, Shandong First Medical University & First Affiliated Hospital), Professor Ping Shuai (Department of Health Management, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital).

4. Independent adverse event adjudication committee

Chair:Professor Lin Yin (Department of Neurology, Second Affiliated Hospital of Dalian Medical University).

Members: Professor Liangping Li (Department of Gastroenterology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Professor Ziliang Wang (Department of Interventional Radiology, Henan Provincial People's Hospital).

5. Independent imaging adjudication committee

Chair: Professor Longlin Yin (Department of Medical Imaging, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital)

Members: Dr. Jiachuan Guo (Department of Medical Imaging, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Dr. Xiaoyan Li (Department of Medical Imaging, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Dr. Yao Huang (Department of Medical Imaging, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Dr. Ying Liu (Department of Medical Imaging, Sichuan Orthopedic Hospital), Professor Tian Zhang (Department of Neurosurgery, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Dr. Meixiong Cheng (Department of Neurosurgery, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Professor Han Zhou (Department of Medical Imaging, Chengdu Third People's Hospital), Dr. Wenbo Li (Department of Medical Imaging, Chengdu First People's Hospital).

Appendix 19. Steering committee recommendations on IVT and EVT procedures

1. Basic recommendations

All eligible patients should undergo trial enrollment, randomization, and subsequent EVT (with or without prior IVT) as quickly as possible after arrival.

The efforts should be made to minimize delays in EVT initiation caused by IVT procedure in the IVT followed by EVT group. For patients undergoing screening evaluation by CTA or MRA, the time from randomization to femoral artery puncture should be as short as possible, with all patients aiming to achieve a median time of 60 minutes or less from randomization to groin puncture and prompt completion of the guiding catheter inserting into the vascular puncture sheath. For patients undergoing screening evaluation by DSA, the guiding catheter insertion into the vascular puncture sheath should be completed as quickly as possible after randomization according to the assigned treatment strategy. We will record and compare the time from randomization to femoral artery puncture, to the guide catheter insertion into the vascular puncture sheath, and to cerebrovascular reperfusion or recanalization between the two groups.

In this trial, the initiation time of EVT procedure is defined as the moment the guiding catheter is inserted into the vascular puncture sheath in preparation for subsequent therapeutic procedures which may include retrievable stent thrombectomy, thrombus aspiration, balloon angioplasty, stent implantation, or combinations thereof. The end time of EVT procedure is defined as the moment all devices in the vascular puncture sheath are removed (regardless of whether the vascular puncture sheath is retained for a short period of time). The specific EVT approach for each patient will be determined by the treatment team based on the individual's clinical condition. Vascular imaging processes conducted before EVT initiation, including CTA, MRA, and DSA, are all considered vascular screening procedures during the screening phase.

We will document the actual dose, type, route, and administration time of IVT medications. Additionally, we will record the time intervals from symptom onset to emergency department arrival, CT/MR/DSA imaging, randomization, IVT initiation, EVT procedure initiation, reperfusion, and EVT procedure completion.

2. Neuroimaging

Neuroimaging to assess the site, severity, and patency of vascular lesions should be performed before or simultaneously with intravenous rtPA administration to save time and resources. The aim is to allow rtPA infusion before EVT without causing delays.

3. IVT agent, dosage, and route

If deemed necessary by the interventionalist, the use of local (intra-arterial) rtPA is permitted for all patients in this trial. Patients who have already received IVT should not be administered more than 30 mg of intra-arterial rtPA during the EVT procedure. The SC recommends that rtPA be given as a 5 mg bolus at a 5–10 min interval and that vascular patency be checked after each bolus.

For patients in the EVT alone group who do not achieve successful reperfusion (defined as eTICI 2b–3) within the 4.5-hour time window and do not achieve the maximum rtPA dose, they may subsequently receive IVT with rtPA at a dose of 0.9 mg/kg. The total amount of rtPA for IVT received before and after EVT should not exceed the dose specified in the guidelines.

4. EVT devices

This trial does not limit the choice of interventional techniques during EVT. NMPA-approved endovascular devices are all allowed to be used as the primary tools in this trial. Secondary devices may be utilized based on the interventionalist's discretion in cases of primary device failure. Further device selection for specific patients are also determined by the interventional specialist. Details of endovascular devices, including model, specifications, quantity, and usage sequence, as well as type of anesthesia and sedatives (if used), will also be recorded.

Appendix 20. Imaging requirements

Baseline Imaging minimum requirements

When

Prior to randomization, a CT/CTA, MRI/MRA, or CT/DSA should be performed to assess eligibility criteria.

How

1. Pre-randomization CT:

(1) Positioning and scope: The patient should lie in a supine position, with both sides of the head symmetrically aligned. The external auditory meatus on both sides should be equidistant from the table, and the chin should be slightly tucked. Scanning should cover a continuous range of 100–120 mm from the baseline upwards.

(2) Scan reference line: Use the standard orbitomeatal line (a line between the outer canthus of the eye and the external auditory canal). This line roughly parallels the skull base, minimizing bone artifacts and improving visualization of posterior fossa structures.

(3) Tube voltage: 120 kV.

(4) Tube current: 200–300 mA.

(5) Slice thickness and interval: Standard slice thickness of 5–8 mm, with an interval of 5–8 mm.

(6) Window width and window level: Brain window: level = 30–40 HU, width = 70–100 HU. Bone window: level = 250–500 HU, width = 1000–1600 HU. Bone windows typically use a bone algorithm.

2. Pre-randomization CTA:

(1) CTA coverage: It is recommended that the CTA cover the entire region from the aortic arch to the top of the head.

(2) Procedure: Contrast agent: Use a non-ionic, iso-osmolar iodine contrast agent with a concentration of 300 mgI/dL, with a total volume of 90 ml. Injector settings: Set the flow rate at 4 ml/second for the first 30 ml, followed by 3 ml/second for the remaining 60 ml. Scanning: Start the CTA scan simultaneously with the high-pressure injector, guided by Bolus tracking software to ensure optimal timing. The scan range should extend from the aortic arch to the cranial vertex. Use a tube voltage of 120 kV, tube current of 150 mA, slice thickness of 0.5–1.5 mm, and set the reconstruction interval to half of the slice thickness.

(3) Image processing: Image Processing: Provide at least one Maximum Intensity Projection (MIP) image from the CTA data set to assess vascular parameters. Generate three-dimensional volume rendering (VR) and three-dimensional MIP images for vascular visualization. Pay special attention to the original CTA data, particularly the bilateral subclavian arteries and vertebral arteries.

(4) CTA original images: Reconstruct the original CTA images with a slice thickness of 10–12 mm to evaluate the presence of acute infarct lesion.

3. Pre-randomization MRI/MRA:

(1) Scan baseline: Parallel to the anterior-posterior commissure line.

(2) Routine MRI Sequences: Axial SE T1WI: Slice thickness 5–8 mm; interslice gap 1–2.5 mm; 15–25 slices; matrix: 256 × 192–512 × 256; field of view (FOV): 220–250 mm. Axial FSE T2WI: Same specifications as above. Sagittal SE T1WI or FSE T2WI: Helps display midline structures.

Coronal SE T1WI or FSE T2WI: Useful for showing lesions near the skull base or vertex.

(3) FLAIR sequence: Axial plane: TR 10000 ms; TE 100 ms; inversion time (TI) 2000 ms; FOV 230 mm × 230 mm; matrix: 128 × 128; slice thickness: 6 mm; interslice gap: 1.8 mm.

(4) DWI sequence: Axial plane, EPI sequence with b-values of 0 and 1000 s/mm²; TR 3100 ms; TE 99 ms; FOV 230 mm × 230 mm; matrix: 128 × 128; slice thickness: 6 mm; interslice gap: 1.8 mm.

(5) MRA (TOF): TR 22 ms; TE 3.86 ms; FOV 230 mm × 230 mm; slice thickness 0.65 mm; interslice gap: -0.15 mm; 48 slices; flip angle: 18°; number of acquisitions: 1. Scanning range from the C1 lower border to the lateral ventricles' upper border.

4. Pre-randomization DSA:

(1) Baseline DSA should avoid guide catheter use to save time for IVT or EVT initiation.

(2) Intracranial artery baseline and final anteroposterior (AP) and lateral views are mandatory.

(3) Baseline DSA must include arterial and venous phases to assess the cause of BAO.

(4) Baseline DSA should assess proximal vessels supplying the basilar artery (subclavian artery, vertebral artery, and anterior/posterior collateral circulations).

Post-acquisition requirements:

1. All imaging (CT/CTA, MRI/MRA, and CT/DSA) must be stored in DICOM format.

2. All imaging data, including CT, CTA, MRA, and DSA, should be interpreted by at least two neurointerventional or radiology specialists at each participating center. These specialists will not be directly involved in the execution of the trial.

3. All imaging series must be submitted to the independent imaging adjudication committee for further evaluation.

Angiography During EVT

When

1. During EVT procedure, perform anteroposterior and lateral angiographic views (covering the entire head, including the venous phase) to evaluate the occlusion site, clot burden, affected area, associated pathologies, and collateral circulation.

2. Perform angiography after each passage of mechanical or aspiration devices.

3. Perform angiography after each bolus injection of thrombolytic agents.

4. At the end of the procedure, repeat anteroposterior and lateral angiography (covering the entire head, including the venous phase).

How

1. Angiography During EVT procedure:

(1) Conduct angiography through a guiding catheter.

(2) Obtain anteroposterior and lateral angiographic views of the intracranial arteries as mandatory requirements. Both views are essential to assess post-procedural reperfusion.

(3) Include both arterial and venous phases in angiography to evaluate collateral circulation and perfusion of distal vascular beds.

(4) Evaluate the subclavian and vertebral arteries supplying the target vessels shown in the screening imaging.

(5) Ensure that angiography is conducted through the same guiding catheter position and views

During EVT procedure to fully assess treatment outcomes.

2. After each device placement:

(1) Obtain radiographs without contrast medium.

(2) The interventional specialist should determine at least one view.

3. After each passage of mechanical or aspiration device, balloon inflation, or bolus injection of thrombolytic agents:

(1) Perform angiography through the guiding catheter.

(2) At least one view, as determined by the interventional specialist.

Post-acquisition requirements:

1. Save the complete angiographic series, including any microcatheter injections (if performed), in DICOM format according to standard practices.

2. Submit all series to the independent imaging adjudication committee for further analysis.

Follow-up imaging minimum requirements

When

1. At 24–72 hours after EVT procedure: Perform CT/CTA or MRI/MRA to evaluate treatment efficacy.

2. At 5–7 days after stroke onset: Perform a CT scan to assess final lesion size and potential hemorrhagic complications.

3. As clinically necessary: Additional procedures can be performed if required (e.g., if the patient's clinical condition deteriorates), as determined by the treating physician.

How

1. CT at 24–72 hours after EVT procedure:

(1) Positioning and scope: The patient should lie in a supine position, with both sides of the head symmetrically aligned. The external auditory meatus on both sides should be equidistant from the table, and the chin should be slightly tucked. Scanning should cover a continuous range of 100–120 mm from the baseline upwards.

(2) Scan reference line: Use the standard orbitomeatal line (a line between the outer canthus of the eye and the external auditory canal). This line roughly parallels the skull base, minimizing bone artifacts and improving visualization of posterior fossa structures.

(3) Tube voltage: 120 kV.

(4) Tube current: 200–300 mA.

(5) Slice thickness and interval: Standard slice thickness of 5–8 mm, with an interval of 5–8 mm.

(6) Window width and window level: Brain window: level = 30–40 HU, width = 70–100 HU. Bone window: level = 250–500 HU, width = 1000–1600 HU. Bone windows typically use a bone algorithm.

2. CTA at 24–72 hours after EVT procedure:

(1) CTA coverage: It is recommended that the CTA cover the entire region from the aortic arch to the top of the head.

(2) Procedure: Contrast agent: Use a non-ionic, iso-osmolar iodine contrast agent with a concentration of 300 mgI/dL, with a total volume of 90 ml. Injector settings: Set the flow rate at 4

ml/second for the first 30 ml, followed by 3 ml/second for the remaining 60 ml. Scanning: Start the CTA scan simultaneously with the high-pressure injector, guided by Bolus tracking software to ensure optimal timing. The scan range should extend from the aortic arch to the cranial vertex. Use a tube voltage of 120 kV, tube current of 150 mA, slice thickness of 0.5–1.5 mm, and set the reconstruction interval to half of the slice thickness.

(3) Image processing: Image Processing: Provide at least one Maximum Intensity Projection (MIP) image from the CTA data set to assess vascular parameters. Generate three-dimensional volume rendering (VR) and three-dimensional MIP images for vascular visualization. Pay special attention to the original CTA data, particularly the bilateral subclavian arteries and vertebral arteries.

(4) CTA original images: Reconstruct the original CTA images with a slice thickness of 10–12 mm to evaluate the presence of acute infarct lesion.

3. MRI/MRA at 24–72 hours after EVT procedure:

(1) Scan reference line: Align parallel to the anterior-posterior commissure line.

(2) Routine MRI examinations:

1) Axial SE T1WI: Slice thickness 5–8 mm, slice gap 1–2.5 mm, 15–25 slices, matrix size 256×192–512×256, field of view (FOV) 220–250 mm.

2) Axial FSE T2WI: Slice thickness 5–8 mm, slice gap 1–2.5 mm, 15–25 slices, matrix size 256×192–512×256, FOV 220–250 mm.

3) Sagittal SE T1WI or FSE T2WI: Useful for evaluating midline structures.

4) Coronal SE T1WI or FSE T2WI: Useful for identifying lesions near the skull base or vertex.

(3) FLAIR sequence: Axial slices, TR 10,000 ms, TE 100 ms, inversion time (TI) 2000 ms, FOV 230×230 mm, matrix size 128×128, slice thickness 6 mm, slice gap 1.8 mm.

(4) DWI sequence: Axial slices using an echo-planar imaging (EPI) sequence, b-value 0 and 1000 s/mm², TR 3100 ms, TE 99 ms, FOV 230×230 mm, matrix size 128×128, slice thickness 6 mm, slice gap 1.8 mm.

(5) MRA using TOF (Time-of-Flight) technique: TR 22 ms, TE 3.86 ms, FOV 230×230 mm, slice thickness 0.65 mm, slice overlap -0.15 mm, 48 slices, flip angle 18°, one acquisition. Scanning range from the lower margin of the atlas (C1) to the upper margin of the lateral ventricles.

4. CT at 5–7 days after stroke onset:

(1) Positioning and scope: The patient should lie in a supine position, with both sides of the head symmetrically aligned. The external auditory meatus on both sides should be equidistant from the table, and the chin should be slightly tucked. Scanning should cover a continuous range of 100–120 mm from the baseline upwards.

(2) Scan reference line: Use the standard orbitomeatal line (a line between the outer canthus of the eye and the external auditory canal). This line roughly parallels the skull base, minimizing bone artifacts and improving visualization of posterior fossa structures.

(3) Tube voltage: 120 kV.

(4) Tube current: 200–300 mA.

(5) Slice thickness and interval: Standard slice thickness of 5–8 mm, with an interval of 5–8 mm.

(6) Window width and window level: Brain window: level = 30–40 HU, width = 70–100 HU.

Bone window: level = 250–500 HU, width = 1000–1600 HU. Bone windows typically use a bone algorithm.

5. MRI at 5–7 days after stroke onset:

(1) Scan reference line: Align parallel to the anterior-posterior commissure line.

(2) Routine MRI examinations:

1) Axial SE T1WI: Slice thickness 5 – 8 mm, slice gap 1 – 2.5 mm, 15 – 25 slices, matrix size 256×192 – 512×256, field of view (FOV) 220 – 250 mm.

2) Axial FSE T2WI: Slice thickness 5 – 8 mm, slice gap 1 – 2.5 mm, 15 – 25 slices, matrix size 256×192 – 512×256, FOV 220 – 250 mm.

3) Sagittal SE T1WI or FSE T2WI: Useful for evaluating midline structures.

4) Coronal SE T1WI or FSE T2WI: Useful for identifying lesions near the skull base or vertex.

(3) FLAIR sequence: Axial slices, TR 10,000 ms, TE 100 ms, inversion time (TI) 2000 ms, FOV 230×230 mm, matrix size 128×128, slice thickness 6 mm, slice gap 1.8 mm.

(4) DWI sequence: Axial slices using an echo-planar imaging (EPI) sequence, b-value 0 and 1000 s/mm^2 , TR 3100 ms, TE 99 ms, FOV 230×230 mm, matrix size 128×128, slice thickness 6 mm, slice gap 1.8 mm.

Post-acquisition requirements:

1. All imaging must be stored in DICOM file format.

2. All imaging series must be submitted to the independent imaging adjudication committee for further assessment.