# Methylprednisolone in adjunctive to endovascular treatment for patients with acute ischemic strokes with established large infarct: A multicenter, randomized, double-blind, placebo-controlled trial (MIRACLE)

# Study Protocol

**Version number：** **V 2.0**

**NCT number：** **NCT06360458**

**Release date：** **July 23, 2024**


**Sponsor：** **The First Affiliated Hospital of Fujian Medical University**

**Principal Investigators：** **Wanjin Chen M D , P h D**

# List of Abbreviations

| Abbreviations | Annotation |
|---|---|
| AE | Adverse Event |
| aSICH | Asymptomatic Intracranial Hemorrhage |
| ASPECTS | Alberta Stroke Program Early CT Score |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTA | Computed Tomography Angiography |
| DSA | Digital Subtraction Angiography |
| DSMB | Data Safety Monitoring Board |
| EQ-5D | European Quality Five-Dimension |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| ITT | Intention-to-Treat |
| MRA | Magnetic Resonance Angiography |
| MRI | Magnetic Resonance Imaging |
| mRS | modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| PPS | Per-Protocol Set |
| QF | Query Form |
| SAE | Serious Adverse Event |
| SICH | Symptomatic Intracerebral Hemorrhage |

# Study Synopsis

| | |
|---|---|
| Study Title | Methylprednisolone in adjunctive to endovascular treatment for patients with acute ischemic strokes with established large infarct: A multicenter, randomized, double-blind, placebo-controlled trial (MIRACLE) |
| Principal Investigators | Wanjin Chen MD, PhD |
| Study Design | A multicentre, prospective, randomized, double-blind, placebo-controlled trial |
| Efficacy Endpoints | |
| Primary Endpoint | Mortality at 90 ±7 days; |
| Secondary Endpoints | 1) mRS score improvement at 90 ±7 days (shift analysis)；<br>2) Proportion of patients with mRS score 0 to 4 at 90 ±7 days (%)；<br>3) Proportion of patients with mRS score 0 to 3 at 90 ±7 days (%)；<br>4) Proportion of patients with mRS score 0 to 2 at 90 ±7 days (%)；<br>5) Proportion of patients with mRS score 0 to 1 at 90 ±7 days (%)；<br>6) mRS score improvement at 1 year（shift analysis）；<br>7) Proportion of patients with mRS score 0 to 2 at 1 year (%)；<br>8) Proportion of patients with mRS score 0 to 1 at 1 year (%)；<br>9) mRS score improvement at 5 years (shift analysis)；<br>10) Proportion of patients with mRS score 0 to 2 at 5 years (%)；<br>11) Proportion of patients with mRS score 0 to 1 at 5 years (%)；<br>12) NIHSS score at 5-7 days or at early discharge；<br>13) Health-related quality of life [European Quality of Life Five-Dimension visual-analogue scale (EQ-5D VAS)] at 90 ±7 days ；<br>14) Proportion of patients with malignant cerebral edema within 48 hours after EVT (%)<br>15) Proportion of patients with secondary decompressive craniectomy(%)<br>16) EQ-5D VAS at 1 year；<br>17) EQ-5D VAS at 5 years。 |
| Safety Endpoints | |
| Primary Endpoints | Proportion of patients with symptomatic intracranial haemorrhage (SICH) within 48 hours after EVT |
| Secondary Endpoints | 1) Proportion of patients with asymptomatic intracranial haemorrhage (aSICH) within 48 hours after EVT;<br>2) Incidence of any complications (including non-hemorrhagic serious adverse events such as gastrointestinal bleeding, urethral bleeding, oral or nasal mucosal bleeding, and subcutaneous hematoma, etc; or complications related to procedures and devices such as arterial rupture, arterial dissection, implantation failure, stent fracture, vascular puncture site complications, vasospasm, and device malposition, etc)；<br>3) Incidence of any adverse events (including cerebral hernia, pneumonia, respiratory failure, circulatory failure, stress ulcer, secondary epilepsy, urinary tract infection, sepsis, renal failure, acute coronary syndrome, venous thrombosis, and psychiatric symptoms, etc)；<br>4) Proportion of patients with gastrointestinal haemorrhage within 7 days after EVT； |

| | |
|---|---|
| | 5) Proportion of patients with pneumonia. |
| Inclusion Criteria | 1) Age 18 years;<br>2) The time from onset to randomization was within 12 hours;<br>3) Anterior circulation ischemic stroke was preliminarily determined according to clinical symptoms or imaging examination;<br>4) Occlusion of the intracranial internal carotid artery, the M1- or M2-segment of the middle cerebral artery confirmed by CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA);<br>5) Baseline National Institutes of Health Stroke Scale (NIHSS)≥6;<br>6) Baseline Alberta Stroke Program Early CT Score (ASPECTS)<6;<br>7) Planned treatment with endovascular therapy (EVT);<br>8) Informed consent obtained from patients or their legal representatives. |
| Exclusion Criteria | 1) Intracranial hemorrhage confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI).<br>2) mRS score ≥ 2 before onset.<br>3) Pregnant or lactating women.<br>4) Allergic to contrast agents or glucocorticoids.<br>5) Participating in other clinical trials.<br>6) Systolic blood pressure >185 mmHg or diastolic pressure >110 mmHg, and oral antihypertensive drugs cannot control.<br>7) Genetic or acquired bleeding constitution, lack of anticoagulant factors, or oral anticoagulants and INR > 1.7.<br>8) Blood sugar < 2.8 mmol/L (50 mg/dl) or > 22.2 mmol/L (400 mg/dl), platelet < 90 x 10^9/L.<br>9) The artery is tortuous so that the thrombectomy device cannot reach the target vessel.<br>10) Bleeding history (gastrointestinal and urinary tract bleeding) in recent 1 month.<br>11) Chronic hemodialysis and severe renal insufficiency (glomerular filtration rate < 30 ml/min or serum creatinine > 220 umol/L [2.5 mg/ dL]).<br>12) Life expectancy due to any advanced disease < 6 months.Follow-up is not expected to be completed.<br>13) Intracranial aneurysm and arteriovenous malformation.<br>14) Brain tumors with imaging mass effect.<br>15) Systemic infectious disease. |
| Treatments | The emergency interventional team is on call 24 hours a day, 7 days a week. Each sub-center selects patients based on the above inclusion and exclusion criteria, and assigns them to either the intravenous methylprednisolone sodium succinate + endovascular treatment group (experimental group) or the placebo (i.e., intravenous methylprednisolone sodium succinate simulator) + endovascular treatment group (control group) in a 1:1 ratio by a web-based APP on mobile phone or computer. Randomization will be stratified by participating centres permutation block size of 8.<br>After patients agree to participate and obtain a random number, they will receive intravenous methylprednisolone sodium succinate or placebo treatment as soon as possible, preferably before the establishment of arterial access and no later than 2 hours after the completion of endovascular treatment. Relevant time points (accurate to the minute) will be recorded truthfully and accurately. The effectiveness and safety of the two treatment regimens will be observed and evaluated. |

<table>
<tr><td></td><td>Specific steps of treatment:<br>1) Apply for a randomization number and obtain the drug number, then quickly open the medicine box. The person opening the box signs the drug list, indicating the date and time of drug administration. Administer intravenous methylprednisolone sodium succinate or placebo, preferably before the establishment of arterial access and no later than 2 hours after the completion of endovascular treatment. The recommended specific dosage of intravenous methylprednisolone sodium succinate or placebo is 2 mg/kg (maximum dose of 160 mg) intravenously once daily, with the first dose administered before surgery for three consecutive days.<br>2) After patients agree to participate and obtain a random number, they will receive intravenous methylprednisolone sodium succinate or placebo as soon as possible, preferably before the establishment of arterial access and no later than 2 hours after the completion of endovascular treatment. Endovascular interventional treatment methods include mechanical thrombectomy, contact aspiration, intra-arterial thrombolysis, balloon dilation, and/or emergency stent implantation.<br>Details of the above treatments must be recorded in detail in the CRF.</td></tr>
<tr><td>Sample Size Calculation and Statistical Methods</td><td>1. Sample size calculation<br>Based on the research results of published literature and combined with clinicians' experience, the 90-day mortality rates of the intravenous methylprednisolone sodium succinate + endovascular treatment group and the placebo + endovascular treatment group were estimated to be 29% and 38%, respectively. The sample size ratio between the two groups was 1:1. Assuming a two-sided $\alpha$ =0.05 and a power of 80%, the estimated sample size was 856 patients. Considering a 5% dropout rate, the maximum estimated sample size was calculated to be 902 patients using PASS 15.0, with 451 patients in each of the intravenous methylprednisolone sodium succinate + endovascular treatment group and the placebo + endovascular treatment group.<br>2. Statistical analysis<br>The intention-to-treat analysis was chosen for statistical analysis of trial efficacy, and the per-protocol dataset (i.e., statistical analysis based on data from all patients who met the trial protocol criteria) was used as a reference. The $\chi 2$ test or Fisher's exact probability method was used to compare event rates, while the t-test or Mann-Whitney U test was used to compare continuous variables. Superiority evaluation indicators were adopted, and statistical tests were performed at a two-sided significance level of 0.05. Differences with $P \leqslant 0.05$ were considered statistically significant. All statistical analyses were performed using SAS.<br>3. Programming and analysis of the statistical analysis system.</td></tr>
<tr><td>Trial Schedule</td><td>
<table>
<tr><th>Serial Number</th><th>Phases</th><th>Start Date</th><th>End Date</th></tr>
<tr><td>1</td><td>Preparation</td><td>2024-02-01</td><td>2024-07-31</td></tr>
<tr><td>2</td><td>Execution</td><td>2024-08-01</td><td>2025-07-31</td></tr>
<tr><td>3</td><td>Follow-up and Data Collection</td><td>2025-08-01</td><td>2025-10-31</td></tr>
<tr><td>4</td><td>Data Processing and Analysis</td><td>2025-11-01</td><td>2025-11-30</td></tr>
<tr><td>5</td><td>Summarizion</td><td>2025-12-01</td><td>2025-12-31</td></tr>
</table>
</td></tr>
</table>

# Table of contents

# 1. Study Background

Acute stroke is a global disease that seriously threatens human life and health, and it is also one of the main causes of death in the global population.[1] Stroke has become the leading cause of death and disability among urban and rural residents in China, with about 2.4 million new stroke patients and about 1.1 million deaths each year, which brings a heavy burden to society and families. Stroke is divided into ischemic stroke and hemorrhagic stroke, and patients with ischemic stroke account for about 60% to 70% of the total. About 40% of acute ischemic strokes are caused by acute occlusion of large intracranial vessels.[2] Currently, early restoration of blood flow reperfusion and salvage of the ischemic penumbra are the theoretical cornerstones of ischemic stroke treatment.

Intravenous thrombolysis and intravenous thrombolysis combined with endovascular therapy have become standard treatment options for restoring blood flow in acute anterior circulation large vessel occlusive stroke, recommended by international guidelines IA.[3,4] In recent years, with the advancement of endovascular therapy materials and the development of multimodal imaging assessment, four studies (RESCUE-Japan LIMIT[5]、ANGEL-ASPECT[6]、SELECT 2[7]、TENSION[8]) have demonstrated the effectiveness and safety of endovascular therapy for patients with acute ischemic stroke caused by large infarct cores (ASPECTS score <6) due to anterior circulation large vessel occlusion. Currently, the recanalization rate of acute anterior circulation large vessel occlusive stroke through endovascular therapy has increased to 80.0%~94.0%, and restoring blood flow reperfusion is no longer a clinically difficult problem. However, a meta-analysis of previous clinical databases found that although blood flow recanalization plays an important role in acute anterior circulation large vessel occlusive stroke, the proportion of patients with good outcomes is less than 50.0%. Recently, the SELECT 2 study published in the New England Journal of Medicine reported that the mortality rate after endovascular therapy for patients with acute large infarct cores reached 38.2%.[8,9] Apparently, a treatment strategy that solely aims to improve the recanalization rate cannot fundamentally improve clinical benefits. Therefore, exploring ways to reduce patient mortality is expected to provide new insights for the treatment of acute anterior circulation large vessel occlusive stroke and help overcome the current research challenges in this field.

Intravascular therapy helps improve the prognosis of patients with acute ischemic stroke, but postoperative complications such as hemorrhagic transformation and malignant brain edema are important causes of death.[10] Hemorrhagic transformation refers to the hemorrhage in the ischemic lesion caused by a variety of underlying mechanisms during ischemic stroke, among which the incidence of hemorrhagic transformation after intravascular treatment is about 46%-49.5%, and the incidence of symptomatic hemorrhagic transformation is 2%-16%. [11] It is currently believed that oxidative stress, inflammatory response, and blood-brain barrier damage may be the underlying mechanisms of hemorrhagic transformation after intravascular treatment of acute ischemic stroke.[12-14]。Malignant cerebral edema is the main cause of early death and disability after ischemic stroke, with an incidence of 10%-78% in patients with ischemic stroke.[15] It is characterized by a malignant course accompanied by severe cerebral edema, leading to cerebral hernia, death, or severe neurological dysfunction.[16] The main mechanisms of cerebral edema after ischemic stroke include early cytotoxic edema and late vasogenic edema. Early cytotoxic edema is due to increased permeability of brain tissue and failure of Na+/K+ pump caused by ischemia and hypoxia, resulting in cell swelling, narrowing of extracellular space, and increased brain volume. Tissue necrosis and basement membrane degeneration cause damage to the blood-brain barrier, and 4-6 hours later, serum proteins begin to enter the brain from the blood,

inducing vasogenic edema and further increasing brain water content. In addition, reperfusion of the blood supply artery in the infarct area leads to more water passing through the damaged blood-brain barrier, combined with ischemia-reperfusion and hyperperfusion injury after mechanical thrombectomy, further exacerbating vasogenic edema, which peaks 1 to several days after ischemia and leads to malignant cerebral edema.[17-20] Therefore, reducing complications such as hemorrhagic transformation and malignant cerebral edema after intravascular therapy is the key to ultimately reducing the mortality rate of patients with acute ischemic stroke.

Glucocorticoids are the most widely used and effective anti-inflammatory and immunosuppressive agents in clinical practice. They have the functions of stabilizing cell membranes, regulating the balance of water and electrolytes inside and outside cells, reducing the production of cerebrospinal fluid, and exerting non-specific antioxidant effects. They can also prevent cell membrane phospholipids from being damaged by free radicals, actively regulate and restore blood circulation in damaged brain tissue, and reduce cerebral edema.[21] Methylprednisolone sodium succinate for injection is a medium-acting glucocorticoid that is widely used in clinical practice due to its small side effects and strong ability to penetrate the blood-brain barrier. Early basic research found that early combination therapy with methylprednisolone sodium succinate for injection can significantly increase cerebral blood flow reperfusion and reduce brain damage in a cat ischemia-reperfusion model.[22] Recent studies have also shown that early combination therapy with methylprednisolone sodium succinate for injection can improve neurological deficits and increase the survival rate of newborn neurons by inhibiting neuronal apoptosis and down-regulating inflammatory responses in a rat ischemia-reperfusion model.[23,24] A recent randomized controlled clinical trial (MARVEL) published in *JAMA* suggests that early combination therapy with methylprednisolone sodium succinate can reduce mortality and the incidence of symptomatic intracranial hemorrhage after intravascular therapy for patients with acute ischemic stroke. However, this study excluded patients with large infarct core strokes (ASPECTS score <6) who have more severe clinical symptoms and higher mortality and disability rates.[25] Currently, there is not enough evidence to support the safety and efficacy of early combination therapy with methylprednisolone sodium succinate for acute large core infarct reperfusion. To address this dilemma, there is an urgent need to conduct research specifically on this subset of patients.

Therefore, we intend to adopt a multi-center, prospective, randomized, double-blind controlled trial design to explore whether early combination therapy with methylprednisolone sodium succinate can improve the clinical prognosis of patients with acute large core infarcts based on revascularization.

## 2. Study Objectives

To explore the safety and efficacy of early combination therapy with methylprednisolone sodium succinate for injection after revascularization in patients with acute large core infarcts within 12 hours of onset.

## 3. Study Design

Using a multi-center, prospective, randomized, double-blind controlled trial design, we aim to investigate whether early combination therapy with methylprednisolone sodium succinate can improve the clinical prognosis of patients with acute large core infarcts based on revascularization.

According to the inclusion and exclusion criteria for clinical study subjects, eligible patients will be randomly assigned (1:1) to either the methylprednisolone sodium succinate for injection + intravascular treatment group

(experimental group) or the placebo (methylprednisolone sodium succinate simulator) + intravascular treatment group (control group). Physicians who are unaware of the clinical data information will follow up and evaluate patients' 90-day modified Rankin Scale (mRS) scores through outpatient visits or phone calls, and conduct safety assessments simultaneously. [26] The specific trial process, trial steps, and items to be evaluated at each time point are shown in Figure 1 and Table 1, respectively.

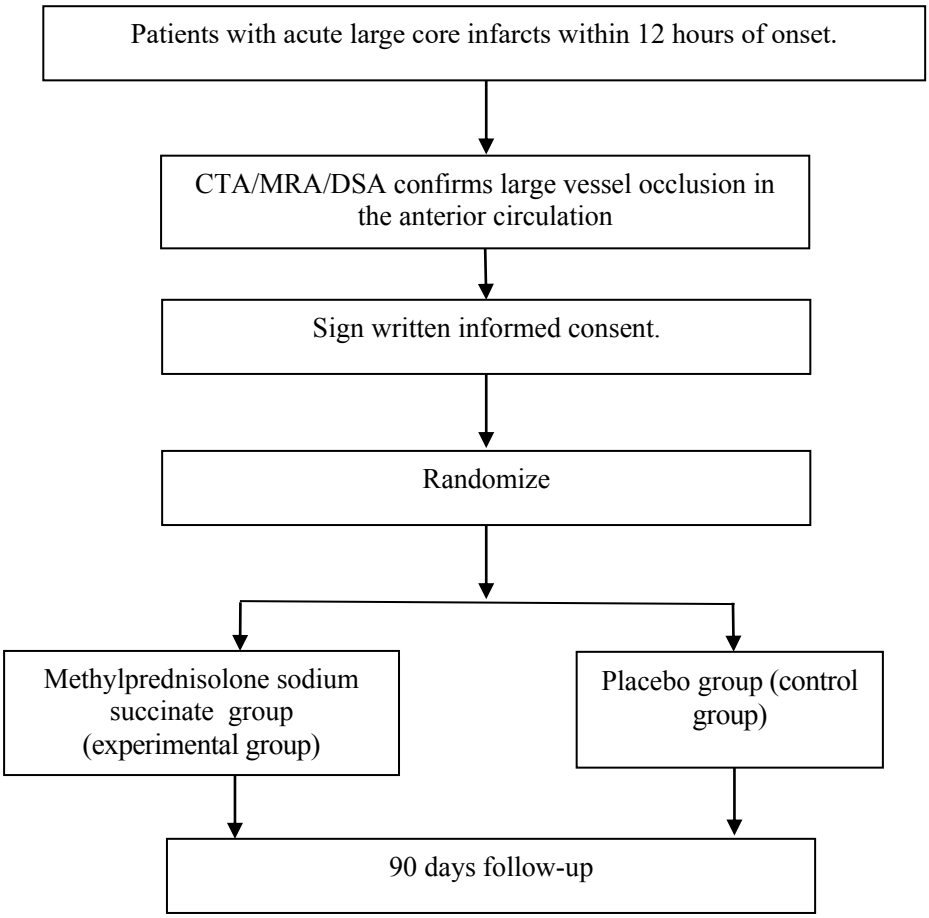



Figure 1 Flow Chart

# 4. Selection of Patients, Criteria for Termination and Privacy Protection

## 4.1. Inclusion Criteria

1) Age ⩾ 18 years.

2) The time from onset to randomization was within 12 hours.

3) Anterior circulation ischemic stroke was determined according to clinical symptoms and imaging examination.

4) Occlusion of the intracranial internal carotid artery, the M1- or M2-segment of the middle cerebral artery confirmed by CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA).

5) Baseline National Institutes of Health Stroke Scale (NIHSS)⩾6.

6) Baseline Alberta Stroke Program Early CT Score (ASPECTS)<6.

7) Planned treatment with endovascular therapy (EVT).

8) Informed consent obtained from patients or their legal representative.

## 4.2. Exclusion Criteria

1) Intracranial hemorrhage confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI).
2) mRS score ⩾ 2 before onset.
3) Pregnant or lactating women.
4) Allergic to contrast agents or glucocorticoids.
5) Participating in other clinical trials.
6) Systolic blood pressure >185 mmHg or diastolic pressure >110 mmHg, and oral antihypertensive drugs cannot control.
7) Genetic or acquired bleeding constitution, lack of anticoagulant factors, or oral anticoagulants and INR > 1.7.
8) Blood sugar < 2.8 mmol/L (50 mg/dl) or > 22.2 mmol/L (400 mg/dl), platelet < 90 x 10^9/L.
9) The artery is tortuous so that the thrombectomy device cannot reach the target vessel.
10) Bleeding history (gastrointestinal and urinary tract bleeding) in recent 1 month.
11) Chronic hemodialysis and severe renal insufficiency (glomerular filtration rate < 30 ml/min or serum creatinine > 220 umol/L [2.5 mg/ dL]).
12) Life expectancy due to any advanced disease < 6 months.
13) Follow-up is not expected to be completed.
14) Intracranial aneurysm and arteriovenous malformation.
15) Brain tumors with imaging mass effect.
16) Systemic infectious disease.

## 4.3. Criteria for Termination

Treatment of patients should be terminated if any of the following situations occur:

1) Voluntary withdrawal, which means withdrawal of informed consent. Patients are free to terminate or withdraw from the study at any time;
2) Objective disease progression of the patient (such as non-cerebrovascular diseases like tumors);
3) In the investigator's view, the patient intentionally or unintentionally fails to comply with the relevant provisions of the study, and it is necessary to terminate the treatment study.

Patients may withdraw from this trial at any stage for any reason. Similarly, the investigator has the right to terminate the enrollment of a patient in an emergency medical situation. For patients who withdraw from the study, the investigator must inquire about their reasons for withdrawal and whether any adverse events (AEs) have occurred. If the termination is caused by an adverse reaction, the AE must be followed up until it is properly resolved or the condition stabilizes. All existing study-related serious adverse events (SAEs) at the time of study termination must be followed up until they resolve, unless in the investigator's opinion, the condition is unlikely to resolve due to the patient's disease itself. The reasons and date of withdrawal from the study must be recorded on the case report form (CRF).

## 4.4. Privacy Protection

The medical records of patients (study medical records/CRF, laboratory test reports, etc.) will be

completely stored in the hospital where they receive treatment, and laboratory test reports and other examination results will be recorded in the patients' medical records. Only the investigators, ethics committees, and food and drug administration departments of this study will be allowed to access patients' medical records. Any public reports on the results of this study will not disclose the personal identities of patients. We will make every effort to protect the privacy of patients' personal medical information within the limits allowed by law.

According to medical research ethics, apart from personal privacy information, trial data will be available for public inquiry and sharing. Inquiry and sharing will be limited to web-based electronic databases to ensure that no personal privacy information is leaked.

# 5. Sample Size Calculation

Based on the research results from published literature and combined with clinicians' experience, the 90-day mortality rates for the intravenous methylprednisolone sodium succinate + endovascular treatment group (experimental group) and the placebo + endovascular treatment group (control group) are estimated to be 29% and 38%, respectively. Assuming a 1:1 ratio for the sample sizes of the two groups, a two-sided α of 0.05, and a power of 80%, the estimated sample size is 856 patients. Considering an expected dropout rate of 5%, the maximum estimated sample size, calculated using PASS 15.0, is 902 patients, with 451 patients in each of the intravenous methylprednisolone sodium succinate + endovascular treatment group (experimental group) and the placebo + endovascular treatment group (control group).

# 6. Randomization

## 6.1. Randomized Grouping

Patients are randomly divided into two groups in a 1:1 ratio. This trial employs block randomization for group assignment, generating a random sequence in a 1:1 ratio. Investigators at each sub-center report to the lead investigator after patients sign the informed consent form, and the latter implements randomized group assignment through a centralized network APP.

## 6.2. Concealing Group Allocation

1) This study employs a centralized randomization method. All odd and even random numbers in the random number sequence, generated by SAS software and corresponding to serial numbers (1, 2, 3...), are assigned to the experimental group and the control group, respectively, and recorded;
2) A dedicated person is responsible for determining the grouping based on random numbers but does not participate in patient recruitment;
3) The randomization schedule is sealed in opaque envelopes. The schedule is kept in triplicate, with one copy each retained by the principal investigator, the pharmacy, and the biostatistician. When unblinding or breaking the blind, the three copies of the randomization schedule must be opened simultaneously and in the presence of all parties. If one or more of the envelopes is damaged, it must be explained; otherwise, it will be announced that the grouping information has been leaked.

# 7. Blinding/Unblinding

This trial is blinded for investigators, patients, endpoint evaluators, and data analysts.

### 7.1. Implementation of Blinding

In this trial, a biostatistician generates two sets of random medication codes using a statistical software package.

The sponsor packages the medications according to the random codes, with the drug boxes labeled as "Medication for the MIRACLE Multicenter, Randomized, Double-Blind Clinical Trial of Early Combination Therapy with Methylprednisolone Sodium Succinate for Acute Large Core Infarct Recanalization." The label also indicates the drug code, random number, properties, specifications, production date, expiration date, storage conditions, and manufacturer.

The external packaging, color, and shape of the investigational drug and placebo are identical, making it impossible to distinguish between the experimental group drug and the control group drug. Grouping or treatment information is not known.

This trial uses envelopes to enclose emergency plans or/and the treatment regimens received by the subjects. This allows for unblinding in case of serious adverse reactions that require trial termination, ensuring prompt and appropriate treatment.

### 7.2. Emergency Unblinding Procedure

In case of emergency situations such as serious adverse events or when a patient requires urgent rescue, the responsible investigator at the center shall report to the sponsoring unit (The First Affiliated Hospital of Fujian Medical University) and the inspector to determine whether it is necessary to open the emergency envelope. Unblinding shall be performed based on the medication information provided in the emergency letter for the patient. The investigator shall complete the unblinding record form (Appendix II) and indicate it on the CRF. If the sponsor cannot be reached before unblinding, they shall be notified promptly after the unblinding. Once the emergency envelope is opened, the case shall be considered as a dropout and will not be included in the efficacy analysis. However, if there are adverse events, they shall be included in the adverse event analysis.

### 7.3. Unblinding Regulations

This trial employs a two-step unblinding method. After blinded verification and data locking, the staff responsible for keeping the blinded data at the statistical center performs the first unblinding, informing the biostatistician of the group corresponding to each case number using the codes A and B. This allows for statistical analysis of all the data. When the statistical analysis is complete and the final report is ready, a second unblinding is conducted at the clinical summary meeting to announce the exact groups represented by A and B.

If during the trial, the entire blinded data is leaked or the rate of emergency envelope opening exceeds 20%, this double-blind trial will be considered invalid.

## 8. Treatment

The emergency interventional team is on standby 24 hours a day, 7 days a week. Each sub-center screens patients according to the above inclusion and exclusion criteria, assigning them to the experimental group and the control group in a 1:1 ratio. After randomization, patients receive intravenous injections of methylprednisolone sodium succinate or placebo (i.e., methylprednisolone sodium succinate simulator) treatment as soon as possible. Relevant time points (accurate to the minute) are recorded faithfully and

accurately, and the efficacy and safety of the two treatment regimens are observed and evaluated.

## 8.1. Treatment Groups

### 8.1.1 Placebo + Endovascular Treatment Group (Control Group)

After applying for randomization and obtaining the drug code, the medication box is quickly opened. The person opening the box signs the medication list, indicating the date and time of drug administration. The patient receives the placebo (methylprednisolone sodium succinate simulator), which is recommended to be administered before the establishment of arterial access and no later than 2 hours after the completion of endovascular treatment. The specific recommended usage of the methylprednisolone sodium succinate simulator (Chongqing Laimei Pharmaceutical Co., Ltd., 40mg) is: intravenous injection of 2mg/kg (maximum dose of 160mg), with the first dose administered before the procedure, once a day for three consecutive days. The endovascular interventional treatment methods include mechanical thrombectomy, contact aspiration, intra-arterial thrombolysis, balloon dilation, and/or emergency stent implantation. Details of the above treatments must be recorded in the CRF.

### 8.1.2 Methylprednisolone Sodium Succinate + Endovascular Treatment Group (Experimental Group)

After applying for randomization and obtaining the drug code, the medication box is quickly opened. The person opening the box signs the medication list, indicating the date and time of drug administration. The patient receives treatment with methylprednisolone sodium succinate, which is recommended to be administered before the establishment of arterial access and no later than 2 hours after the completion of endovascular treatment. The specific recommended usage of methylprednisolone sodium succinate (Chongqing Laimei Pharmaceutical Co., Ltd., 40mg) is: intravenous injection of 2mg/kg (maximum dose of 160mg), with the first dose administered before the procedure, once a day for three consecutive days. The endovascular interventional treatment methods include mechanical thrombectomy, contact aspiration, intra-arterial thrombolysis, balloon dilation, and/or emergency stent implantation. Details of the above treatments must be recorded in the CRF.

## 8.2. Concurrent Medications and Precautions

1) Injectable methylprednisolone sodium succinate should not be used concurrently with live vaccines or attenuated live vaccines;
2) During the trial treatment period, all used injectable methylprednisolone sodium succinate and corresponding simulators, as well as empty bottles and remaining medications, must be recovered after use.

## 8.3. Anesthesia Method

It is recommended to perform the procedure under intravenous sedation, and operators at sub-centers can also choose the anesthesia method independently based on the actual situation.

## 8.4. Cerebrovascular Angiography

To obtain comprehensive information that is conducive to endovascular treatment, aortic arch angiography is required. To embody the concept of "time is brain," the responsible vessel angiography for stroke can be performed first to clarify the characteristics of the lesion. After completing the endovascular treatment of the responsible vessel, other complex angiographies can be performed. When large artery occlusion is detected and thrombectomy is considered, it should be handled according to routine procedures.

### 8.5. Management of Patients Without Target Large Vessel Occlusion

In this study, if no large vessel occlusion is detected by DSA angiography, the surgeon should declare the end of the procedure without further intervention.

### 8.6. Management of Residual Stenosis

Arterial ischemic stroke can be classified into thrombotic stroke, embolic stroke, and combined stroke of both. Among them, thrombosis often develops secondary to stenosis. In this study, after successful thrombectomy, if >70% stenosis is found at the site of thrombosis formation, to further prevent re-occlusion after recanalization, the surgeon will decide whether to perform emergency stent implantation and other necessary measures after 10 minutes of observation.

## 9. Schedule of Assessments

Each patient, after signing the informed consent form, will undergo baseline examination, randomized group treatment study, and follow-up with mRS scoring at 90 days. The trial steps and items to be evaluated at each time point are listed in Table 1.

Table 1: Trial steps and items to be evaluated at each time point.

| Evaluations/ Steps | Screening period | Treatment period | | Follow up period |
|---|---|---|---|---|
| | 12h | 12h~48h | 2d~discharge | 90 (±7) day |
| Informed consent | X | | | |
| Demographic data | X | | | |
| Medical history | X | | | |
| Pre-stroke mRS | X | | | |
| Blood pressure and heart rate | X | X | X | |
| NIHSS score | X | X | X[a] | |
| ASPECTS score | X | | | |
| mRS score | | | | X |
| EQ-5D score | | | | X |
| Blood routine examination | X | | | |
| Blood biochemistry | X | | X | |
| Coagulation function | X | | | |
| Urine pregnancy test (women of childbearing age) | X | | | |
| Head CT/MRI and CTA/MRA/DSA | X | | | |
| ECG | X | | | |
| Inclusion/exclusion criteria | X | | | |
| Randomization | X | | | |
| Study medication[b] | X | X | | |
| DSA Endovascular treatment | | X | | |
| Head CT/MRI | | X | | |
| Treatment medication | | X | | X |
| Intracranial hemorrhage | | X | | |
| Adverse events | | X | X | X |
| Complications | | X | X | X |
| Completion status of clinical research | | | | X |

Note: [a]5-7 days or at discharge (if hospital stay is <5 days); [b] 2mg/kg, with a maximum of 160mg, administered consecutively for 3 days.

### 9.1. Collection of Baseline Data

Written informed consent must be obtained from the patient or their family members before implementing the research steps required by the protocol. The patient should be given a copy of the signed informed consent form to keep.

During the screening period, the following data should be evaluated and recorded in the original medical records and the single-disease database (intended to use the Yidu Cloud Scientific Research Collaboration Platform):

1) Patient information and informed consent form;
2) Evaluation of inclusion and exclusion criteria;
3) Demographic characteristics;
4) Past medical history and related treatment history;
5) For women of childbearing age: urine pregnancy test.

### 9.2. Randomized Group

After patients are screened and qualified, their randomized group information is obtained. Eligible patients are assigned to the experimental group and the control group in a 1:1 ratio.

During the treatment and visit periods, the following data should be evaluated and recorded in the original medical records and the Yidu Cloud Scientific Research Collaboration Platform:

1) Treatment method;
2) Neurological function assessment;
3) Laboratory test results such as blood routine, blood biochemistry, and coagulation function;
4) Imaging data such as CT/CTA/MRA/DSA;
5) Adverse reactions or events;
6) Study completion status.

### 9.3. Follow-up

The prognostic information of the patients was recorded in detail by two neurologists blinded to the treatment information within one week and 90 days after surgery. In case of inconsistent records between the two, the corresponding information was filled in the CRF after discussion and consensus.

Safety monitoring continued until 30 days after the end of follow-up. For patients who did not continue to participate in the study due to adverse reactions, follow-up should be conducted as far as possible until the adverse reactions were relieved or the condition was stable.

After the end of the trial, the follow-up treatment plan for patients with invalid or poor efficacy was implemented according to the Chinese Guidelines for the Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack 2014.[28]

# 10. Endpoints of the Clinical Trial

## 10.1. Primary Endpoints

### 10.1.1. Primary Efficacy Endpoint

Mortality at 90±7 days .

### 10.1.2. Primary Safety Endpoint

Proportion of patients with symptomatic intracranial haemorrhage (SICH) within 48 hours.

## 10.2. Secondary Endpoints

### 10.2.1. Secondary Efficacy Endpoints

1）mRS score improvement at 90 ±7 days;

2）Proportion of patients with mRS score 0 to 4 at 90 ±7 days；

3）Proportion of patients with mRS score 0 to 3 at 90 ±7 days;

4）Proportion of patients with mRS score 0 to 2 at 90 ±7 days;

5）Proportion of patients with mRS score 0 to 1 at 90 ±7 days;

6）mRS score improvement at 1 year;

7）Proportion of patients with mRS score 0 to 2 at 1 year;

8）Proportion of patients with mRS score 0 to 1 at 1 year;

9）mRS score improvement at 5 years;

10）Proportion of patients with mRS score 0 to 2 at 5 years;

11）Proportion of patients with mRS score 0 to 1 at 5 years;

12）NIHSS score at 5-7 days or at early discharge;

13）Health-related quality of life [European Quality of Life Five-Dimension visual-analogue scale (EQ-5D VAS)] at 90 ±7 days;

14）Proportion of patients with malignant cerebral edema within 48 hours after EVT

15）Proportion of patients with secondary decompressive craniectomy

16）EQ-5D VAS at 1 year

17）EQ-5D VAS at 5 years

### 10.2.2. Secondary Safety Endpoints

1) Proportion of patients with asymptomatic intracranial haemorrhage (aSICH) within 48 hours after EVT;
2) The incidence of non-intracranial hemorrhage complications (including gastrointestinal bleeding, urethral bleeding, oral or nasal mucosal bleeding, and subcutaneous hematoma, etc.);
3) The incidence of non-hemorrhagic serious adverse events (including cerebral hernia, pneumonia, respiratory failure, circulatory failure, stress ulcer, secondary epilepsy, urinary tract infection, sepsis, renal failure, acute coronary syndrome, venous thrombosis, and psychiatric symptoms, etc.);
4) Operation and device-related complications (including artery rupture, artery dissection, implant failure, stent

fracture, vascular puncture site complications, vasospasm, and device not in place, etc.);

5) Glucocorticoid-related adverse events (including insulin use in hospital, new-onset diabetes, lung infection during hospitalization, gastrointestinal bleeding within 7 days after surgery, etc.).

# 11. Adverse Events

## 11.1. Definition

### 11.1.1. Definition of Adverse Events (AE)

AE refers to an adverse medical event that occurs after a patient or clinical trial participant receives a drug or device, but it does not necessarily have a causal relationship with the treatment.

### 11.1.2. Severity Determination of Adverse Events

The intensity or severity of AE is divided into four levels according to the following criteria:

Mild: Does not affect daily activities;

Moderate: Affects the patient's daily activities;

Severe: Loss of daily activity;

Serious: Refer to SAE definition.

### 11.1.3. Definition of Serious Adverse Events (SAE)

SAE refers to events that occur during a clinical trial and result in: death; severe deterioration in the health of the patient, user, or others; life-threatening illness or injury; permanent impairment of body structure or bodily function; hospitalization or prolongation of existing hospitalization; medical or surgical intervention to prevent permanent impairment to body structure or bodily function, resulting in fetal distress, fetal death, or congenital anomalies/birth defects.

Note: Hospitalization that is planned in advance for pre-existing conditions or as required by the clinical trial protocol, without severe deterioration in health, is not considered an SAE.

## 11.2. Reporting Procedures

### 11.2.1. Adverse Event Reporting

Adverse events (AEs) that occur during this trial will be reported by the investigators and clinical units to the corresponding national and local regulatory authorities within the prescribed time, in accordance with national regulations. They will assist the competent authorities in investigating the AEs and take appropriate corrective and preventive measures.

The investigators shall follow up, observe, and record detailed information and outcomes of all AEs, and track patients who withdraw from the study due to AEs until the AEs are completely resolved. The investigators must determine whether the AEs are related to the investigational device and provide evidence to support this judgment.

### 11.2.2. Serious Adverse Event Reporting

The investigator shall report any serious adverse event (SAE) to the lead unit within 16 hours of becoming aware of it (Contact: Wanjin Chen, Phone: 13860601359; Fax: 0591-87982772) and to the Chinese Ethics Committee for

Registered Clinical Trials within 24 hours.

## 11.3. Prediction and Countermeasures of Adverse Events

All adverse events (AEs) that occur during the trial must be recorded truthfully in the AE form. Investigators should provide targeted treatment for AEs and conduct follow-up visits until the symptoms disappear or stabilize. For cases of serious adverse events (SAEs), investigators should immediately take necessary treatment measures upon learning of them to protect the safety of patients. Common AEs that may occur during interventional procedures include, but are not limited to:

1) Thromboembolic events

Possible causes include inadequate anticoagulation or incomplete anticoagulation, insufficient antiplatelet aggregation therapy or aspirin resistance, and the absence of continuous perfusion in the coaxial system. Reasonable and standardized anticoagulation and antiplatelet aggregation should be performed. If embolism occurs in important blood vessels, it should be managed by a professional doctor based on the patient's condition.

2) Cerebrovascular spasm

Cerebrovascular spasm can be caused by subarachnoid hemorrhage or irritation from intravascular catheters or guidewires. If cerebrovascular spasm occurs, symptomatic treatment should be provided by a professional doctor based on the patient's condition.

3) Acute occlusion

Possible causes include endothelial injury, platelet aggregation, and thrombosis, which usually occur within 30 minutes after balloon angioplasty or are related to endothelial avulsion.

Preventive measures: Antiplatelet agents such as aspirin or clopidogrel can effectively reduce acute thrombosis events.

Treatment measures: In case of acute occlusion, reasonable treatment should be immediately provided based on the cause of the occlusion.

4) Thrombosis and plaque dislodgment

These are mainly caused by the crushing and dislodgment of plaques during stent deployment or balloon dilation, and sometimes also due to thrombosis induced by catheters or guidewires. The use of cerebral protection devices and intraoperative anticoagulation are basic measures to prevent such events.

5) Vascular rupture

This type of complication can directly lead to patient death. When performing stent angioplasty in certain areas, it is advisable to choose an inner stent that is slightly smaller than the diameter of the target vessel. In case of vascular rupture, immediate symptomatic treatment should be provided by a professional doctor.

6) Cerebral hyperperfusion syndrome

In cases of large vessel occlusive disease, the regulatory capacity of distal vessels decreases due to long-term ischemia. Sudden recanalization of the occluded vessel significantly increases blood flow, and the distal vessels, especially the cortical arteries, cannot immediately adapt to this sudden increase in blood flow, leading to passive dilation and consequently, cerebral hyperperfusion syndrome.The main clinical manifestations are headache, head distension, nausea, vomiting, epilepsy, consciousness disturbance, and severe patients can have

intracranial hemorrhage.

The possibility of occurrence should be fully recognized before surgery, and blood pressure should be appropriately lowered during and after the procedure. If cerebral hyperperfusion syndrome occurs after surgery, symptomatic treatment (such as analgesics, antiepileptic drugs, etc.), dehydrating agents to reduce intracranial pressure, and surgical management of cerebral hemorrhage can be provided based on the patient's actual condition.

# 12. Statistical Analysis

## 12.1. Statistical Analysis Process

### 12.1.1. Statistical Analysis Plan

The statistical analysis plan will be discussed and developed jointly by statistical analysts and medical experts. It will be initiated before the end of the study and finalized before database lock. The plan will provide all the content to be covered by the statistical analysis, including the definition of datasets used for analysis, derived algorithms of data, and statistical description and analysis methods adopted for different indicators.

### 12.1.2. Statistical Analysis Report

Statistical analysis will be strictly conducted according to the requirements of the statistical analysis plan. SAS programs will be prepared using the SAS 9.3 system, debugged, and verified before conducting statistical analysis. Statistical charts and tables that meet the requirements of the statistical analysis plan will be generated. A statistical analysis report will be written based on the generated statistical charts and tables.

## 12.2. Statistical Analysis Sets

### 12.2.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all patients who were enrolled, randomized, and received relevant interventions. Following the principle of Intent-to-Treat (ITT) analysis, patients who did not meet the inclusion criteria, did not receive relevant interventions after randomization, or had no evaluation results should be excluded from this dataset and not included in the statistical analysis. The FAS population is used for non-inferiority evaluation analysis of the primary evaluation indicators.

### 12.2.2. Per Protocol Set (PPS)

The Per Protocol Set (PPS) includes all cases that comply with the trial protocol, have good compliance, and have completed the required CRF entries. The PPS population is used for non-inferiority evaluation analysis of the primary evaluation indicators and statistical analysis of all secondary evaluation indicators.

### 12.2.3. Safety Set

All patients who have undergone relevant procedures for this trial and have evaluation records are included in this analysis set. Safety and stability evaluations are based on this analysis set.

### 12.2.4. Missing Data

No imputation will be made for missing data (if any) in this study.

### 12.3. Statistical Analysis Methods

Statistical tests will be performed using a two-sided significance level of 0.05 for indicators evaluated with superiority. Differences with a *P*-value ≤ 0.05 will be considered statistically significant.

Statistical analysis will be conducted on baseline indicators (such as medical history) and demographic characteristics. Intent-to-treat analysis will be used for statistical analysis of trial efficacy, with the per-protocol dataset (i.e., data from patients who meet all trial protocol criteria) as a reference.

Quantitative data will be described using means, medians, standard deviations, maximum and minimum values, and 25th and 75th percentiles. Comparisons between two groups will be made using the independent t-test or Mann-Whitney U test. Categorical or ordinal data will be described using frequencies and proportions. Comparisons between two groups for categorical data will be made using the chi-square test or Fisher's exact test, and for ordinal data, the Mann-Whitney *U* test will be used.

Previous studies have suggested that the following factors may affect the 90-day mRS score, and this study plans to conduct subgroup analysis based on these variables.

1) Age；
2) Gender；
3) Time of onset；
4) NIHSS score；
5) ASPECTS score；
6) TOAST classification [22]；
7) Vascular occlusion site；
8) Collateral circulation score；
9) Anesthesia method；
10) Intravenous thrombolysis.

## 13. Quality Control and Assurance

### 13.1. Quality Control

1) Requirements for Participating Personnel

Personnel participating in the clinical trial should have corresponding professional expertise, qualifications, and research capabilities. They must carefully study and discuss the clinical research protocol and trial manual, and be selected after qualification review. The personnel should remain relatively stable. Qualified personnel are required for the management of archives, drug or device usage, and calibration of relevant testing instruments.

To ensure that all surgical procedures are performed by neurointerventionalists with a certain level of experience, the operators of interventional surgeries must meet the following requirements: Operators should have more than 3 years of experience in cerebrovascular interventional therapy and have independently completed at least 30 stent-like thrombectomy surgeries.

2) Training of Participating Personnel

Through pre-clinical trial training, participating personnel should fully understand and recognize the clinical trial protocol and the specific connotations of its indicators. The description of subjective symptoms should be objective, without inducement or suggestion. The prescribed objective indicators should be examined according to the time, location, and method specified in the protocol. Attention should be paid to observing adverse reactions, and follow-up observations should be conducted.

3) Quality Control Measures for Laboratories

Unified experimental testing indicators, standard operating procedures, and quality control programs should be established. The criteria for abnormal laboratory test results should be based on the normal reference ranges of each center. Special test items must be conducted by dedicated personnel.

### 13.2. Quality Assurance

1) Establishment of a Multi-center Coordination Committee

The Central Trial Coordination Committee consists of the principal investigators and key researchers from each clinical trial unit. The Coordination Committee is responsible for the implementation of the entire trial and addressing issues related to the trial.

2) Data and Safety Monitoring Board (DSMB)

This study establishes a Data and Safety Monitoring Board (DSMB) responsible for providing recommendations on whether to terminate or continue the trial during the execution phase. The DSMB members consist of experienced neurologists, neurointerventionalists, and statisticians who are not involved in the execution of the clinical trial. The DSMB is formed by the DSMB chair and operates according to the DSMB charter. A data report will be conducted after every 100 eligible patients have completed follow-up, and adverse events will be reported to the DSMB chair under strict confidentiality measures. Based on the analysis results, the DSMB will provide recommendations to the principal investigator on continuing the trial, modifying the trial protocol, or suspending the trial.

The DSMB will carefully review all clinical and safety endpoint events.

This study does not establish a stopping endpoint for safety events.

3) Imaging Core Laboratory

The Imaging Core Laboratory is composed of expert committee members: Professors Dejun She, Tieqiang Li, and Ying Liu. Two experts will independently evaluate all imaging data from patients, and the third expert will make the final decision in case of disagreement. All patients' imaging data will be uploaded via storage media and the internet and evaluated by the Imaging Core Laboratory. The evaluation content of the Imaging Core Laboratory includes: ①Baseline and 12-hour CT-based ASPECTS score; ②Baseline CTA/MRA/DSA assessment of vascular occlusion and postoperative DSA vascular recanalization; ③CT-based evaluation of SICH and aSICH within 48 hours.

Additionally, before patient enrollment, CT/CTA and other imaging interpretations will be evaluated by at least two neurointerventional or radiology physicians arranged by each sub-center, and the evaluating physicians will not be directly involved in the trial execution.

## 14. Ethical Requirements

### 14.1. Development, Revision, and Ethical Review of the Study Protocol

The clinical trial protocol shall be finalized and signed by the principal investigators after joint discussion and revision before the start of the clinical trial. It shall be implemented after being approved by the Chinese Registered Clinical Trial Ethics Review Committee.

If any issues arise during the actual implementation of the clinical trial that require revisions to the protocol, such revisions must be discussed by the Coordination Committee and made by the lead unit. The revised protocol shall be submitted again to the Chinese Registered Clinical Trial Ethics Review Committee for approval and record-keeping before implementation.

### 14.2. Patient Informed Consent

Before the start of the clinical trial, the investigator must provide detailed information about the clinical trial to the patient or their legally authorized representative (guardian), including the nature of the trial, its purpose, potential benefits and risks, alternative treatment options available, and the patient's rights and obligations as stipulated in the Declaration of Helsinki. This ensures that the patient or their representative is fully informed and aware of their right to withdraw from the study at any time. The clinical trial can only begin after the patient or their legally authorized representative (guardian) has expressed consent and signed the Informed Consent Form. The Informed Consent Form shall be kept as one of the original documents of the clinical trial for future reference.

Contact information must be collected from every patient, and the doctor should provide their own contact information to the patient, to ensure that the investigator can be reached in case of any changes in the patient's condition. This also facilitates the investigator's ability to stay informed about changes in the patient's condition.

To protect patient privacy, patient names should not appear on the Yiducloud Scientific Research Collaboration Platform. Investigators should confirm patient identity and make records using patient codes.

## 15. Patient Recruitment and Management System

### 15.1. Patient Recruitment

When a patient arrives at the hospital's emergency department or outpatient clinic, a neurologist or relevant specialist will inquire about the patient's medical history, conduct a physical examination, and make an initial diagnosis of acute ischemic stroke in the anterior circulation. Imaging examinations such as head CT/CTA/MRA/DSA will be performed to further confirm the diagnosis of acute large artery occlusive stroke in the anterior circulation. The patient will then be assessed against the inclusion and exclusion criteria to determine eligibility. While discussing the patient's condition with the patient and/or their family members, they will be informed about the basic details of the clinical trial (title, purpose, basic process, significance, etc.) and the associated risks. The patient and/or their family members will be asked if they wish to participate in the trial. If they agree, a written informed consent form will be signed, and the patient will be randomized into a group by the lead unit investigator through an app. If they decline, treatment will be provided according to the patient's and/or their family's preferences.

### 15.2. Patient Management System

1) Investigators will promptly collect personal information such as the patient's name, ID number, home address, and contact details, as well as data on current medical history, past medical history, and auxiliary examination results.

2) When signing the informed consent form, investigators will fully inform patients about the trial and respect their right to decide, either voluntarily or after discussing with family members, whether to participate in the trial.

3) Arrange patient follow-ups during the trial and strictly complete all examinations as specified in the protocol.

4) Educate patients that if they need to undergo other examinations or treatments due to comorbidities, they should inform the investigator promptly or during the next follow-up. Investigators should record relevant information timely after being informed.

5) Inform patients about possible adverse reactions that may occur during the study. Advise patients to promptly notify the investigator of any physical discomfort experienced during the trial, and the investigator will determine the appropriate management plan.

6) Inform patients that their study data will be kept confidential by the research team and request that they not disclose any trial-related information to external sources.

## 16. Trial Schedule

| | Start date | End date |
|---|---|---|
| Preparation Stage | 2024-02-01 | 2024-07-31 |
| Implementation Stage | 2024-08-01 | 2025-07-31 |
| Follow-up and Data Collection | 2025-08-01 | 2025-10-31 |
| Data Compilation and Analysis | 2025-11-01 | 2025-11-30 |
| Summary | 2025-12-01 | 2025-12-31 |

## 17. Data Management and Data Traceability Regulations

### 17.1. Case Report Form (CRF) Completion and Transfer

The CRF shall be completed by the investigator for each selected case in a timely manner. After review by the monitor, the first copy of the completed CRF shall be transferred to the data manager for data entry and management. No changes shall be made to the content of the CRF after the transfer of the first copy.

### 17.2. Data Entry and Modification

The data manager shall use the Yiducloud Scientific Research Collaboration Platform to develop a data entry program for data entry and management. To ensure data accuracy, two data entry clerks shall independently perform double entry and proofreading.

For any questions regarding the CRF, the data manager will send a Query Form (QF) to the investigator, and contact them through the monitor for a prompt response. The data manager will make data modifications, confirmations, and entries based on the investigator's responses. If necessary, additional QFs may be issued until correct confirmation is obtained.

## 17.3. Requirements for Investigators to Fill Out Clinical Trial Records

1) For all patients who have signed the informed consent form and been screened as eligible, detailed medical records and eCRFs on the Yiducloud Scientific Research Collaboration Platform must be carefully completed. All items must be filled in, with no blanks or omissions (see filling instructions).

2) Original laboratory test reports, urine pregnancy test reports, CT reports, etc., must be complete and attached to the original medical records. All these documents require the signatures and dates of the clinicians and investigators participating in the clinical trial. The data recorded in the eCRF on the Yiducloud Scientific Research Collaboration Platform must be accurately checked against the medical records and original test reports.

3) The original medical records (inpatient medical records) serve as the primary source of information. Any corrections can only be made by drawing a line through the incorrect information, noting the corrected data alongside, and providing a reason. These corrections must be signed and dated by the clinicians and investigators participating in the clinical trial. No erasure or covering of original records is allowed.

4) Data that is significantly higher than expected or outside the clinically acceptable range must be verified, and a necessary explanation must be provided by the clinician participating in the clinical trial.

During the trial, clinical records shall be completed by investigators at each sub-center in paper-based CRFs, accurately documenting the condition and treatment of each patient.

## 17.4. Inspection of Data Records by the Inspector

If an inspector is assigned to this trial, the following requirements shall be met:

1) The inspector shall regularly check the informed consent forms of patients and the screening and inclusion of cases during the trial;
2) Confirm that the content of the eCRF on the Yiducloud scientific research collaboration platform is filled in correctly and consistent with the original data;
3) Changes in treatment, concomitant medications, comorbid diseases, loss to follow-up, and missed examinations for each patient shall be confirmed and recorded; reasons for withdrawal and loss to follow-up of hospitalized patients shall be verified and explained;
4) Confirm that all adverse events are recorded, and SAEs are reported within the specified time and recorded;
5) Verify that the trial devices and medications are supplied, stored, and used in accordance with relevant regulations, and make corresponding records;
6) When checking the original medical records, attention should be paid to ensure that the records are timely, accurate, authentic, standardized, and complete, especially:

a) The consistency of the informed consent time and screening number sequence recorded in

the original medical records;

b) The observation and examination items and records should be consistent with the eCRF on the Yiducloud scientific research collaboration platform;

c) Check whether the judgment of the severity of the disease, efficacy evaluation, and safety evaluation are correct;

d) The patient's name, communication address, and hospitalization number on the medical record must be filled in and ensure their authenticity.

### 17.5. Database Locking

After the data is reviewed and the established database is confirmed to be correct, the data management personnel, principal investigators, statistical analysts, sponsors, and inspectors shall jointly review the data, complete the final definition and judgment of the analysis population, and then the database shall be locked by the data administrator.

The locked database or files generally cannot be modified.

## 18. Data Preservation and Trial Summary

### 18.1. Data Preservation

To ensure evaluation and supervision by the National Medical Products Administration, researchers should agree to preserve all research data according to the requirements of the "Good Clinical Practice (GCP)", including confirmation of all participating patients (able to effectively cross-check different records such as original hospital records and laboratory test reports), all original signed patient informed consent forms, etc., for a period of 5 years after the termination of the clinical trial.

All data from this clinical trial belongs to the First Affiliated Hospital of Fujian Medical University. Unless required by the National Medical Products Administration, researchers shall not provide any data to third parties in any form without the written consent of the First Affiliated Hospital of Fujian Medical University.

### 18.2. Trial Summary

After the completion of the trial, the Department of Biostatistics of Fujian Medical University will be responsible for establishing a clinical data database and conducting unified data processing. The statistical analysts will perform statistical analysis on the data from each participating unit separately and on the combined data from all units. The statistical results of each participating unit will be summarized in a brief format, which will be confirmed by each unit and used as the basis for writing the "Clinical Trial Summary Report". The completed summary report, after being stamped, will be submitted to the Department of Neurology of the First Affiliated Hospital of Fujian Medical University for archiving. The Department of Neurology of the First Affiliated Hospital of Fujian Medical University will be responsible for completing the "Clinical Trial Final Report".

The final report of the trial shall be publicly published only after agreement from all participating units. No party shall unilaterally publish the report without the consent of the other party.

# 19. Composition of Functional Institutions for Clinical Trials

## 19.1. Trial Principal Investigator

Wanjin Chen

## 19.2. Coordinating Committee

The coordinating investigator is Wanjin Chen, and the members of the coordinating committee consist of the heads and principal investigators of each clinical trial unit.

## 19.3. Executive Committee

The members of the executive committee for this trial are: Wanjin Chen, Wenjie Zi, Ying Fu, Ling Fang, Yi Lin, Wenlong Zhao, Qianqian Lin, Jinshan Yang, Jie Yang, Xu Xu, Jinfu Ma, Liangliang Qiu, Chengsong Yue, Kunxin Lin, Quanhong Wu.

## 19.4. Data and Safety Monitoring Committee

| Institution | Name | Professional title |
|---|---|---|
| Shenzhen Second People's Hospital | Gelin Xu | Professor |
| Tianjin Medical University General Hospital | Jinghua Wang | Professor |
| Tianjin Medical University General Hospital | Wen Qin | Professor |

## 19.5. Imaging Core Laboratory

| Institution | Name | Professional title |
|---|---|---|
| The First Affiliated Hospital of Fujian Medical University | Dejun She | Professor |
| Karolinska Institutet, Sweden | Tieqiang Li | Professor |
| The First Affiliated Hospital of Fujian Medical University | Ying Liu | Professor |

# 20. Responsibilities of Each Party and Other Regulations

Researchers must carefully read and understand the content of the trial protocol and strictly implement it in accordance with the Good Clinical Practice (GCP) guidelines and the protocol. They are responsible for recording patients' original data, obtaining informed consent forms, and promptly filling out Case Report Forms (CRFs) and the eCRF on the Yiducloud scientific research collaboration platform. Researchers should accept regular monitoring by inspectors to ensure the quality of the clinical trial. They must also ensure that patients receive appropriate treatment in case of adverse events during the trial. After the completion of the clinical trial, researchers must write a summary report, sign and date it, and submit it to the principal investigator.

This study adopts a competitive enrollment format, and the authorship order of published articles will be determined based on the number of qualified cases enrolled.

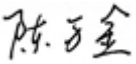
# 21. Declaration of Conflict of Interest

There are no personal financial or non-financial interests between the researchers and subjects of this clinical trial.

# 22. Protocol Signature Page

**Researcher's Declaration:**

1) I agree to conduct the clinical trial strictly in accordance with the design and specific provisionss of this protocol.
2) I understand that I may interrupt or terminate the clinical trial at any time to ensure the best interests of the patients.
3) I agree to personally conduct or supervise the clinical trial and ensure that all research personnel assisting me in the execution of the clinical trial at my institution are aware of their responsibilities in the trial.
4) In the process of conducting the clinical trial, I will strictly adhere to the current Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. I also commit to ensuring that the entire trial process will comply with ethical, moral, and scientific principles.
5) During the execution of the clinical trial, I will strictly follow all laws and regulations related to clinical trials to protect the rights and interests of patients.
6) I guarantee that I will meet the requirements for review and approval by the ethics committee.
7) I agree to maintain adequate and accurate medical records and ensure that these records are available for inspection and audit in accordance with relevant laws and regulations.
8) I agree to promptly report any changes in clinical trial activities, as well as any unexpected issues involving risks to patients or other personnel, to the ethics committee. Additionally, I will not make any modifications to the clinical trial protocol during the trial activities without the approval of the ethics committee, except for those modifications necessary to reduce patient risk in emergency situations.

Signature of the Principal Investigator:  Date: July 23, 2024

Wanjin Chen

# 23. Appendix

## I Names, contacts, and contact information of each sub-center.

| Serial Number | Organization Name | Contact Person | Contact Phone |
|---|---|---|---|
| 1 | Fujian Provincial Hospital | Yongkun Li | 135****1830 |
| 2 | Union Hospital of Fujian Medical University | Wenhuo Chen | 138****6089 |
| 3 | The 900th Hospital of the Chinese People's Liberation Army | Xiaoping Cui | 158****2996 |
| 4 | The Second People's Hospital of Fujian University of Traditional Chinese Medicine | Min Lin | 136****6522 |
| 5 | Fuqing City Hospital of Fujian Province | Jian Ye | 139****0500 |
| 6 | The Second Hospital of Fujian Medical University | Jixing Chen | 158****2707 |
| 7 | The First Hospital of Quanzhou City | Quanlong Hong | 189****1196 |
| 8 | The 910th Hospital of the Joint Logistic Support Force of the Chinese People's Liberation Army | Maolin Fu | 159****5130 |
| 9 | Anxi County Hospital | Zhenjie Chen | 136****7380 |
| 10 | Anxi County Traditional Chinese Medicine Hospital | Qiushi Shi | 139****1310 |
| 11 | Zhongshan Hospital of Xiamen University | Xingyu Chen | 180****4488 |
| 12 | The First Hospital of Xiamen University | Quan Lan | 183****1317 |
| 13 | The Second Hospital of Xiamen City | Na Xu | 133****5170 |
| 14 | Fujian Zhangzhou Hospital | Tingyu Yi | 158****5985 |
| 15 | The Second Hospital of Zhangzhou City | Kunjun Yang | 152****7213 |
| 16 | The Third Hospital of Zhangzhou City | Yaoyi Zhong | 137****3070 |
| 17 | The 909th Hospital of the Joint Logistic Support Force of the Chinese People's Liberation Army | Yuhui Han | 136****8287 |
| 18 | The First Hospital of Sanming City | Guiyun Luo | 187****4053 |
| 19 | Mindong Hospital of Ningde City | Mingyan Ye | 150****9000 |
| 20 | Area 1 of The First Hospital of Nanping City | Xiang Fang | 139****0862 |
| 21 | Area 2 of The First Hospital of Nanping City | Xiaoli Lin | 139****0057 |
| 22 | Shaowu City Hospital | Jianqiu Fu | 180****5507 |
| 23 | The First Hospital of Longyan City | Chong Zheng | 158****9252 |
| 24 | The First Hospital of Putian City | Ping Chen | 159****3537 |
| 25 | Affiliated Hospital of Putian University | Jianyang Peng | 138****8565 |
| 26 | Ganzhou People's Hospital | Guoyong Zeng | 135****9530 |
| 27 | The First Affiliated Hospital of Nanchang University | Xiaobing Li | 139****5284 |
| 28 | Jiangxi Provincial People's Hospital | Wenfeng Cao | 138****5608 |
| 29 | Affiliated Hospital of Jiujiang University | Zhongbin Xia | 138****9614 |

| Serial Number | Organization Name | Contact Person | Contact Phone |
|---|---|---|---|
| 30 | Jiujiang First People's Hospital | Tuanyuan Zheng | 135****5845 |
| 31 | Yingtan People's Hospital of Jiangxi Province | Jingjing Liu | 139****1861 |
| 32 | Xiushui First People's Hospital | Yuehui Ding | 151****0111 |
| 33 | Zigong Third People's Hospital | Li Wang | 159****0816 |
| 34 | Tianjin Huanhu Hospital | Yalin Guan | 139****5508 |
| 35 | Ezhou Central Hospital | Qiangfeng Pi | 189****9912 |
| 36 | Jingmen Central Hospital | Ying Wei | 158****5500 |
| 37 | Xiaogan Central Hospital | Huan Yang | 159****6086 |
| 38 | Zhongnan Hospital of Wuhan University | Bin Mei | 130****6699 |
| 39 | Union Hospital, Tongji Medical College, Huazhong University of Science and Technology | Shengcai Chen | 159****1353 |
| 40 | The Third Hospital of Hubei Province | Yue Wan | 158****2880 |
| 41 | Wuhan Central Hospital | Ping Jing | 136****6889 |
| 42 | Wuhan Third Hospital | Jianguang Liu | 177****1936 |
| 43 | Hubei General Hospital | Wei Ke | 153****5139 |
| 44 | Hubei Provincial Hospital of Traditional Chinese Medicine | Jie Pu | 189****8690 |
| 45 | Wuhan Hankou Hospital | Wenyong Gao | 133****9356 |
| 46 | The First People's Hospital of Jiangxia District, Wuhan | Canmin Zhu | 13006178063 |
| 47 | Huangshi Central Hospital | Wenju Gu | 134****1181 |
| 48 | Huanggang Central Hospital | Gang Zhou | 189****2028 |
| 49 | Xiangyang First People's Hospital | Peiyang Zhou | 135****1119 |
| 50 | Xiangyang Hospital of Traditional Chinese Medicine | Jincheng Liu | 150****8106 |
| 51 | Xiangyang Central Hospital | Xuan Liu | 186****9393 |
| 52 | Shiyan People's Hospital | Guanghui Chen | 139****6363 |
| 53 | Taihe Hospital of Shiyan City | Zhibing Ai | 139****3207 |
| 54 | Taihe Hospital of Shiyan City | Hancheng Li | 150****0053 |
| 55 | Qianjiang Hospital of Traditional Chinese Medicine | Chengwu Hu | 159****1120 |
| 56 | Jingmen First People's Hospital | Shaoliang Zhu | 189****1867 |
| 57 | Jingzhou Central Hospital | Junfeng Su | 181****7810 |
| 58 | Suizhou Central Hospital | Wei Cheng | 158****6447 |
| 59 | Yichang Central People's Hospital-Wujia District | Jinghua Zhou | 159 **** 3190 |

| Serial Number | Organization Name | Contact Person | Contact Phone |
|---|---|---|---|
| 60 | Yichang Central People's Hospital-Xiling Branch | Xichang Liu | 157****2891 |
| 61 | Yichang Second People's Hospital | Yongqiang Zheng | 133****6802 |
| 62 | Enshi Central Hospital | Congping Wang | 132****6628 |
| 63 | Enshi Xianfeng County Traditional Chinese Medicine Hospital | Zhao Li | 155****5090 |
| 64 | Lichuan Ethnic Traditional Chinese Medicine Hospital | Yi Chen | 139****8833 |
| 65 | Tianmen First People's Hospital | Xiaohua Yang | 130****3563 |
| 66 | Wuhan First Hospital | Wenhua Liu | 188****8816 |
| 67 | Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology | Xiang Luo | 133****3413 |
| 68 | Xianning Central Hospital | Jinwu Zhang | 189****7836 |
| 69 | MinDa Hospital of Hubei Minzu University | Changhua Zhai | 177****8660 |
| 70 | Xianyang First People's Hospital | Xingyun Yuan | 159****3943 |
| 71 | Guangzhou First People's Hospital | Honghao Wang | 136****0775 |
| 72 | Dongguan People's Hospital | Peigen Luo | 134****2332 |
| 73 | Zhanjiang Central People's Hospital | Junjie Gao | 134****1247 |
| 74 | Yunfu People's Hospital | Zhilin Wu | 139****6321 |
| 75 | Shantou Central Hospital | Chuming Huang | 137****6150 |
| 76 | Maoming Traditional Chinese Medicine Hospital | Wenguo Huang | 139****5299 |
| 77 | Affiliated Hospital of Guangdong Medical University | Feng Liao | 183****5047 |
| 78 | The First Affiliated Hospital of Jinan University | Hongyu Qiao | 186****1881 |
| 79 | Chengdu Fifth People's Hospital | Tangming Peng | 193****6783 |
| 80 | The First Affiliated Hospital of Hainan Medical University | Zhenqiang Zhao | 139****5677 |
| 81 | Guangdong Provincial Hospital of Traditional Chinese Medicine Hainan Hospital | Deliang Liu | 139****6559 |
| 82 | Miyang County People's Hospital | Jinchuan Han | 183****3902 |
| 83 | Zhumadian First People's Hospital | Xuemei Li | 135****5177 |
| 84 | Gongyi City People's Hospital | Siwei Liu | 135****5133 |
| 86 | Pingdingshan Second People's Hospital | Ynkuo Wang | 156****2390 |
| 87 | Dezhou Seventh Hospital | Enzhen Lv | 137****8606 |
| 88 | Affiliated Hospital of Jining Medical College | Yongnan Hao | 137****5767 |
| 89 | Qingdao Central Hospital | Shanlong Du | 178****5711 |

| Serial Number | Organization Name | Contact Person | Contact Phone |
|---|---|---|---|
| 90 | Affiliated Hospital of Shandong University of Traditional Chinese Medicine | Jingping Zhang | 156****8933 |
| 91 | Zoucheng People's Hospital, Shandong Province | Xin Liu | 138****5421 |
| 92 | Qilu Hospital of Shandong University Dezhou Hospital | Guo Lu | 186****1566 |
| 93 | Affiliated Hospital of Shandong University of Traditional Chinese Medicine | Jinping Zhang | 150****0655 |
| 94 | The First Affiliated Hospital of University of Science and Technology of China | Wei Hu | 151****0611 |
| 95 | Yiji Mountain Hospital of Wannan Medical College | Xianjun Huang | 181****3940 |
| 97 | Zhejiang Provincial People's Hospital | Zongjie Shi | 182****4645 |
| 99 | Nanning Third People's Hospital | Tong Li | 139****6120 |
| 100 | Yulin Red Cross Hospital | Lifu Xie | 159****8791 |
| 101 | Shanxi Provincial People's Hospital | Yaxuan Sun | 138****8394 |
| 102 | Qingzhen First People's Hospital | Hang Fu | 153****1820 |
| 103 | The First Affiliated Hospital of Xingtai Medical College | Bin Zhu | 139****8584 |
| 104 | Baoji People's Hospital | Zhangyong Bo | 181****6158 |
| 105 | Bozhou People's Hospital | Xinchen Zhang | 185****0802 |
| 106 | The Second Affiliated Hospital of Chongqing Medical University | Chang Liu | 156****1121 |
| 107 | Yan'an University Xianyang Hospital | Xiongfei Zhao | 136****7368 |
| 108 | Ruijin Hospital Affiliated to School of Medicine, Shanghai Jiao Tong University | Zhen Hu | 157****8619 |
| 111 | Baotou Central Hospital | Changchun Jiang | 133****0510 |
| 112 | Gansu Provincial Central Hospital | Rong Yin | 139****0466 |
| 113 | Sun Yat-sen Memorial Hospital of Zhongshan University | Xinguang Yang | 130****5666 |
| 114 | The Second Affiliated Hospital of the Army Military Medical University | Wenjie Zi | 185****3816 |
| 115 | *The First Affiliated Hospital of Fujian Medical University | Wenlong Zhao | 159****6029 |
| … | … | … | … |

Note: * refers to the sponsoring unit and group leader unit of this study. New centers are allowed to continuously join in this study until the end of case enrollment.

## II Unblinding record form

Unblinding record form

| | |
|---|---|
| Date: _____/ _____/ _____(YYYY/MM/DD) | |
| Patient number: | Random number: |
| Unblinding Date: _____/ _____/ _____(YYYY/MM/DD) | |
| Unblinding Reason: | |
| Signature of unblinding personnel: | |

# 24. References


1. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* 2021;20(10):795-820.
2. Wang W, Jiang B, Sun H, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation.* 2017;135(8):759-771.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344-e418.
4. Chinese Society of Neurology, Cerebral Vascular Group, Neurovascular Intervention Group, Chinese Society of Neurology. Chinese Guidelines for early intravascular Interventional treatment of acute ischemic Stroke 2022, *Chinese Journal of Neurology*. 2022;55(6):16.
5. Yoshimura S, Sakai N, Yamagami H, et al. Endovascular Therapy for Acute Stroke with a Large Ischemic Region. *N Engl J Med.* 2022;386(14):1303-1313.
6. Huo X, Ma G, Tong X, et al. Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *N Engl J Med.* 2023;388(14):1272-1283.
7. Sarraj A, Hassan AE, Abraham MG, et al. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. *N Engl J Med.* 2023;388(14):1259-1271.
8. Bendszus M, Fiehler J, Subtil F, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. *Lancet.* 2023;402(10414):1753-1763.
9. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387(10029):1723-1731.
10. van Kranendonk KR, Treurniet KM, Boers AMM, et al. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *J Neurointerv Surg.* 2019;11(5):464-468.
11. Chinese Society of Neurology, Cerebrovascular Group, Chinese Society of Neurology. Chinese Consensus on Diagnosis and Treatment of Hemorrhage Transformation after acute cerebral Infarction 2019, *Chinese Journal of Neurology.* 2019;52(4):14.
12. Leigh R, Jen SS, Hillis AE, Krakauer JW, Barker PB. Pretreatment blood-brain barrier damage and post-treatment intracranial hemorrhage in patients receiving intravenous tissue-type plasminogen activator. *Stroke.* 2014;45(7):2030-2035.
13. Desilles JP, Rouchaud A, Labreuche J, et al. Blood-brain barrier disruption is associated with increased mortality after endovascular therapy. *Neurology.* 2013;80(9):844-851.
14. Jiang X, Andjelkovic AV, Zhu L, et al. Blood-brain barrier dysfunction and recovery after ischemic stroke. *Prog Neurobiol.* 2018;163-164:144-171.
15. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. *Cerebrovasc Dis.* 2008;25(1-2):176-184.

16. Huttner HB, Schwab S. Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. *Lancet Neurol.* 2009;8(10):949-958.
17. Liebeskind DS, Jüttler E, Shapovalov Y, Yegin A, Landen J, Jauch EC. Cerebral Edema Associated With Large Hemispheric Infarction. *Stroke.* 2019;50(9):2619-2625.
18. Rungta RL, Choi HB, Tyson JR, et al. The cellular mechanisms of neuronal swelling underlying cytotoxic edema. *Cell.* 2015;161(3):610-621.
19. Stokum JA, Gerzanich V, Simard JM. Molecular pathophysiology of cerebral edema. *J Cereb Blood Flow Metab.* 2016;36(3):513-538.
20. Parrella E, Porrini V, Benarese M, Pizzi M. The Role of Mast Cells in Stroke. *Cells.* 2019;8(5).
21. Timmermans S, Souffriau J, Libert C. A General Introduction to Glucocorticoid Biology. *Front Immunol.* 2019;10:1545.
22. de Courten-Myers GM, Kleinholz M, Wagner KR, Xi G, Myers RE. Efficacious experimental stroke treatment with high-dose methylprednisolone. *Stroke.* 1994;25(2):487-492; discussion 493.
23. Altamentova S, Rumajogee P, Hong J, et al. Methylprednisolone Reduces Persistent Post-ischemic Inflammation in a Rat Hypoxia-Ischemia Model of Perinatal Stroke. *Transl Stroke Res.* 2020;11(5):1117-1136.
24. Jing YH, Hou YP, Song YF, Yin J. Methylprednisolone improves the survival of new neurons following transient cerebral ischemia in rats. *Acta Neurobiol Exp (Wars).* 2012;72(3):240-252.
25. Yang Q, Guo C, Yue C, et al. MARVEL: A Randomized Double-Blind, Placebo-Controlled Trial in Patients Undergoing Endovascular Therapy: Study Rationale and Design. *Stroke: Vascular and Interventional Neurology.* 2024.
26. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke.* 1988;19(12):1497-1500.
27. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol.* 2001;22(8):1534-1542.
28. Wang Yongjun, Liu Ming, Pu Chuanqiang, Cerebrovascular Diseases Group, Chinese Society of Neurology, Chinese Medical Association. Chinese Guidelines for Secondary Prevention of Ischemic Stroke and transient Ischemic Attack 2014, *Chinese Journal of Neurology.* 2015.