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Angioplasty and/or stenting following successful mechanical thrombectomy for intracranial atherosclerosis-related emergent large vessel occlusive stroke (ASSET): protocol of a multicentre randomised trial

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ABSTRACT

Rationale The management of residual stenosis after mechanical thrombectomy in patients with intracranial atherosclerotic stenosis-related emerge large vessel occlusive (ICAS-LVO) stroke is still unclear question in clinical practice.

Aim To demonstrate the design of a clinical trial on emergency balloon angioplasty and/or stenting (BAS) combined with standard medical treatment (SMT) for residual stenosis of ICAS-LVO stroke patients with successful recanalisation.

Design ASSET is a multicentre, prospective, randomised, open-label, blinded end-point, controlled clinical trial designed (PROBE) by investigators. This trial evaluates the effectiveness and the safety of emergency BAS in combination with SMT compared with SMT alone in ICAS-LVO stroke patients with successful recanalisation (defined as expanded treatment in cerebral ischaemia grade of 2b50-3 and maintained for more than 20 min) and residual stenosis (defined as ≥50%) up to 24 hours after the onset of symptoms or the last known well.

Outcome The primary outcome assessed at 90 (±7) days after randomisation is the incidence of ischaemic stroke in the responsible vessel. Symptomatic intracranial haemorrhage within 24 (±3) hours is the primary safety outcome.

Discussion The ASSET trial is designed to provide strong evidence on the effectiveness and safety of emergency BAS to treat residual stenosis after successful recanalisation in patients with ICAS-LVO stroke.

Trial registration number ChiCTR2300079069

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Whether balloon angioplasty and/or stenting (BAS) is beneficial for patients with intracranial atherosclerotic stenosis-related emerge large vessel occlusive (ICAS-LVO) stroke remains controversial.

WHAT THIS STUDY ADDS

⇒ This protocol demonstrated the rationale and design of ASSET.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The ASSET trial will provide objective data to evaluate whether standard medical treatment (SMT) combined with BAS can reduce the 90-day stroke recurrence rate in the residual stenosis of ICAS-LVO stroke patients with successful recanalisation compared with SMT alone.

INTRODUCTION AND RATIONALE

Intracranial atherosclerosis disease (ICAD) is the most common cause of ischaemic stroke in the Asian population, and intracranial atherosclerotic stenosis-related large vessel occlusion (ICAS-LVO) is one of the main causes of acute large vessel occlusion (LVO) stroke in China, accounting for 34%–50% of total cases.[1–4] ICAS-LVO strokes often have the following diagnostic indicators: (1) no atrial fibrillation, (2) no vessel hyperdensity signs on CT or susceptibility vessel signs on MRI, (3) watershed infarction, (4) trunk occlusion, (5) residual stenosis on digital subtraction angiography (DSA) after stent release or after undergoing three thrombectomies and (6) early reocclusion.[5–9] Mechanical thrombectomy (MT) by stent retriever and direct aspiration are the two most commonly recommended first-line treatments for patients with ICAS-LVO stroke. However, the management of residual stenosis after thrombectomy remains an unsolved question.[10 11] Although randomised controlled trial (RCT) evidence is lacking, administration of antiplatelet agents, such as tirofiban, following MT is widespread in clinical practice and guidelines recommend that they can be used as remedial drug therapy in the case of thrombectomy failure.

Whether balloon angioplasty and/or stenting (BAS) should be performed following MT in patients with ICAS-LVO stroke is still unclear in clinical practice. In patients with failed thrombectomy, where revascularisation is the primary objective, European Stroke Organisation guidelines suggest using BAS as a rescue therapy, especially where an acute ischaemic stroke is suspected to have been caused by underlying ICAD.[12] However, for ethical reasons, there are few RCTs to support this recommendation. Likewise, there are few relevant studies on whether to perform emergency BAS in ICAS-LVO stroke patients after successful thrombectomy. Some retrospective studies and subgroup analyses have suggested the possible benefit of BAS for residual stenosis after ICAS-LVO stroke, although these studies do not strictly define whether thrombectomy in these patients was successful. Subgroup analysis of the Endovascular Therapy for Acute Ischemic Stroke Trial data suggested BAS following thrombectomy may benefit ICAS-LVO stroke patients with (1) stenosis >70%, (2) stenosis with distal flow disturbance or (3) reocclusion. The multicentre North American and European Stroke Thrombectomy and Aneurysm Registry showed that in ICAS-LVO stroke patients with 50%–99% residual stenosis there was no statistical difference in positive outcome rate (modified Rankin Scale (mRS) 0–2 points) over 90±7 days between patients who received emergency BAS following MT and patients who received embolisation.[4]

CASSISS trial also found no stenting benefit for symptomatic intracranial artery stenosis, but this was conducted on non-acute ischaemic stroke and transient ischaemic attack (TIA) patients with a low risk of stroke or death in the medication and stent groups (8.0% vs 7.2%, respectively).[13] A retrospective analysis of 338 patients with ICAS-LVO stroke after MT showed that the recurrence or reocclusion of ischaemic stroke rate in 20±7 days was 22.5%.[14] The recurrent stroke rate in ICAS-LVO patients is much higher than that in patients with symptomatic intracranial artery stenosis. Does this suggest that medical providers should be more active in performing BAS to prevent reocclusion after successful thrombectomy? A study showed that for patients with severe stenosis following MT, undergoing additional rescue angioplasty or stenting results in better outcomes compared with those who receive only thrombectomy. The specific benefits observed in the angioplasty or stent group include: (1) better functional outcomes: patients had better functional results, as measured by the mRS, with scores between 0 and 2 indicating minimal to no disability. (2) Lower National Institutes of Health Stroke Scale Scores (NIHSS): the 7-day NIHSS were lower, suggesting less severe neurological impairment. (3) Lower reocclusion rates: there were fewer instances of reocclusion within 24 hours. These findings highlight the potential advantages of incorporating rescue angioplasty or stenting in the treatment protocol for severe stenosis after MT.[15] This suggests that the proportion of early stroke reoccurrence or vascular occlusion is still high in ICAS-LVO stroke patients with successful thrombectomy, and emergency management of the stenotic vessels may be required.

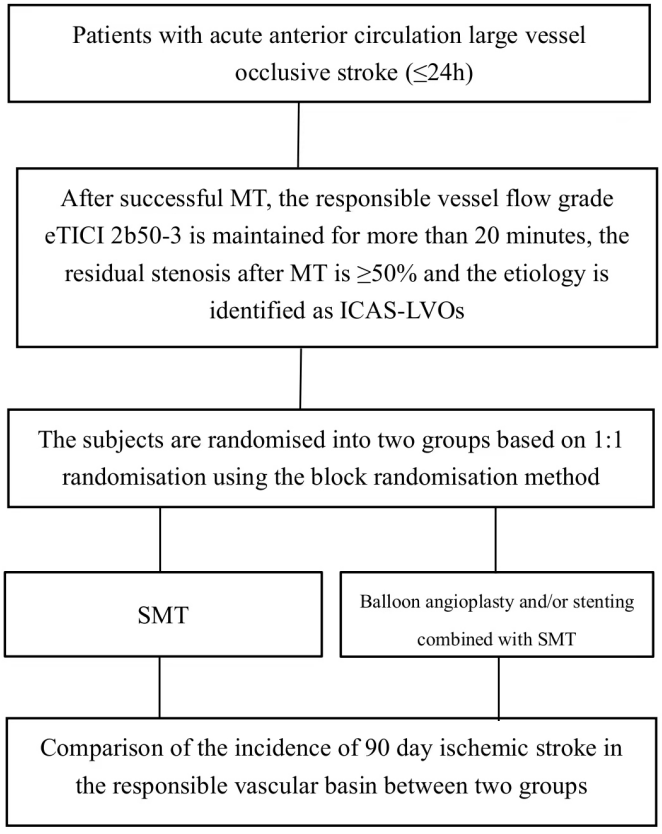

Figure 1 Study flowchart. eTICI, expanded treatment in cerebral ischaemia grade; ICAS-LVOs, intracranial atherosclerotic stenosis-related emerge large vessel occlusive stroke; MT, mechanical thrombectomy; SMT, standard medical treatment.

Overall, there are insufficient well-designed RCT studies comparing the safety and efficacy between ICAS-LVO stroke after MT using BAS combined with standard medicine treatment and simple standard medicine treatment. The angioplasty and/or stenting following successful MT for ICAS-LVO stroke trial, henceforth denoted as the ASSET trial, thus aims to explore this issue by performing an RCT with a focus on BAS in cases of ICAS-LVO stroke after successful MT.

METHODS

Design

The ASSET trial is a PROBE trial that will be conducted in China. This trial aims to evaluate the effectiveness and the safety of emergency BAS in combination with standard medical treatment (SMT) compared with SMT alone in acute anterior circulation ICAS-LVO stroke patients after successful recanalisation with residual stenosis up to 24 hours after the onset of symptoms or the last known well (LKW).

A flow chart depicting the ASSET trial is shown in figure 1. Patients who are eligible for the ASSET trial will be randomised to one of the two treatment groups: BAS

combined with SMT or SMT alone. The trial will have a prospective open-label design, and end-point assessments will be conducted in a blinded fashion. The trial plans to recruit at least 20 comprehensive stroke centres, and the first batch is expected to include 5 centres.

Patient and public involvement

1. Development of research question and outcome measures.
- We conducted three focus group discussions with patients to identify their priorities and experiences. These insights directly informed our research question formulation and the selection of outcome measures.
2. Patient involvement in study design.
- If ICAS-LVO stroke patients with successful recanalisation and residual stenosis (defined as ≥50%), the researcher will inform the patient's family. Once the family signs the informed consent form and all inclusion and exclusion criteria are met, the patient will be officially enrolled in the clinical trial.
3. Patient involvement in recruitment and conduct.
- First, the condition of the patient with ICAS-LVO stroke is critical. Second, our study subjects are all patients undergoing endovascular treatment for acute stroke. The patients belong to a specific population, making it impossible to recruit eligible patients.
4. Dissemination of results.
- The study results include stroke recurrence during hospitalisation and stroke recurrence during the follow-up period. Stroke recurrence during hospitalisation is clearly understood by the PIs at each subcentre, while stroke recurrence during the follow-up period is monitored by a dedicated follow-up team. After data collection, the analysis team remains blinded to patient group assignments. The final data analysis is conducted by a specialised team.
5. Assessment of burden for RCTs.
- After obtaining informed consent from the patient's family, the costs of further interventional treatment for stenosis have also been clearly explained to them.

Patient inclusion and exclusion criteria

Candidates will be enrolled and randomised when meet all of the criteria that follow.

Inclusion criteria

- Age ≥18 years; gender is not limited.
- Symptomatic intracranial anterior circulation large artery occlusion (occlusion of the intracranial segment of the internal carotid artery (ICA), the whole segment of the middle cerebral artery (MCA) M1, and the proximal part of the segment of the M2) as determined by CT angiography, magnetic resonance angiography or DSA; has undergone MT, with an expanded treatment in cerebral ischaemia (eTICI) grade of 2b50-3 maintained for more than 20 min[16]; and residual stenosis ≥50% with an aetiology of atherosclerotic stenosis. The degree of stenosis will be measured with reference to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria.[17]
- Within 24 hours of onset to puncture time. This includes patients with wake-up stroke or unwitnessed stroke; the time of symptom onset is defined as LKW. Alberta Stroke Programme Early CT Score (ASPECTS) ≥6 on non-contrast CT scan if onset to puncture is <6 hours. If the onset to puncture is 6–24 hours, either CT perfusion or MR perfusion imaging is used as the neurological imaging assessment tool. The volume of the ischaemic core is less than 70 mL.
- Prestroke mRS score 0–1, or mRS >1, but not related to neurological disease (eg, blindness or amputation).
- The patient or legal representative signs the informed consent.

Exclusion criteria

- Those with severe organ (heart, lung, kidney or liver) failure.
- Platelet count less than 40×10^9/L.
- Those who are applying anticoagulants and have severe bleeding tendency (international normalised ratio >3) or have active bleeding.
- Those with severe hypertension that cannot be controlled.
- Imaging showing intracranial haemorrhage, severe occupancy, tumours requiring surgical treatment, occlusion of the extracranial segment of the ICA, simultaneous occlusion of multiple large arterial trunks, smouldering occlusion or tandem occlusion.
- Non-intracranial atherosclerotic stenoses such as arterial inflammatory stenosis, vasospasm, entrapment or NIHSS ≥25 scores at admission.
- Pregnant women.
- Participation in other trials in conflict with this trial.
- Other circumstances that, in the opinion of the investigator, make participation in this trial inappropriate or may pose a significant risk to the patient (eg, cognitive impairment that prevents comprehension and/or compliance with study procedures and/or follow-up).

Randomisation

In this clinical trial, the Linklab EDC system (FRM-DM-005-03, version 1.0) is employed using the permuted block randomisation technique. Here are the detailed steps and procedures involved:

- Enrolment: subjects who meet all the inclusion criteria will be enrolled in the study.
- Treatment groups: group 1: intracranial BAS combined with SMT; group 2: SMT alone.
- Randomisation process:
  - Subjects will be randomly assigned to one of the two treatment groups.
  - The randomisation is conducted through the web-based Linklab EDC system.

- An authorised member of the study site staff will log into the system using their individual account information to carry out the randomisation.
- To ensure accurate documentation and management, only one subject can be randomised at a time.
- All randomisation assignments will be thoroughly documented for each subject.

This structured approach ensures that subjects are allocated to treatment groups in an unbiased manner, maintaining the integrity and reliability of the study outcomes.

Blinding

In the ASSET open-label trial, both the patient and the treating physician are aware of the treatment allocation. To minimise bias and ensure the integrity of the data, several measures are implemented:

1. Blinded outcome collection:
   - A blinded and trained investigator, who is not involved in the treatment, will collect the 90-day clinical outcomes.
   - Standardised forms and procedures will be used to ensure consistency and accuracy in data collection.
2. Clinical events committee (CEC):
   - The CEC is responsible for reviewing clinical events that occur during the trial.
   - Members of the CEC are blinded to the treatment assignments to maintain objectivity in their assessments.
3. Imaging Core Laboratory (Core-Lab):
   - The Core-Lab is tasked with reviewing imaging data collected during the trial.
   - Similar to the CEC, the Core-Lab personnel are blinded to the treatment assignments to prevent bias in the interpretation of imaging results.

These measures help to ensure that the evaluation of clinical outcomes and imaging data is conducted impartially, despite the open-label nature of the trial.

Identification of ICAS-LVO stroke

The aetiology of ICAS-LVO stroke is identified on the basis of medical history, clinical features, emergent laboratory evaluations, brain imaging, the first angiographic run and following initial reperfusion. Following reperfusion, any of the following criteria have been proposed as an acceptable definition of ICAS-LVO stroke: (1) residual fixed stenosis that measures ≥50%; (2) evidence of distal hypoperfusion; (3) stenosis with reocclusion on follow-up angiography and (4) the absence of vasospasm and uncommon cerebral arterial diseases, such as moyamoya disease, intracranial arteritis, chronic total occlusion, dissection and potential sources of embolism.

The aetiology of ICAS-LVO stroke will be determined by the consensus of a stroke team. Each member of the team has 10–20 years of clinical experience.

Intervention

All of the selected subjects will receive endovascular treatment. The choice of anaesthesia method will be made by the investigator. During the operation, heparin saline will be maintained continuously in the catheter (recommended 500–3000 units/500 mL). The preferred MT methods and surgical instruments are determined by the investigator, including stent retriever technique (SRT), a direct aspiration first pass technique (ADAPT) and SRT with ADAPT. Supplementary endovascular therapy usually consists of balloon dilatation angioplasty and stent placement.

Emergency balloon angioplasty: according to the WASID standard for residual stenosis, for ≥50%, the balloon is selected as the intracranial balloon system, and the diameter of the balloon should be equal to or slightly less than the diameter of the normal blood vessel. With the assistance of a microwire and the guidance of a road map, the balloon covers the stenosis and the pressure is dilated for 21–30 s, until nominal pressure is achieved. This may be repeated two or three times. Target residual stenosis is 30% or lower.

Emergency stenting: stenting is performed if balloon angioplasty is insufficient. The choice of stent type will be determined by the investigator. Target residual stenosis is less than or equal to 30%.

SMT: after excluding the intracranial haemorrhage, both groups will be routinely treated with platelet glycated protein IIb/IIIa inhibitor. It is recommended to use a loading dose of 10 µg/kg, followed by a continuous intravenous injection of 0.15 µg/kg/min for 24 hours. Oral antiplatelet drugs overlap with platelet glycated protein IIb/IIIa inhibitors for 4–6 hours. After operation, intensive lipid-lowering drugs (such as statins or statins combined with PCSK9 inhibitor) will be administered. Oral antiplatelet and anticoagulant agents will be avoided until intracranial haemorrhage is ruled out within 24 hours of randomisation. Both groups will be treated with dual antiplatelet drugs (aspirin 100 mg; clopidogrel 75 mg) for 3 months, and thereafter switched to single oral antiplatelet maintenance therapy. If there is laboratory or genetic testing suggesting resistance to a particular antiplatelet agent, treatment may be switched to another antiplatelet agent (eg, tegretol or cilostazol). If the transformation of intracranial haemorrhage or other adverse event occurs after endovascular treatment, the medical group will reassess treatment.

Clinical and imaging assessment

In the study, all assessments are outlined in table 1. Subjects will be closely monitored and evaluated at specific time points to ensure comprehensive data collection and analysis. The assessment schedule and responsibilities are as follows:

1. Clinical evaluations:
   - At 24 hours: patients will be evaluated by a trained local neurologist to assess immediate post-treatment outcomes.

Table 1 Summary of study assessments

	Screening and enrolment period	Postrandomisation treatment period		Visiting period
Assessment/steps	**0 hours–24 hours**	**1 day**	**2 days–1 week**	**90, 180, 360 days**
Signed informed consent	X			
Review of inclusion/exclusion criteria	X			
Basic information	X			
Medical history	X			
Cholesterol	X	X	X	
mRS	X			X
NIHSS	X	X	X	
GCS	X	X	X	
Routine blood test	X		X	
Blood biochemistry	X		X	
Coagulation	X		X	
Cranial CT	X	X		
CTA	X*		X*	X
MRA	X*		X*	
Electrocardiography	X			
DWI			X	X
DSA imaging	X*	X*	X*	
Medication		X	X	X
Symptomatic intracranial haemorrhage			X	
Asymptomatic intracranial haemorrhage			X	
Reocclusion		X	X	X
Dead		X	X	X
Adverse event		X	X	X
Complications (undesired side-effect of medical procedure)		X	X	X
Debridement flap decompression		X	X	
Clinical study completion				

*CTA, MRA or DSA may be used during the screening period and the late 1 week of randomisation; CTA/MRA may be used for follow-up during postrandomisation treatment.
CTA, CT angiography; DSA, digital subtraction angiography; DWI, diffusion weight image; GCS, Glasgow Coma Scale; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale Scores.

- At 7 days: a follow-up evaluation will be conducted by the same trained local neurologist to monitor the progress and any complications.

2. Imaging assessments by Core-Lab:
   - Baseline LVO: the Core-Lab will confirm the presence of LVO at the start of the study.
   - Baseline ASPECTS: the Core-Lab will assess the baseline ASPECTS to evaluate the extent of early ischaemic changes.
   - Intracerebral haemorrhage (ICH) assessment: at 24 (±3) hours postrandomisation, the Core-Lab will evaluate the presence and characterisation of any ICH.
   - Core infarct volumes: the Core-Lab will measure the volumes of the core infarcts to assess the extent of brain damage.

These assessments are designed to ensure a thorough and standardised evaluation of the subjects throughout the study. Close monitoring and specific time-point evaluations will provide critical data on the efficacy and safety of the treatments being studied.

Primary outcome

The primary outcome is the incidence of ischaemic stroke in the responsible vessel, which will be assessed at 90 (±7) days following randomisation.

The incidence of ischaemic stroke in the responsible vessel should be diagnosed if the patient develops the following:

- Within one week after MT, an aggravated neurological deficit with NIHSS at 24 hours increased by more than 2 points from baseline. In such a case, the CT or MR angiography and brain diffusion weight image sequences will be reviewed. If the responsible vessel stenosis is aggravated or occluded, new ischaemic stroke should be considered; otherwise, the disease is considered as progressive.
- More than one week after MT, a new ischaemic stroke in the responsible vascular area with new clinical symptoms and brain imaging may show new infarct lesions in the territory. will be determined by neurologists based on the consensus of a stroke team with 10–20 years of experience.

Secondary outcome

- Rate of reocclusion of the responsible vessel within 7 (±1) days of randomisation.
- mRS 0–2 score at 90 (±7) days after randomisation.

Safety outcomes

- Symptomatic ICH (SICH) defined by the Heidelberg classification within 24 (±3) hours postrandomisation.
- Mortality within 90 (±7) days postrandomisation.

Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will convene regularly throughout the study period to review aggregated data and evaluate the safety endpoints of the trial. The following outlines the responsibilities and processes of the DSMB:

1. Regular meetings:
   - The DSMB will hold regular meetings to review the collected data and monitor the trial's progress.
2. Safety endpoint evaluation:
   - The DSMB will apply a predefined protocol definition to determine the occurrence of clinical study safety endpoints.
3. Review and advice:
   - The DSMB will review all available summary data to:
   - Advise the sponsors on the safety of enrolled and potential participants.
   - Monitor the continued effectiveness and scientific integrity of the trial.
4. Independence and conflict of interest:
   - Members of the DSMB will be independent and not affiliated with the Sponsor.
   - DSMB members will have the right to declare any conflicts of interest that may arise during the study.

This independent review process ensures that participant safety is prioritised and that the trial maintains high scientific standards.

Sample size calculation

The trial will be conducted by statistical methods according to the test of superiority. Sample size estimation and allocation: There were 338 patients who were retrospectively analysed after MT for ICAS-LVO strokes, and the rate of ischaemic stroke recurrence or reocclusion at 90±7 days was 22.5%.[2] Single-centre data from the First Affiliated Hospital of Jinan University showed a 90±7-day ischaemic stroke recurrence or reocclusion rate of 7.8% in patients who underwent emergency BAS combined with SMT after MT for ICAS-LVO strokes. Using a superiority trial design, cut-offs will be 0.05, power=0.8 and α=0.05, with 162 cases in each group. Assuming a 10% dropout rate, a total of 360 cases will be needed, with 180 cases in each group.

Statistical analysis

We will compare the rates of ischaemic stroke in the responsible vessel at 90 (±7) days, mRS 0–2 at 90 (±7) days, reocclusion in the responsible vessel at 7 (±1) days, and SICH within 24 (±3) hours using a generalised linear model. The mortality rate within 90 days will be compared between two groups using a Cox proportional hazard regression model, with HR and 95% CI. We will perform subgroup analyses on the influence on treatment effect by residual stenosis rate (50%–69% or 70%–99%), site of vascular occlusion (ICA or MCA), eTICI before randomisation (2b 50/2b 67 or 2c/3), number of MT (<3 or ≥3) and the rate of reocclusion in the responsible vessels (≤3d or 4–7d).

DISCUSSION

There is an association between recanalisation of LVO and increased odds of achieving a positive clinical outcome. Successful MT treatment of LVO cases can significantly improve patient outcomes. MT is the preferred treatment recommended by the guidelines for the patient with ICAS-LVO stroke. However, the management of residual stenosis after successful thrombectomy is still unclear. At present, retrospective studies have suggested that the proportion of early stroke recurrence or vascular occlusion in ICAS-LVO stroke patients with successful thrombectomy is still high, and the stenotic vessels may need urgent treatment. The ASSET trial is a prospective, randomised, open-label treatment, controlled and blinded outcome assessment (PROBE) clinical trial,[18] which aims to generate substantial evidence regarding the efficacy and safety of BAS as a treatment for residual stenosis after successful MT in patients with ICAS-LVO stroke. The primary outcome of this trial is the incidence of ischaemic stroke in the responsible vessel, which will be assessed at 90 (±7) days. This study is projected to reach completion, including the collection of 90-day outcomes, by 2025.

SUMMARY AND CONCLUSIONS

ASSET will provide new evidence regarding the necessity of BAS for residual stenosis after successful MT in patients with ICAS-LVO stroke. This will refine the endovascular treatment strategy for ICAS-LVO stroke patients.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the ASSET trial was approved by ethics committee at the First Affiliated Hospital of Jinan University (No. KY2023-282) and all participating centres. Participants gave informed consent to participate in the study before taking part.

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