A Randomized, Double-blind, Placebo Controlled Evaluation, Multicenter Clinical Study of Tongxinluo Capsule in Ischemic Stroke Patients（TISS)

Clinical Study Protocol

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Study Organizer: Shijiazhuang Yiling Pharmaceutical Co., Ltd.

Scheduled Start Time: June 2013

Scheduled End Time: December 2015

Proposed Participating Centers

(In no particular order, the final participating centers are subject to the signed contract)

	Center Name	**Responsible Person**
1	Beijing Tiantan Hospital, Capital Medical University	Wang Yongjun
2	Beijing Chao-Yang Hospital, Capital Medical University	Hu Wenli
3	China-Japan Friendship Hospital	Jiao Jinsong
4	Beijing Shijitan Hospital	He Maolin
5	PLA Lanzhou General Hospital	Shi Xiangqun
6	Lanzhou University Second Hospital	Chen Jun
7	The Third Affiliated Hospital, Sun Yat-sen University	Hu Xueqiang
8	Guangzhou First People's Hospital	Pan Xiaoping
9	The First Affiliated Hospital of Jinan University (Guangzhou Overseas Chinese Hospital)	Xu Anding
10	The First Affiliated Hospital, Sun Yat-sen University	Zeng Jinsheng
11	Xiangya Hospital Central South University	Xiao Bo
12	The Second Xiangya Hospital of Central South University	Tan Limin
13	The First Hospital of Changsha	Tang Hongyu
14	Siping Central People's Hospital	Zhang Xiaoying
15	The First Hospital of Jilin University	Wu Jiang
16	The First Affiliated Hospital, Zhejiang University School of Medicine	Luo Benyan
17	The Second Affiliated Hospital, Zhejiang University School of Medicine	Ding Meiping
18	Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine	Hu Xingyue
19	The First Affiliated Hospital of Bengbu Medical College	Qu Hongdang
20	Fujian Provincial Hospital	Lei Huixin
23	The First Affiliated Hospital of Henan University of Science and Technology	Huang Lina
24	Henan Provincial People's Hospital	Zhang Jiewen
25	The First Affiliated Hospital of Zhengzhou University	Zhang Boai
26	Heilongjiang Provincial Hospital	Wei Guangkuan
27	The 2nd Affiliated Hospital of Harbin Medical University	Yan Xiaobo
28	The First Hospital of Qiqihar	Song Benhua
29	The Second Affiliated Hospital of Kunming Medical University	Zhu Yuhong
30	The First Affiliated Hospital of Chongqing Medical University	Qin Xinyue
31	Daping Hospital, Third Military Medical University	Zhou Huadong
32	The Second Hospital of Hebei Medical University	Guo Li
33	Cangzhou Central Hospital	Shao Rusheng
34	Jiangxi Provincial People's Hospital	Wu Xiaomu
35	The First Affiliated Hospital of Nanchang University	Xu Renxu
36	The Fourth Affiliated Hospital of Nanchang University	Lou Xiaoliang
37	The First Affiliated Hospital of Xinjiang Medical University	Zhang Xiaoning

38	The First Hospital of China Medical University	He Zhiyi
39	Shengjing Hospital of China Medical University	Guo Yang
40	The People's Hospital of Liaoning Province	Chen Xiaohong
41	The First Affiliated Hospital with Nanjing Medical University	Wan Qi
42	Nanjing Drum Tower Hospital	Xu Yun
43	The Affiliated Hospital of Xuzhou Medical University	Shen Xia
44	The First Affiliated Hospital of Guangxi University of Chinese Medicine	Liu Tai
45	The First Affiliated Hospital of Guangxi Medical University	Qin Chao
46	The Second Hospital of Shanxi Medical University	Li Guanglai
47	Shanxi Provincial People's Hospital	Hu Fengyun
48	Ankang Central Hospital	Liu Yi
49	The First Affiliated Hospital of Xi'an Jiaotong University	Qu Qiumin
50	The Second Affiliated Hospital of Xi'an Jiaotong University	Wu Haiqin
51	Shaanxi Provincial People's Hospital	Song Yunzhang
52	West China Hospital of Sichuan University	Liu Ming
53	Sichuan Provincial People's Hospital	Sun Hongbin
54	Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Chen Shengdi
55	Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University	Sun Xiaojiang
56	The Third People's Hospital of Chengdu	Gao Li
57	Mianyang Central Hospital	Duan Jinfeng
58	Affiliated Hospital of Guiyang Medical University	Chu Lan
59	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Sun Shenggang
60	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	Bu Bitao
61	Shiyan Taihe Hospital	He Guohou
62	Tianjin Changzheng Hospital	Shi Hui
63	Tianjin Medical University General Hospital	Shi Fudong
64	Tianjin Huanhu Hospital	Zhou Yuying
65	Baotou Central Hospital	Wang Baojun
66	The Affiliated Hospital of Inner Mongolia Medical University	Zhao Shigang
67	Qilu Hospital of Shandong University	Yan Chuanzhu
68	Shandong Provincial Hospital	Du Yifeng
69	Qingdao Municipal Hospital	Xing Chengming

Abbreviations

ACA	Anterior cerebral artery
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ASA	Aspirin
BP	Blood pressure
BI	Barthel index
BUN	Urea nitrogen
CRP	C-reactive protein
CRF	Case report form
CRO	Contract Research Organization
Cr	Creatinine
CT	Computed tomography
CTA	Computed tomography angiography
DRF	Deviation resolution form
DSMB	Data Safety Monitoring Board
DWI	Magnetic resonance diffusion weighted imaging
ECG	Electrocardiogram
EMS	Emergency medical services
ER	Emergency room
FAS	Full analysis set
FIB	Fibrinogen
HDL	High density lipoprotein
HR	Heart rate
ICH	Intraparenchymal hemorrhage
INR	International normalized ratio
IRB	Institutional Review Board
IVH	Intraventricular hemorrhage

IS	Ischemic stroke
LDL	Low density lipoprotein
MCA	Middle cerebral artery
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Score
N	Neutrophil
NINDS	National Institute of Neurological Disorders and Stroke
NIHSS	National Institutes of Health Stroke Scale
NNT	Number needed to treat
NOS	Nitric oxide synthase
OR	Odds ratio
PE	Pulmonary embolism
PG	Prostaglandin
PP	Per-protocol set
RBC	Red blood cell
RCT	Randomized controlled trial
rtPA	Recombinant tissue plasminogen activator
SAE	Serious adverse event
SFDA	National Medical Products Administration
TIA	Transient ischemic attack
TC	Total cholesterol
TCD	Transcranial Doppler
TG	Triglyceride
t-PA	Tissue plasminogen activator
WBC	White blood cell

Protocol Synopsis

Objective(s)	1. The primary efficacy outcome was measured the proportion of patients with modified Rankin Scale (mRS) score ≤1 at 90 days after randomization. Subgroup analyses for the primary outcome were conducted, based on TOAST classification, reperfusion treatment, baseline NIHSS score (4-7, 8-14 and 15-22), and AIS onset time to randomization (≤24, 24-48 and 48-72 hours). 2. The secondary efficacy outcomes measured the proportion of patients recovered to NIHSS 0-1 or reduction by 4 points or more at 90 days, the proportion of patients with 85 or more Bathel Index (BI) score at 90 days, distribution of scores on the mRS (ordinal shift analysis) at 90 days, incidence of ischemic cerebrovascular disease (ischemic stroke, transient ischemic attack) and incidence of new combination clinical vascular events (ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, vascular death). 3. The following safety outcomes were also systematically recorded: The incidence of adverse events, serious adverse events, 12-lead electrocardiogram, physical examination and laboratory test values (blood routine, urine routine, serum biochemistry, coagulation).
Design	A randomized, double-blind, placebo-controlled, and multicenter clinical study.
Inclusion and exclusion criteria	**Inclusion criteria:** 1. Ischemic stroke within 72 after onset, confirmed by MRI or CT. 2. Age 35–75 years, inclusive. 3. Patients with the first attack or patients with stroke

	history (modified Rankin Scale score 0–1); 4. Clear signs of localization of nervous system, NIHSS score 4 to 22. 5. Patient or proxy has signed *Informed Consent Form*. **Exclusion criteria:** 1. Hemorrhage diseases according to head CT or MRI, such as hemorrhagic stroke, epidural hematoma, intracranial hematoma, intraventricular hemorrhage, subarachnoid hemorrhage, hemorrhage after cerebral infarction. 2. Transient Ischemic Attack (TIA). 3. Severe disturbance of consciousness: 1a of NIHSS score >1 point; Difficulty in swallowing, unable to take oral capsules; any of 5a, 5b, 6a, 6b of NIHSS score >2 point. 4. Convinced of stroke caused by brain tumor, brain trauma, hemopathy, etc. 5. Hemorrhagic tendency patients. 6. Patients with endovascular treatment after the onset of stroke. 7. Patients with dementia, severe Parkinson's disease, mental disorders, limb dysfunction caused by other diseases or other conditions that may affect the therapeutic efficacy. 8. Uncontrolled hypertension (≥200 mmHg systolic or ≥110 mmHg diastolic) or hypotension (≤90 mmHg systolic or ≤60 mmHg diastolic); severe hyperglycemia (blood glucose ≥400 mg/dL) or hypoglycemia (blood glucose ≤50 mg/dL). 9. Severe hepatic insufficiency defined as transaminase

<table>
<tr><td></td><td colspan="2">values >2x upper limit of normal; severe renal insufficiency defined as values serum creatinine >1.5x upper limit of normal; cardiac dysfunction or other serious systemic disease with life expectancy ≤3 months.
10. Patients with concurrent malignancy or ongoing anti-tumor therapy.
11. Patients with history of being allergic to the trial medicine.
12. Pregnancy, breastfeeding or potential pregnancy.
13. Within three months or currently participating in another investigational study.
14. Any other condition that in the opinion of the investigator should preclude study participation.</td></tr>
<tr><td rowspan="2">Efficacy endpoints</td><td>Primary efficacy endpoint</td><td>The proportion of patients with modified Rankin Scale (mRS) score ≤1 at 90 days after randomization.</td></tr>
<tr><td>Secondary efficacy endpoint</td><td>1. Proportion of patients recovered to NIHSS 0-1 or reduction by 4 points or more at 90 days;
2. Proportion of patients with 85 or more Bathel Index (BI) score at 90 days;
3. D istribution of scores on the mRS (ordinal shift analysis) at 90 days;
4. Incidence of ischemic cerebrovascular disease (ischemic stroke, transient ischemic attack);
5. Incidence of new combination clinical vascular events (ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, vascular death).</td></tr>
<tr><td>Safety indicators</td><td colspan="2">Blood and urine routine tests, ECG, comprehensive biochemical analysis, coagulation function, adverse events,</td></tr>
</table>

	physical examination.
Sample size	The total number of observed cases is 1,968, with 984 cases in the treatment group and 984 cases in the control group.
Dosage regimen	Treatment group: Standard treatment + Tongxinluo Capsules, 4 capsules/time, tid, po Control group: Standard treatment + Tongxinluo Capsules placebo, 4 capsules/time, tid, po
Course of treatment	90 days
Statistical unit	Peking University Clinical Research Institute

Table of Contents

1. Title

A Randomized, Double-blind, Placebo Controlled Evaluation, Multicenter Clinical Study of

Tongxinluo Capsule in Ischemic Stroke Patients (TISS)

2. Purpose

Primary objective: To assess the effects in improving life self-care ability of stroke patients after taking Tongxinluo Capsule (within 72 hours after onset) versus Placebo for 90 days;
Secondary objective: To compare the improvement in neurological deficit, improvement in activities of daily living, disability rate, incidence of combined vascular events, and incidence of ischemic cerebrovascular events in stroke patients after taking Tongxinluo Capsule (within 72 hours after onset) versus Placebo for 90 days, evaluate the medication safety, evaluate the efficacy and safety of Tongxinluo Capsules in various etiological subtypes, different randomization times, radiology subgroup analysis, and through further exploratory analysis.

3. Background

With the changing demographic structure, the issue of population aging has become more prominent in the 21st century. Furthermore, with the fast-paced lifestyle and an irrational dietary structure, the incidence of cerebral strokes is exhibiting a noticeable upward trend. According to the 10-year study results from the world's largest collaborative cardiovascular research institution released by the WHO in 2002, the incidence of stroke in China has reached 250 per 100,000, ranking second in the world.[1] Moreover, based on pertinent survey findings, the incidence of this disease is rising at an annual rate of 8.7%. At present, on average, one person dies from stroke every 21 seconds, with a mortality rate ranging from 10% to 15%. About 75% of patients endure varying degrees of severe disabilities, including hemiplegia and aphasia, following the onset of the disease, placing a substantial burden on both society and families.[2] Furthermore, as stated in the China Guidelines for Cerebrovascular Disease Prevention and Treatment (2010 edition), it is foreseen that cerebrovascular diseases will persist in their upward trend in China, leading to increasingly severe consequences. Hence, it is imperative to escalate efforts in prevention and control, swiftly reducing the incidence and mortality of strokes, making it an urgent and pivotal task.

Among them, ischemic stroke (IS), also known as cerebral infarction, accounts for 60%–80% of all strokes. Ischemic stroke (IS) mainly occurs due to atherosclerosis and thrombus formation in the arteries supplying blood to the brain, leading to narrowing or even occlusion of the vessel

lumen, thus causing focal cerebral hypoperfusion and the onset of the disease. It can also be caused by abnormal objects (solid, liquid, gas) entering the cerebral arteries or carotid arteries that supply blood to the brain along the blood circulation, causing obstruction of blood flow or a sudden decrease in blood flow, leading to softening and necrosis of the corresponding area of brain tissue. It primarily occurs in the elderly population aged 50 to 60 years and above, often associated with conditions such as atherosclerosis, hypertension, and cardiovascular diseases like rheumatic heart disease. Additionally, it frequently occurs in patients with diabetes and those with unhealthy habits such as smoking and alcohol consumption. The main pathological manifestations include brain ischemia, hypoxia, edema, and necrosis.[3] Patients mainly present with hemiplegia, hemidysesthesia, aphasia and cognitive dysfunction. The pathophysiological mechanisms of ischemic brain injury are intricate, exhibiting a “cascade” reaction. This involves various processes, such as the release of excitatory amino acids, depolarization around the infarct, inflammatory responses, and neuronal apoptosis. Ischemia leads to a decrease in cerebral blood flow and energy metabolism failure, resulting in cell membrane depolarization and the release of toxic amino acids, such as glutamate. Activation of glutamate receptors causes intracellular calcium overload and pathological release of nitric oxide (NO). These interrelated processes form a vicious cycle, ultimately leading to irreversible cell necrosis.[4] In recent years, the research focus has primarily revolved around various measures to improve cerebral blood circulation (such as thrombolysis, antiplatelet therapy, anticoagulation, fibrinolysis reduction, volume expansion), and neuroprotection. The role of antiplatelet and anticoagulant therapy in the clinical treatment of acute ischemic stroke is primarily confined to secondary stroke prevention and the prevention and treatment of deep vein thrombosis. Up to now, recombinant tissue plasminogen activator (rt-PA) remains the only drug proven to be effective in treating ischemic stroke.[5][6] In November 1996, the U.S. FDA approved the clinical validation of rt-PA and authorized its use in acute ischemic stroke cases meeting the indications within 3 h after onset. However, thrombolytic therapy is costly, comes with a narrow treatment window, and poses potential side effects such as bleeding. Only a very small percentage of patients benefit from it. In foreign countries, 95% of acute ischemic stroke patients do not receive timely thrombolytic therapy due to the narrow treatment window. In China, less than 1.0% of patients have access to thrombolytic therapy. The research findings from the Stroke Unit Task Force in

Shanghai indicate that only 3.6% to 5.2% of patients are admitted within 3 to 6 h and receive thrombolytic therapy.[7] Given this situation, experts both domestically and internationally have shifted their research focus towards neuroprotective agents. Basic research suggests that neuroprotective drugs primarily function through the following pathways: Preventing calcium influx, reducing the excitotoxicity of excitatory amino acids, and regulating microvascular inflammatory responses. Currently, the most widely evaluated neuroprotective drugs include voltage- and receptor-mediated calcium channel antagonists, as well as antioxidants that directly inhibit oxygen free radical-mediated cell damage. Measures to protect ischemic brain tissue involve pre-synaptic regulation of excitatory amino acids, and the use of calcium channel antagonists, adenosine enhancers, peptide growth factors, and mediators that block cell apoptosis. In theory, drugs (neuroprotective agents) targeting cellular damage after acute ischemia or reperfusion can protect brain cells and enhance tolerance to ischemia and hypoxia. However, what is confusing is that currently, no neuroprotective agent has been proven to be effective and safe for the treatment of acute ischemic stroke. There is a notable disconnect between the clinical application and the theoretical framework of neuroprotective agents, and a lack of sufficient evidence in clinical practice. Therefore, their widespread promotion and utilization are currently impractical. In addressing the cascade mechanism of ischemic injury, early multi-pathway (cocktail) treatments may represent a reasonable approach for neuroprotective therapy. Traditional Chinese medicine, distinguished by its holistic viewpoint and the principle of syndrome differentiation and treatment, has the capacity to interrupt the cascade reaction of ischemia at different stages and levels through various pathways and multiple targets. This strategy extends the treatment window, inhibits delayed cell death, exerts neuroprotective effects, and contributes to preventing the onset of ischemic stroke. Such a comprehensive protective treatment optimally harnesses the advantages inherent in traditional Chinese medicine.

Tongxinluo Capsule is a compound traditional Chinese medicine that, domestically, was the first to employ the theory of collateral diseases to explore the pathological mechanisms and treatment of vascular lesions. Guided by the principle of treating vascular diseases by promoting collateral circulation, it organically combines various collateral treatment methods with medications. It intervenes in the common pathological processes of “meridian-collateral-

vascular system diseases" and is widely used in vascular diseases such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease, making it a representative drug for the prevention and treatment of "meridian-collateral-vascular system diseases".[8] It was awarded the national new drug certificate in 1996 and subsequently launched into the market in 1997. It has also successively received recognition as a nationally protected traditional Chinese medicine (1999), been classified as a class A reimbursable drug under the national medical insurance (2000), and was honored with a Second Prize of the National Scientific and Technological Progress Award (2000).

Tongxinluo Capsule is composed of ingredients such as Ginseng Radix, Hirudo nipponia whitman, Buthus martensi karsch, Scolopendra, Eupolyphaga Steleophaga, Cicadae Periostracum, Paeoniae Radix Rubra, and Borneolum Syntheticum. It possesses the effects of invigorating Qi, promoting blood circulation, dredging collaterals, alleviating pain, relieving coronary artery spasm, and protecting and improving endothelial function. In recent years, multiple domestic research centers have confirmed that Tongxinluo Capsules have a definite and affirmative protective effect on blood vessels, especially microvessels. Tongxinluo can protect the structural and functional integrity of microvessels in the ischemic area, facilitate the establishment of collateral circulation in the ischemic area, promote therapeutic angiogenesis in the ischemic area, intervene in the pathological damage process of cerebral infarction, and enhance neurological function recovery. Furthermore, Tongxinluo Capsules demonstrate a significant intervention effect on the cascade pathological chain of neuronal damage caused by ischemia while protecting the microvessels in the ischemic area. Studies indicate that Tongxinluo significantly inhibits intracellular Ca 2^{+} overload in cortical neurons by increasing Na^{+}-K^{+}-ATPase activity. Tongxinluo reduces the release of excitatory amino acids, inhibits the generation of free radicals, suppresses inflammation damage post cerebral ischemia, and inhibits the expression of apoptosis-related factors such as Caspase-3, P 53 mRNA, and proteins. It also promotes the expression of stress-protective factor HSP 70 mRNA, thereby exerting a blocking effect on multiple links and targets in the neural cascade injury.

A Meta-analysis of 40 publicly available publications on the treatment of cerebrovascular diseases with Tongxinluo also indicates that Tongxinluo Capsule, as a drug for treating cerebrovascular diseases, significantly improves clinical efficacy. It has a positive impact on

promoting neurological function recovery in patients with acute cerebral infarction, and it is safe with no apparent toxic side effects.[9]

While Tongxinluo Capsules have been widely utilized in clinical practice and basic research in the field of cerebrovascular diseases, most of its clinical studies are single-center, involve relatively small sample sizes, or are retrospective case-control studies. There is a lack of large-sample, multi-center, and prospective randomized controlled trials.[10][11] To further standardize the study on the clinical efficacy and safety of Tongxinluo in ischemic stroke patients, this study will, based on standardized drug treatment, employ the principles of modern evidence-based medicine to assess Tongxinluo Capsule's effects on the self-care ability (modified Rankin Scale), activities of daily living (Barthel Index score), and the degree of neurological deficit (NIHSS score) in acute and recovery phases of ischemic stroke, and comprehensively evaluate the functional level and quality of life of ischemic stroke patients, thereby assessing the clinical efficacy of early administration of Tongxinluo Capsules in ischemic stroke patients.

4. Overall Design and Arrangement

This study is a randomized, double-blind, placebo Controlled, parallel-group multicenter clinical trial conducted in ischemic stroke patients.

4.1. Randomization phase (Day 0 to Day 90):

Patients will be randomized into the treatment group or the control group at a 1:1 ratio. Patients will receive the study drug in addition to the current standard treatment.

Treatment group:Standard treatment + Tongxinluo Capsules (4 capsules/time, tid, po);

Control group: Standard treatment + Tongxinluo Capsules placebo (4 capsules/time, tid, po);

During the treatment period, the use of other traditional Chinese medicines or proprietary Chinese medicines with similar functional components to those of Tongxinluo Capsules should be avoided.

Patients should visit the hospital on Day 7 after randomization, at discharge (if the hospital stay exceeds 21 days, evaluation will be conducted on Day 21), and on Day 90 for efficacy and safety assessments until the completion of the study.

4.2. Number of cases, grouping and study centers

According to the China National Stroke Registry (CNSR), 39.59% of patients with NIHSS

score of 4–22 at admission had mRS ≤1 at 3 months. Assuming a 40% proportion of patients with mRS ≤1 at 90 days in the control group and a 47% proportion in the treatment group, with an equal ratio design, and utilizing PASS 2008 to calculate the required sample size, with α = 0.05 (two-sided test) and β = 0.2 (test power 80%), the calculated sample size for both the treatment and control groups is 787 cases. To account for potential dropouts in clinical studies, an additional 20% of the sample size is added. Therefore, a total of 1,968 patients are planned to be included in this study.

Patients will be allocated in a 1:1 ratio to the treatment group and the control group, and the study is planned to be conducted at 50 centers nationwide.

5. Study Population

Patients entering the study must meet all the inclusion criteria listed below and must not meet any of the exclusion criteria. In addition to the criteria listed below, any medical conditions or use of prohibited medications during the standard treatment that are considered contraindications will also be grounds for excluding patients from the study.

5.1. Inclusion criteria

1. Ischemic stroke within 72 h after onset, confirmed by MRI or CT;
2. Age 35–75 years, inclusive;
3. Patients with the first attack or patients with stroke history (modified Rankin Scale score 0-1);
4. Clear signs of localization of nervous system, NIHSS score 4 to 22;
5. Patient or proxy has signed *Informed Consent Form*.

5.2. Exclusion criteria

1. Hemorrhage diseases according to head CT, such as hemorrhagic stroke, epidural hematoma, intracranial hematoma, intraventricular hemorrhage, subarachnoid hemorrhage and hemorrhage after cerebral infarction;
2. Transient ischemic attack (TIA);
3. Severe disturbance of consciousness: 1a of NIHSS score >1 point; Difficulty in swallowing, unable to take oral capsules; any of 5a, 5b, 6a, 6b of NIHSS score >2 point.

4. Convinced of stroke caused by brain tumor, brain trauma, hemopathy, etc.;
5. Hemorrhagic tendency patients;
6. Patients with endovascular treatment after the onset of stroke;
7. Patients with dementia, severe Parkinson's disease, mental disorders, limb dysfunction caused by other diseases or other conditions that may affect the efficacy determination;
8. Uncontrolled hypertension (≥200 mmHg systolic or ≥110 mmHg diastolic) or hypotension (≤90 mmHg systolic or ≤60 mmHg diastolic); severe hyperglycemia (blood glucose ≥400 mg/dL)
   (22.2 mol/L) or hypoglycemia (blood glucose ≤50 mg/dL) (2.8 mol/L);
9. Severe hepatic insufficiency defined as transaminase values >2x upper limit of normal; severe renal insufficiency defined as values serum creatinine >1.5x upper limit of normal; cardiac dysfunction or other serious systemic disease with life expectancy ≤3 months;
10. Patients with concurrent malignancy or ongoing anti-tumor therapy;
11. Patients with history of being allergic to study drug and control drug;
12. Pregnancy, breastfeeding or potential pregnancy;
13. Within three months or currently participating in another investigational study;
14. Any other condition that in the opinion of the investigator should preclude study participation.

5.3. Dropout (withdrawal) criteria

Any subjects who have signed the *Informed Consent Form* and been screened for eligibility, regardless of when or why they withdraw, will be considered dropouts if they do not complete the protocol-defined procedures.

Patients have the right to withdraw from the study at any time and for any reason. The investigators also have the right to withdraw a patient from the study if the patient experiences illness, adverse events, protocol violations, or for management reasons or any other reason. Efforts should be made to minimize unnecessary patient withdrawals, and proactive measures should be taken to complete the final assessment whenever possible, to facilitate the analysis of their efficacy and safety. However, when a patient decides to withdraw, the investigators should contact the patient or their responsible family member through telephone or in-person visits to confirm the reasons for withdrawal. Investigators should retrieve any remaining study

drug, complete the final assessment, strive to finalize case reports, explain the reasons for withdrawal, and conduct follow-up on endpoint events for withdrawn patients whenever possible. If a patient withdraws from the study due to adverse events, the primary event should be documented in the study medical records.

Common reasons for dropouts: Adverse events, lack of efficacy, patients undergoing endovascular therapy during the follow-up period, protocol violations (including poor compliance), loss to follow-up (including voluntary withdrawal by patients), discontinuation by the sponsor, etc.

5.4. Termination criteria

1) Occurrence of allergic reactions clearly related to the study drug;
2) Occurrence of adverse symptoms, signs, or abnormal test results clearly related to the study drug, as judged by the investigator, necessitating the termination of the study;
3) Occurrence of pregnancy in females during the study period;
4) Termination of continued participation in the study at the patient's request;
5) Undergoing endovascular therapy during the study period;
6) The occurrence of vascular events will be evaluated on a case-by-case basis: In the event of hemorrhagic stroke, the study drug should be discontinued, the study terminated, and the details documented in the relevant sections of the study medical records. If a TIA/ischemic stroke/myocardial infarction occurs, the subject does not need to discontinue the study drug or withdraw from the study unless the use of concomitant medication contraindicated in this study is necessary.

5.5. Criteria for comprehensive study discontinuance

1) During the study, the entire multi-center study may be fully suspended for the following reasons:

- The investigator discovers serious safety issues;
- The efficacy is too poor, and there is no need to continue the study;
- Significant error in the protocol is found;
- The sponsor decides to discontinue the study due to financial or managerial reasons;
- The study may be terminated midway in its entirety if the administrative regulatory

authority revokes the study.

The comprehensive discontinuance of the study can be either temporary or permanent. When the study is discontinued, all study records should be retained for future reference.

6. Treatment

6.1 Study drug

6.1.1 Source of drug

Investigational medicinal product: Tongxinluo Capsules

Ingredients: Ginseng Radix, Hirudo nipponia whitman, Buthus martensi karsch, Eupolyphaga Steleophaga, Scolopendra, Cicadae Periostracum, Paeoniae Radix Rubra, Borneolum Syntheticum, Santali Albi Lignum, Dalbergiae Odoriferae Lignum, Frankincense and Ziziphi Spirosae Semen.

Description: This product is a hard capsule, with content consisting of gray-brown to grayish-brown granules and powder. It has a fragrant odor, a slight fishy smell, and a mildly salty and bitter taste.

Strength: 0.26 g/capsule

Batch No.: GYZZ Z 19980015

Manufacturer: Shijiazhuang Yiling Pharmaceutical Co., Ltd.

Investigational medicinal product: Placebo

Tongxinluo Capsule Simulant (The simulant is identical to Tongxinluo Capsules in terms of color, strength, packaging, labeling, and description of the content).

All the investigational medicinal products mentioned above are provided free of charge by Shijiazhuang Yiling Pharmaceutical Co., Ltd., and come with COAs.

6.1.2 Formulation, packaging, and labeling

Tongxinluo Capsules will be provided in the form of 0.26 g capsule formulation, and the placebo will have an appearance identical to it.

Drug packaging

Small packaging: The appearance is as follows, with the words “For Clinical Study Use” printed on it. Each small box contains 30 capsules packed in aluminum-plastic sheets.

Large packaging: It is a white cardboard box measuring 29.5 cm × 12 cm × 22 cm. Each large packaging contains 38 small packages, and each large box is labeled as follows:

GYZZ Z19980015 **Drug No.: XXXX** **Investigational Medicinal Product for Clinical Study of Tongxinluo Capsules in the Treatment of Ischemic Stroke** (For Clinical Study Use Only)
[Packaging] Each small box contains 30 capsules, and there are 38 small boxes in each package (a 90-day supply for one subject) [Dosage and administration] 3 times a day, 4 capsules/time [Production Batch No.] xxxx [Valid until] xxxx [Storage] Seal and store in a dry place, out of reach of children. [Supplier] Shijiazhuang Yiling Pharmaceutical Co., Ltd.
Thank you for your trust and support! Please be sure to follow the doctor's advice and attend the hospital for treatment on the specified dates. Thank you for your cooperation!

6.1.3 Storage method

The investigational medicinal product should be securely stored with a lock in a controlled indoor area, with attention to preventing moisture. Each center must designate a person in charge of storage and management of investigational medicinal products.

6.1.4 Dispensing and retrieval of drug

Every time the investigator dispenses drug to the subject during a follow-up visit, it is necessary to complete the Drug Dispensing Register, accurately and promptly record the quantity of dispensed drug, and remind the subject to bring back the remaining drug during the next visit. Additionally, when retrieving drug, verify the returned quantity and document it in the Drug Dispensing/Return Register. At the end of the study, all remaining drug should be returned to

the sponsor. The Drug Retrieval Form should be completed, and any unused drug must be sealed when returned. After the study concludes, the remaining drug will be retrieved by the sponsor's CRA and disposed of uniformly.

6.1.5 Drug inventory

After self-administration of the drug, the subject should return all remaining drug during each visit. The investigator will count the remaining drug and record the quantity, which is used to assess compliance.

6.1.6 Handling plan for temporary discontinuation, permanent discontinuation, or loss to follow-up of patients

The study drugs should be continued for as long as possible. If discontinuing the study drug, temporary discontinuation should be considered in case of loss to follow-up, and permanent discontinuation is the last resort. Any discontinuation of drug should be thoroughly documented on the corresponding pages of the CRF. In any circumstance, patients should participate in the study for as long as feasibly possible. Under any circumstance, pregnancy will result in permanent discontinuation from the study.

6.1.6.1 Temporary suspension of study drug

Once the investigator, based on their best clinical judgment, deems it unlikely that the study drug is related to the events that occurred, and in the absence of other study contraindications, the drug should be resumed. Resumption of drug should be carried out under close and rational monitoring. If it is determined that the trial can be resumed, the investigator should document the time of resumption for all temporary discontinuations (less than 10 days) on the corresponding pages of the CRF.

6.1.6.2 Definite indications for discontinuing study drug

Patients should discontinue the study drug in the following circumstances:

Clinical conditions necessitating discontinuation of the drug (e.g., abnormal laboratory values)

Pregnancy or a desire to become pregnant

6.1.6.3 Handling plan for patients permanently discontinuing the drug

The follow-up of patients should adhere to the procedures specified in the study protocol, continuing until the scheduled completion date of the study or until the patient recovers to normal or stable condition from adverse events (whichever is longer).

The investigator should record all confirmed withdrawals from the study on the corresponding pages of the CRF.

Patients who discontinue the study drug before the last follow-up should complete the endpoint follow-up at 3 months.

For patients lost to follow-up, relevant information should be documented up to the last follow-up in their CRFs. The investigator should make every effort to contact each patient, ascertain the reason for loss to follow-up, and assess their health status.

6.1.6.4 Outcomes

Patients who have withdrawn from the study cannot re-enter the study. The patient's random number and treatment drug will no longer be applicable.

The investigator should communicate with the sponsor to jointly confirm the interruption and/or withdrawal of the patient.

Randomized patients will not be replaced.

6.2 Treatment regimen

6.2.1 Study process:

Screening period (Day −3 to Day 0):

If patients meet the treatment criteria outlined in this protocol, they can undergo all examinations during this period. Patients who meet the inclusion criteria will proceed to the randomization phase.

Random treatment period (Day 1 to Day 90): Designated as Day 1 from the first dose administration.

Treatment group: Standard treatment + Tongxinluo Capsules (4 capsules/time, tid, po)

Control group: Standard treatment + Tongxinluo Capsule Simulant (4 capsules/time, tid, po)

It is recommended to take the study drugs in approximately 30 minutes after daily meals. Patients should not take the drug in the morning of the day of visit at home. If a patient misses a dose on a certain day, the dose the following day should not exceed the daily dose. Dose adjustment of the study drug is not allowed. If a patient develops an intolerable adverse event, which is considered by the investigator to be related to the study drug, he/she should terminate the treatment with the study drug.

6.2.2 Standard treatment

Refer to the *Guidelines for diagnosis and treatment of acute ischemic stroke in China 2010* for the recommended Standard treatment plan (see Appendix 7).

6.2.3 Concomitant medications

During the study, the use of concomitant medications as needed is as follows: General supportive treatment includes antipyretics, diuretics, antihypertensive drugs, lipid-lowering agents, hypoglycemic agents, antibiotics, and other symptomatic medications. However, during the study, it is advisable to avoid the use of traditional Chinese medicines or proprietary Chinese medicines that may affect the assessment of therapeutic efficacy.

From the onset of the illness until the end (discontinuation) of the study, the use of other investigational drugs is prohibited.

All concurrently used medications and other treatment modalities should be thoroughly documented in the study medical records, along with appropriate explanations.

6.2.4 Course of treatment: 90 days.

6.3 Compliance assessment

Compliance assessment of subjects will be conducted by thoroughly documenting the dispensing and retrieval of drugs. Actual drug intake within the range of 80% to 120% of the prescribed dosage will be considered as compliant with the protocol requirements.

6.4 Adverse drug reactions

Individual patients may experience mild stomach discomfort after taking the drug.

7 Clinical observation endpoints and indicators

7.1 Clinical observation endpoints

7.1.1 Primary efficacy endpoint

Improvement in self-care ability (proportion of patients with mRS score ≤1) after 90 days of treatment

7.1.2 Secondary efficacy endpoint

1. Improvement in neurological deficit (proportion of patients with NIHSS ≤1 or NIHSS improved by 4 points or more)

2. Improvement in activities of daily living (proportion of patients with BI index ≥85)
3. Disability rate (proportion of patients with mRS score ≥3 points);
4. Continuous changes of mRS scores;
5. Incidence of ischemic cerebrovascular disease during follow-up;
6. Incidence of combined vascular events during follow-up;

7.2 Safety indicators:

- Adverse event assessment
- Clinical laboratory indicators include blood routine (hemoglobin, red blood cells, white blood cells, platelets), urine routine (urine protein, urine white blood cells, urine red blood cells), serum biochemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glutamine, urea nitrogen, creatinine, total bilirubin, blood glucose, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein).
- Coagulogram: Coagulation 4-item (PT, APTT, TT, FIB)
- 12-lead ECG
- Physical examination

8 Study Process

Refer to Table 1 for details of the study process.

8.1 Visit 1 (V1, Day −3 to Day 0)

(Complete the following tasks within 3 days)

- Sign the *Informed Consent Form*
- Collect general information: gender, age, height, weight, etc.
- Perform brain CT and/or head MRI examination
- Laboratory tests (If the patient has undergone tests during the current hospitalization that overlap with the study examination items, there is no need to repeat the tests. Instead, the report of these tests should be reprinted or copied and attached to the study medical record. The copy must be signed by the investigator.)
- Physical examination
    - 12-lead ECG
    - Pregnancy test

- Assess NIHSS score, mRS score, and BI index score
    - Record concomitant diseases and concomitant medications
- Review inclusion criteria and exclusion criteria
    - Dispense randomized study drugs
- Advise the subjects of the next follow-up date and inform them not to take the drug on the day of the follow-up

Since neuroimaging is routinely recommended for all stroke patients, this study will not cover the cost of this portion during this visit.

8.2 Visit 2 (V2, 7d)

- Record adverse events
- Record concomitant medications
- Physical examination
- Perform scale assessment (NIHSS, mRS, BI Index)
- Record combined vascular events
- Advise the subjects of the next follow-up date and inform them not to take the drug on the day of the follow-up

8.3 Visit 3 (V3, at discharge)

- Record adverse events
- Record concomitant medications
- Physical examination
- Perform brain CT and/or head MRI examination (If this examination is conducted at discharge, the results should be recorded in the CRF. If the patient did not undergo imaging examination at discharge, record it as “None” in the CRF)
- Laboratory test
    - Measure 12-lead ECG (Both of the above are routine examinations at discharge for patients. This study will not cover the cost of these examinations during this visit, but the results of these two examinations need to be collected for safety observation.)
    - Perform scale assessment (NIHSS, mRS, BI Index)

- Record combined vascular events
- Advise the subjects of the next follow-up date and inform them not to take the drug on the day of the follow-up

8.4 Visit 4 (V4, 90 d)

- Laboratory test
- Physical examination
- Record adverse events
    - 12-lead ECG
    - Head MRI examination: Centers participating in the radiology subgroup should complete the TI + T2 + DWI + FIAIR + MRA + T2* examination. All images should be saved in DICOM format, and the DICOM CD will be transferred to the Central Imaging Evaluation Laboratory. (Refer to Appendix 6–Summary of the Radiology Subgroup Study for details)
    - Perform scale assessment (NIHSS, mRS, BI Index)
    - Record combined vascular events
    - Retrieve the remaining drug and assess medication compliance
    - Record the completion status of the study

8.5 Visit 5 (follow-up visit if necessary) *

*Due to the persistent adverse events or clinically significant laboratory abnormalities or vital sign abnormalities that exist at the end of treatment, the investigator considers it necessary to conduct a follow-up visit to obtain follow-up measurement results. The investigator will conduct follow-up visits based on the specific situation, which may also be done via telephone.

8.6 Follow-up for potential events

If a patient experiences potential clinical neurological events, including clinical symptoms due to ischemia or new transient or persistent neurological symptoms, each center is required to generate a determination document within 72 hours. The content should include:

- Conduct neurological examination (mRS, NIHSS, BI)
- Perform physical examination, record body weights and vital signs
- Collect information on concomitant medications and adverse events since the last

follow-up.

- Patients participating in the radiology subgroup should undergo MRI sequence examinations, and their imaging results should be transmitted to the central imaging reading room.

If a patient experiences a new potential cardiovascular event, a cardiac assessment, including an ECG, will be conducted based on clinical need. Any information supporting a potential myocardial infarction will be collected in the determination document and communicated to the CRA within 72 hours.

9 Efficacy and Safety Determination Criteria

9.1 Efficacy determination criteria

9.1.1 Primary efficacy assessment

- The proportion of patients with improvement in activities of daily living 90 days after treatment (mRS score ≤1): mRS ≤1 indicates complete or substantial recovery of activities of daily living, representing a favorable prognosis. Comparison of the proportion of patients with favorable prognosis in the treatment group and the control group 90 days after randomization;

9.1.2 Secondary efficacy assessment:

- Improvement in neurological deficit, i.e., the proportion of patients with NIHSS ≤1 or NIHSS improved by 4 points or more: NIHSS score ≤1 or reduction of ≥4 points is considered effective; compare the proportion of effective and ineffective patients and continuous changes of NIHSS in the treatment group and the control group after 90 days of randomized treatment;
- Proportion of patients with BI index ≥85: BI score ≥85 indicates the ability to live independently. Compare the proportion of patients able to live independently between the treatment group and the control group 90 days of randomized treatment, as well as continuous changes in BI scores between the two groups;
- Disability rate, defined as the proportion of patients with an mRS score ≥3: An mRS score ≥3 indicates the inability to live independently. Compare the percentage of disabled patients between the treatment group and the control group 90 days of

randomized treatment;

- Continuous changes in mRS scores: Compare the changes in mRS scores between the treatment group and the control group at different visit points, including baseline, 7 d, discharge, and 90 d;
- Incidence of ischemic cerebrovascular events during the follow-up period: The proportion of ischemic stroke or TIA within 90 days of randomized treatment, or newly occurring ischemic lesions detected on MRI at the last visit, will be assessed as a group or separately;
- Incidence of combined vascular events during the follow-up period: The cumulative incidence of newly occurring combined vascular events within 90 days of randomized treatment will be assessed as a group or separately;

  Definition of combined vascular events: Consist of any type of stroke (ischemic stroke, hemorrhagic stroke), TIA, myocardial infarction, and vascular death.

  Vascular death: Hemorrhagic death of any organ or fatal pulmonary embolism.

9.1.2.1 Assessment and Procedures for Combined Vascular Events

After the occurrence of a combined vascular event, the study center must notify the sponsor within 24 hours upon receipt of the event notice. Vascular events will be reviewed by an independent Clinical Events Committee (CEC). Therefore, the endpoint event classification table will be included as part of the CRF. The investigator will record events in the aforementioned table and promptly submit supporting documents (admission and discharge records, medical records, death records, ECG, etc.). This information will be provided to the CEC for the determination of events.

The CEC is composed of a chairperson and 5–6 members. Each event will be independently reviewed by two members of the committee, and the conclusions will be submitted to the chairperson of the committee. If there is a disagreement between the two reviewing members or between the two reviewing members and the chairperson, when the number of dissenting events reaches a certain threshold, the entire committee will schedule a meeting to review the events.

9.2 Safety determination:

- Adverse event assessment

- Clinical laboratory indicators:

  Collect blood and urine samples in a fasting state (at least 10 hours of fasting, with water intake allowed but no consumption of coffee or tea) and send them to the laboratories of each center for testing according to uniform standards

  Blood routine (hemoglobin, red blood cells, white blood cells, platelets), urine routine (urine protein, urine white blood cells, urine red blood cells), serum biochemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, glutamine, urea nitrogen, creatinine, uric acid, blood glucose, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein), coagulation 4-item
- 12-lead ECG
- Physical examination:

  Comprehensive physical examination: General condition (including height, weight), vital signs (including blood pressure, pulse rate), skin (including hair and nails), eyes, ears, nose, and throat, neck/thyroid, chest/lungs, cardiovascular system, abdomen/gastrointestinal system, reproductive-urinary system (optional), nervous system, lymphatic system, and musculoskeletal system;

  Simplified physical examination: General condition (including weight), vital signs (including blood pressure, pulse rate), chest/lungs, cardiovascular system

  Vital signs: Patient's sitting blood pressure, pulse rate, respiratory rate, and heart rate will be recorded after at least 5 minutes of rest. Blood pressure measurements will be conducted using an appropriately calibrated and validated sphygmomanometer with the auscultatory method. The patient should remain seated for at least 5 minutes, both feet on the ground, and arms at heart level. An appropriately sized cuff should be used (the cuff bladder should encircle at least 80% of the arm) to ensure the accuracy of the measurement. Each blood pressure measurement should be performed twice, with an interval of at least 5 minutes, and the average of the two measurements should be recorded.

10 Observation of Adverse Events

10.1 Definition:

- Adverse event **(AEs)**: Any untoward medical event that occurs from the time the subject signs the *Informed Consent Form* and is enrolled in the study until the last follow-up visit, regardless of whether there is a causal relationship with the study drug.
- Significant adverse event: Any adverse event that, in addition to serious adverse events, leads to the use of targeted medical measures (e.g., drug withdrawal, dose reduction, and symptomatic treatment), and hematological or other laboratory abnormalities.

10.2 Determination criteria for adverse event intensity:

All clinical adverse events occurring in this clinical study will be recorded on the Adverse Events page of the CRF. The intensity of adverse events will be graded. For standardization, the grading of event intensity is as follows:

Mild: Perceptible discomfort, which does not affect daily activities

Moderate: Significant discomfort, affecting or reducing daily activities

Severe: Unable to work or engage in daily activities

The severity and intensity of adverse events should be distinguished. Severe is used to describe intensity, which is not necessarily a serious adverse event (SAE). For example, headache may be severe in intensity but cannot be classified as a SAE unless it meets the SAE criteria.

10.3 Criteria for determining the relationship between adverse events and study drug

For causal analysis of all adverse events with the study drug, assessments will be made using five levels: definitely related, probably related, possibly related, unlikely related, and definitely unrelated. The first three are categorized as adverse drug reactions. The considerations for causal analysis include the following five aspects:

1) Whether there is a reasonable temporal relationship between the initiation of drug use and the onset of suspected Adverse Drug Reactions (ADR).
2) Whether the suspected ADR aligns with the known ADR of the drug (as per the literature).
3) Whether the suspected ADR can be explained by concurrent medication, previous medication, the patient's clinical condition, or the influence of other therapies (other

explanations).

4) Whether the suspected ADR resolves or diminishes after discontinuation or dose reduction of the drug (withdrawal response).
5) Whether the suspected ADR reappears upon re-exposure to the same drug (rechallenge).

10.4 Determination of serious adverse events

10.4.1 Definition of common serious adverse events

A serious adverse event refers to any clinical event that suggests significant harm, contraindications, side effects, or requires caution. An adverse event is classified as a serious adverse event if it meets one or more of the following criteria:

- Death
- Life-threatening (referring to instances where patients experiencing the event are at an immediate risk of death at the time of occurrence; excludes events that, if more severe, could potentially lead to patient death)
- Leading to hospitalization or prolonged hospital stay
- Results in persistent or significant labor loss or disability
- Congenital malformation or defect

Some medical events that have not resulted in death, are not life-threatening, or do not require hospitalization, but, in the investigator's medical judgment, may jeopardize the patient's well-being or require medical or surgical intervention to prevent one of the outcomes listed above, should also be considered as an SAE.

10.4.2 Study-specific definition of serious adverse events

The following events are recorded only as endpoint events and are not considered as AE/SAE

1. Ischemic stroke
2. TIA
3. Myocardial infarction

The following events are considered both endpoint events and AE/SAE

1. Hemorrhagic stroke
2. Vascular death

All deaths and any hemorrhagic events should be reported as AE/SAE

10.5 Operational procedures

(1) In the process of drug clinical study, personnel at all positions have their own responsibilities and duties, and perform their tasks in accordance with the regulations.

(2) Strictly adhere to the standard operating procedures at each stage of the drug clinical study.

(3) During the drug clinical study, study staff should closely observe or follow up on various reactions occurring in subjects after drug administration, in order to promptly detect adverse events or serious adverse events and provide timely intervention.

(4) During the drug clinical study, once a subject experiences an adverse reaction, regardless of its causal relationship with the study drug, the investigator should record all adverse events in the original records and sign them. If it is an adverse drug reaction, a preliminary assessment and diagnosis or suspected diagnosis of the adverse reaction should be made based on the criteria for determining the causality between adverse drug reactions and the drug.

(5) For subjects experiencing common adverse reactions to the study drug, the investigator should immediately report to the PI, determine necessary diagnostic and treatment measures based on the condition, decide whether to discontinue the clinical study, follow up and investigate all adverse events, record the detailed process and outcomes until the issue is resolved or the condition stabilizes. If there are laboratory abnormalities, follow-up should continue until recovery to normal. The follow-up method can be chosen based on the severity of the adverse reactions, including options such as hospitalization, outpatient visits, home visits, phone calls, and communication.

(6) In the case of serious adverse events, the doctor should immediately initiate rescue according to the Emergency Response SOP and record it. Consultation with relevant specialized departments should be requested, and in cases of urgency, the subject should be urgently transported to the ICU for treatment, accompanied by medical staff. In addition, the PI should be immediately notified, and the Subject Injury and Adverse Event Handling Team should be promptly informed. During holidays, hospital on-call personnel should be notified, and reporting should be escalated as appropriate. The emergency response flowchart can be found in Appendix 5.

(7) Report and unblind according to the “Standard Operating Procedure for Reporting Serious Adverse Events” (see 10.6.3.1) and the “Standard Operating Procedure for Emergency Unblinding” (see 11.2).

10.6 Handling measures

10.6.1 Measures for handling adverse drug reactions

The symptoms, signs, or laboratory test results, onset time, duration, severity, handling measures, course of events, etc., should be documented in the medical records. The correlation with the study drug should be assessed, and the investigator should sign and date the record. According to the adverse drug reaction reporting system, report the adverse drug reactions to the hospital’s ADR monitoring center. The hospital’s ADR monitoring center will then report to the provincial and national ADR monitoring centers.

10.6.2 Measures for handling adverse events

When an adverse event is identified, the investigator should immediately address it and report to the department head, determine necessary diagnostic and treatment measures based on the patient’s condition, and decide whether to suspend the clinical study observation. All adverse events should be thoroughly investigated, with detailed records of the handling process and outcomes until a satisfactory resolution or stabilization of the condition. If there are laboratory abnormalities, follow-up should continue until recovery to normal. The follow-up method can be chosen based on the severity of the adverse reactions, including options such as hospitalization, outpatient visits, home visits, phone calls, and communication.

10.6.3 Measures for handling serious adverse events

10.6.3.1 Reporting

Investigators should report to the department head and promptly inform relevant personnel in the center project team based on the nature of adverse events. In the case of holidays or nighttime incidents, the on-duty medical staff should immediately notify the on-call administrative staff at the hospital and inform the director of the office of the drug clinical trial institution. The office of the drug clinical trial institution should report to the hospital’s medical ethics committee, the study sponsor (lead center), relevant hospital departments, and Shijiazhuang Yiling Pharmaceutical Co., Ltd. within 24 hours. In emergency situations, including serious events, especially fatal adverse reactions and other serious adverse events, the

fastest communication methods (including phone, fax, express delivery, email, etc.) should be used to report to the above-mentioned departments.

Unit	Contact Person	Tel.	Fax
Ethics Committee of XXXX Hospital	XXXX	XXXX	XXXX
Beijing Tiantan Hospital, Capital Medical University	Wang Yongjun	010-67098350	010-67013383
Shijiazhuang Yiling Pharmaceutical Co., Ltd.	Han Shuolong	0311-85902352	0311-85902352

(In case of a serious adverse event, report to relevant authorities within 24 hours)

10.7 Abnormal laboratory results

The investigator should assess whether the abnormal laboratory results are clinically significant and provide possible explanations. Abnormal laboratory results caused by reported adverse events should be simultaneously documented as adverse events in the adverse event table. Abnormal laboratory test results with clinical significance meeting one or more of the following conditions should be recorded as an independent diagnosis on the adverse event page of the study medical records (excluding abnormal laboratory results caused by reported adverse events):

- Accompanied by clinical symptoms;
- Resulting in changes to the study medication;
- Requiring modifications to concomitant medication and/or other therapeutic measures.

11 Blinding and Randomization

11.1 Code blinding, and blind code preservation

The biostatistician not involved in the data management and statistical analysis of this study uses the central randomization system to generate random drug packaging numbers. The randomization parameters cannot be modified or viewed after the project has commenced.

Based on the assigned drug packaging number, the drug is encoded by statisticians not involved in this study. The blind codes used for encoding must be sealed and preserved thereafter.

11.2 Emergency unblinding

In case of a serious adverse event requiring emergency unblinding, the responsible investigator at the center will log in to the randomization system for emergency unblinding. If, during the unblinding process, there are limitations due to internet speed or other reasons, directly call the 24-hour hotline of Peking University Clinical Research Institute. The system administrator will then proceed with the emergency unblinding. This unblinding process only involves the individual subject, and the system will not disclose information about the group assignment of other subjects. If the case undergoes emergency unblinding, it will be treated as a dropout; however, if adverse reactions occur, it will be included in the adverse event analysis.

11.3 Unblinding regulations

This study is double-unblinded. After blind verification, data locking is performed. The Principal Investigator, medical statistician, data administrator, and sponsor's representative conduct the first unblinding. The groups corresponding to each random number are labeled as A and B, to facilitate statistical analysis of all the data. When the statistical analysis is concluded, and the summary report is completed, the second unblinding is conducted to reveal the exact group assignments of A and B.

11.4 Randomization

11.4.1 Randomization method

Method of centralized dynamic randomization, with each center competing for enrollment. The centralized randomization procedure will be performed using the Interactive Web-based Randomization System (IWRS) provided by Peking University Clinical Research Institute. The principal investigators at each study center will have their own unique login credentials, ensuring the security and integrity of the login system. After screening each eligible subject at all participating centers in this study, the investigator will log in to the randomization system with their accounts, input relevant information about the subject and obtain the drug packaging number for that subject. The investigators will administer the relevant drug based on the drug

packaging number. Subjects will be randomized into treatment and control groups based on stratification factors, which include:

1. Whether thrombolytic therapy has been administered: Yes, No
2. NIHSS Score: 4–7 points, 8–14 points, 15–22 points

The randomization method is the Pocock and Simon minimization algorithm. Patients must initiate the study treatment within 24–48 hours after randomization. This study employs non-repeated randomization.

12 Statistical Analysis

After the study protocol is finalized, statistical professionals will collaborate with the principal investigator to develop the statistical analysis plan. The statistical analysis software used is SAS® 9.2 software (Software installation point authorization code: 11202165). The sample size calculation software used is PASS 11.

12.1 Analysis population

The study population is divided into the following categories:

- Full Analysis Set (FAS): The set of subjects according to the Intention To Treat (ITT) principle. It refers to the dataset composed of all subjects who participated in the randomization process and underwent baseline assessments. For subjects for whom complete efficacy assessments are not observed, data truncation will be carried out following the Last Observation Carried Forward (LOCF) principle.
- Per-Protocol Set (PPS): It refers to the collection of cases that meet the inclusion criteria, do not meet the exclusion criteria, and complete the treatment regimen. This includes cases that adhere to the study protocol, exhibit good compliance, and complete the specified CRF entries for analysis (PP analysis).
- Safety Set (SS): It refers to the set of all randomized subjects who received the study drug and had at least one safety assessment after baseline.

The efficacy analysis will be conducted based on the FAS and the PPS. The analysis of all baseline demographic data will be conducted based on the FAS, and safety assessment will be performed on the SS.

12.2 Statistical analysis method

- All statistical tests will be two-sided, and a *P*-value ≤0.05 (two-sided) will be considered statistically significant for the tested differences. (Unless specifically stated otherwise)
- Descriptive analysis: For count data, describe with proportions. For measurement data,

describe with mean, standard deviation, maximum, and minimum values. For non-normally distributed data, describe with median, 25th percentile, and 75th percentile.

- The comparison of general conditions between the two groups will be analyzed using appropriate methods based on the type of indicator. Inter-group comparisons of quantitative data will be performed using paired t-tests or Wilcoxon rank-sum tests. For categorical data, the chi-square test or exact probability method will be employed. For ordinal data, Wilcoxon rank-sum tests or CMH tests will be used.

12.2.1. Enrollment and study completion:

Summarize the number of enrollments and completions for each center and provide a list of dropouts. Different dataset sizes for each group, distribution of cases in each center, comparison of overall dropout rates, and a detailed list of reasons for termination. Describe the demographic characteristics of patients (age, height, weight, vital signs, etc.), medical history, and medication history. Compare age, height, and weight between the two groups to assess their comparability.

12.2.2. Compliance analysis:

- Medication compliance analysis: Compare whether patients in the two groups use the study drug on time and in the correct dosage, and whether they refrain from using prohibited drugs and foods according to the protocol.
- Concomitant medication analysis: Tally the number of patients in each group using concomitant medications and provide a detailed list.

12.2.3. Efficacy evaluation:

- Baseline: Describe the baseline characteristics of each efficacy indicator. Refer to general methods for inter-group comparisons.
- Primary efficacy endpoints:

Conduct both PP and FAS analyses concurrently. The primary time point for evaluating the proportion of patients with improved modified Rankin (mRS) scores ≤1 in terms of activities of daily living is at Day 90 (for the PP population) or at the time of premature discontinuation (for the FAS population). The primary indicator will be compared between the two groups using the CMH-χ^2 analysis method, controlling for center effects.

The primary indicator will be assessed using a superiority test, testing the following hypothesis:

$$H_0: \pi_{Test\ group} - \pi_{Control\ group} \leq 0$$

$$H_1: \pi_{Test\ group} - \pi_{Control\ group} > 0$$

$$\alpha = 0.025(One - sided)$$

If the H_0 is rejected at the significance α level, or if the lower limit of the 95% CI for the difference in retention rates between the two groups is greater than 0, it can be considered that the treatment group is superior to the control group.

Other secondary indicators will be compared using the same statistical method as the primary indicator.

12.2.4. Safety evaluation:

Describe the number and proportion of subjects with normal values before treatment and abnormal values after treatment for both the treatment group and the control group separately. Describe adverse events using the number of cases, the number of subjects, and the incidence rate. Conduct inter-group significance tests will be conducted on the incidence rate. Additionally, provide a detailed description of the specific manifestations, severity, and the relationship with the drug for all adverse events observed in each group. Provide a cross-tabular description of the changes in laboratory indicators before and after the treatment. Compare vital sign indicators before and after the treatment.

13 Data Management

13.1 Completion and transfer of the case report form

Investigators should ensure that data from subjects' original observation records are accurately, completely, clearly, and promptly entered into the case report form. CRAs are required to monitor whether the study adheres to the study protocol, confirm the accuracy and completeness of all case report forms, and ensure consistency with the original data. In case of errors or omissions, investigators should be promptly requested to make corrections. After inspection by the CRA, the case report forms must be promptly transmitted to the data administrator for clinical study.

13.2 Data entry and modification

The data entry and management are the responsibility of the designated data administrator appointed by Peking University Clinical Research Institute. The data administrator will prepare data entry procedures for data entry and management. In order to ensure the accuracy of the data, two data administrators will conduct independent double entry and check.

For query of case report form, the data administrator will generate data request query (DRQ) and will inquire of investigators through CRAs. The investigators will solve problems quickly and give feedback. The data administrator will revise, confirm and enter data based on feedback given by the investigator. DRQ will be sent again if necessary.

13.3 Blind review and unblinding

Blind review refers to the verification and evaluation of database data from the time of the last case report form entry into the database until the first unblinding.

When all case report forms have been entered twice and verified without discrepancies, the data administrator will generate a database check report. The contents include an overview of the study completion status (including a list of dropouts), inclusion/exclusion criteria check, completeness check, logical consistency check, outlier data check, time window check, concomitant medication check, adverse event check, etc.

At the blind review meeting, the principal investigator, sponsor, CRA, data administrator, and biostatistician professional will conduct a review of the maintenance of blinding during the study process and the emergency unblinding situations, make resolutions to issues raised in the database check report and generate a blind review report. The database will be simultaneously locked. Generally, no modification will be made for data or documents locked.

14 Quality Control

1) The sponsor and investigators should fulfill their respective responsibilities and strictly adhere to the clinical study protocol. Standard operating procedures should be followed, and all relevant observational results and findings must be verified to ensure the implementation of quality control and quality assurance systems in clinical study.
2) In the clinical study, subject allocation must follow the randomization plan determined by the study design. The treatment group codes for each subject should be kept confidential,

with the sponsor and investigator each maintaining their own blind codes.

3) The investigator must provide necessary training to all personnel participating in the clinical study, explaining relevant information, operating procedures, and responsibilities, to ensure that data are recorded truthfully, accurately, completely, timely, and legally in medical records and CRF. The study medical records and CRF must be kept under the custody of designated personnel.
4) The CRAs appointed by the sponsor should adhere to standard operating procedures, oversee the implementation of the study protocol, confirm the correctness and completeness of all data records and reports, ensure accurate completion of all CRFs, and verify consistency with the original data.
5) The sponsor may delegate inspectors to conduct systematic inspections of clinical study-related activities and documents to assess whether the study is conducted in accordance with the protocol, standard operating procedures, and relevant regulatory requirements.
6) All laboratory examination data in the clinical study must be accurate and should be documented or copies of the original reports pasted onto the case report forms.
7) For patients participating in the radiology subgroup, MRI sequence examinations are conducted. To ensure consistency in their assessments, the imaging data will be transmitted to the central imaging reading room for simultaneous readings by two individuals.
8) The medical statisticians should accurately and completely incorporate the study data into the report. All steps involving data management must be documented for the purpose of checking data quality and the implementation process.
9) The statistical analysis process and the presentation of its results for clinical study data must adhere to standardized statistical methods. At each stage of the clinical study, medical statisticians must be involved. The clinical study summary report must be consistent with the statistical report.
10) All parties involved must strictly adhere to the approved protocol for conducting the clinical study, and any deviations from the protocol should be documented. Any modifications to the study protocol require the development of an explanation, and it must be approved by the ethics committee before implementation.
11) Each study center has one study director and several fixed members of the study team.

Strictly adhere to the requirements of the clinical study protocol. The technical personnel from the lead center should maintain close contact with each study center at all times, and visit each study center in the early, middle, and late stages of the study to inspect the case observation records and promptly address any potential issues.

15 Ethical Considerations

1. Throughout the process of clinical study, it is essential to provide adequate protection for the personal rights of the subjects and ensure the scientific rigor and reliability of the study. The rights, safety, and health of the subjects should take precedence over considerations of scientific and societal interests.
2. The study protocol must be reviewed and approved by the ethics committee before it can be implemented. Any modifications to the study protocol during the study should be approved by the ethics committee. In case of a serious adverse event during the study, prompt reporting to the ethics committee is required.
3. The investigator or their designated representative must explain the details of the clinical study to the subjects. After a thorough and detailed explanation of the study, *Informed Consent Form* is obtained.

16 Study Progress

August 2012	Complete the study protocol development, and hold a protocol discussion meeting
February to May 2013	Finalize the study protocol
May to June 2013	Conduct center ethics review, prepare study drugs and data
June 2013	International registration of the current study
July 2013	Sub-center registration and initiation
August 2013	Screening and enrollment of the first case
December 2014	Complete the random enrollment for all cases
April 2015	Each center completes the follow-up work for all cases
June 2015	Complete data entry and blind review
October 2015	Statistical analysis work
December 2015	Complete the study statistical report

17 Data Storage

The study center should retain these original data for 5 years after the termination of the clinical study. This includes confirmation for all participating subjects (which can effectively verify different record data, such as CRFs and hospital original records), all original subject Informed Consent Forms, CRFs, and detailed records of drug distribution.

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Appendix 1: Study Flowchart

Study Stage	Screening/Randomization	Double-blind Treatment Period			Follow-up Visit*
Visit	1	2	3	4	5
Days	Day -3 to Day 0	Day 7 ± 2	Discharge*	Day 90 ± 7	
Basic information					
Informed Consent Form	●				
General data	●				
Medical history	●				
Physical examination	●	●	●	●	◎
Treatment					
Inclusion/exclusion criteria	●				
Allocation of random numbers	●				
Distribution of study drugs	●				
Recording concomitant medications	●	●	●	●	
Collection and counting of drugs			●	●	
Determination of compliance			●	●	
Completion status				●	
Inclusion/exclusion indicators					
CT or MRI*	●		◎	●	
Pregnancy test	●				
Safety indicators					
Blood routine	●		◎	●	◎
Urine routine	●		◎	●	◎
Biochemistry	●		◎	●	◎
Coagulation 4-item	●		◎	●	◎
12-lead ECG	●		◎	●	◎
Adverse event assessment		●	●	●	◎
Efficacy indicators					
Modified Rankin	●	●	●	●	

score					
NIHSS score	●	●	●	●	
BI index score	●	●	●	●	
Combined vascular event		●	●	●	
Review					
Review by investigator				●	●
Review by CRA	●	●	●	●	●
Review by sub-center director				●	●

Note: Inclusion/exclusion indicators: CT or MRI*: For patients who have undergone a head CT or MRI examination during the current illness process at the clinical study unit and within 72 h before enrollment, the report or a copy may be attached to the study medical records and re-examination is not required. The centers participating in the radiology subgroup will perform baseline and final follow-up MRI sequence examinations (T1 + T2 + DWI + FLAIR + MRA + T2*). The baseline examination can be completed either before randomization or within 3 days after randomization.

At discharge*: If the patient's hospital stay exceeds 21 days, this follow-up visit will take place on Day 21.

Follow-up visit*: Due to the persistent adverse events or clinically significant laboratory abnormalities or vital sign abnormalities that exist at the end of treatment, the investigator considers it necessary to conduct a follow-up visit to obtain follow-up measurement results. The investigator will conduct follow-up visits based on the specific situation, which may also be done via telephone.

Appendix 2: Modified Rankin Scale (mRS)

Modified Rankin Scale is used to measure the functional recovery of patients after stroke. The scale is divided into six levels, and the formal definition of each level is provided in bold below. Italics give further instructions with a view to reducing possible errors among different observers, but there is no requirement for the architecture of the interview. Note that only symptoms occurring since stroke were considered. Patients were considered to be able to walk independently provided they could walk with the aid of certain auxiliary devices without external assistance.

If two levels seem equally applicable to the patient and further questioning is unlikely to lead to an absolutely correct choice, the higher level should be chosen.

Level 0: completely asymptomatic

Although mild symptoms may occur, the patient has not noticed any new functional limitations and symptoms since stroke.

Level 1: Symptomatic, with no significant disability: Able to perform all routine duties and activities.

Patients have certain symptoms caused by stroke, either physically or cognitively (such as affecting speech, reading, writing; or body movement; or sensation; or vision; or swallowing; or emotion), but can continue to engage in all work, social, and leisure activities they have previously engaged in before the stroke. The key question used to distinguish between level 1 and 2 (see below) can be, “Are there things you used to do regularly, but you can’t do again after stroke?” Activities more frequently than once a month are considered “frequent”.

Level 2: Mild disability: Unable to perform all previous activities but can manage personal affairs without assistance.

Some activities that can be done before stroke (such as driving, dancing, reading, or working) can no longer be performed by people after stroke, but they can take care of themselves daily without assistance. Patients are able to dress, walk, eat, go to the bathroom, prepare simple food, shop, travel locally, etc., without the help of others. Patients do not require supervision in life. It is envisaged that patients at this level can live alone for one week or longer without

the care of others.

Level 3: Moderate disability: Need some assistance, but can walk without assistance.

At this level, the patient can walk independently (with the aid of auxiliary machinery) and be able to dress independently, go to the bathroom, eat, etc., but need the assistance of others for more complex tasks. For example, need others to perform tasks like shopping, cooking, or cleaning, and visit from others more than once a week to ensure that these activities are completed. What needs assistance is not just caring for the body, but giving advice: for example, patients at this level will need supervision or encouragement to deal with finances.

Level 4: Severe disability: Unable to walk without assistance from others and unable to attend to one's own bodily needs.

Patients need help with everyday life, whether it be walking, dressing, going to the bathroom or eating. Patients need to be cared for at least once a day, usually twice or more, or must live close to the caregiver. To distinguish between level 4 and 5 (see below), consider whether patients can routinely live alone for an appropriate amount of time during the day.

Level 5: Severe disability: bedridden, incontinent, requiring constant nursing care and attention.

Although trained care is not required, it requires caring for several times during the day and night.

Completely asymptomatic		0
Symptomatic	Not very severe, no significant disability; able to perform ordinary tasks or activities	1
Mild disability	Lose some capacity, unable to complete all the above actions, but can take care of oneself without assistance from others	2
Moderate disability	Lose most of the capacity, complete many things with assistance from others, but can walk without assistance	3
Moderate to severe disability	Unable to walk or take care of oneself without assistance from others	4
Severe disability	Bedridden, incontinent, requiring constant care and attention from others	5

Appendix 3: Bathel Index (BI) Scale for Activities of Daily Living

The Barthel Index is commonly used to assess functional prognosis, not only in stroke but also in various neurological disorders.

Overview

The Barthel Index has been in use since 1955 in some hospitals in the state of Maryland, USA. It is primarily designed for assessing the ADL capabilities of certain chronic patients. In 1965, American scholars Mahoney and Barthel formally published their work on it. Due to its simplicity, high reliability, sensitivity, and applicability for predicting treatment outcomes, hospitalization duration, and prognosis, the Barthel Index is widely utilized in the field of rehabilitation medicine. The Barthel Index comprises 10 items, examining activities such as eating, bathing, grooming, dressing, bowel function, bladder function, toilet use, chair transfer, walking, and going upstairs. The normal score is 100 points.

The Modified Barthel Index (MBI) is a revised version of the BI, developed by Shah et al. in 1989. There are multiple versions of the MBI, and the one modified by Shah, Vanclay, and Cooper in 1989 is similar to the BI, demonstrating good reliability and validity. The MBI, compared to the BI, provides finer grading of scoring criteria, and better objectivity and accuracy. It is widely used in clinical settings as a primary functional assessment scale.

Management

The Barthel Index examination can be conducted by any healthcare provider. It takes approximately 5 minutes.

Validity

Extensive research has been conducted on the Barthel Index, demonstrating a high level of construct validity. In addition to indicating opportunities for independent living, the scale also reflects the length of hospital stay. The Barthel Index scores obtained from telephone interviews show a high correlation with scores obtained from direct examinations. It also indicates high reliability among assessors.

Advantages/Disadvantages

The advantages include easy application, short examination and evaluation time. The

disadvantages include only being able to assess very basic functions primarily related to movement. Patients with significant cognitive impairment and partial disability may still score 100 on the Barthel Index, indicating a ceiling effect in this scale.

Summary

The Barthel Index is a widely used ADL scale, demonstrating high reliability and construct validity. It is commonly used as a primary endpoint in many clinical treatment trials.

Barthel Index

1. Eating	10 = Independent. Able to use any necessary tools. Able to eat within a reasonable time. 5 = Requires some assistance (e.g., picking up food, serving rice, stirring, cutting food) 0 = Completely dependent on others.
2. Bathing	5 = Can perform without assistance. 0 = Requires assistance from others.
3. Grooming	5 = Can independently wash face, comb hair, brush teeth, and shave (if using an electric shaver, can use a socket). 0 = Requires assistance from others.
4. Dressing	10 = Independent. Tie shoelaces, fasten buttons, use assistive devices. 5 = Requires some assistance, but can complete at least half of the tasks within a reasonable time. 0 = Requires assistance from others.
5. Bowel function	10 = As expected. If necessary, enema or suppository can be applied. 5 = Occasionally unexpected, or can apply enema or suppository with assistance. 0 = Frequent incontinence or unconsciousness.
6. Bladder function	10 = As expected, can self-care and tidy up with tools if necessary. 5 = Occasionally unexpected or can use tools with assistance. 0 = Frequent incontinence or unconsciousness.

7. Use the restroom	10 = Independent in going to the bathroom or using a bedpan, and able to dress/undress or perform personal hygiene independently. 5 = Requires assistance for keeping balance, dressing/undressing, or personal hygiene. 0 = Dependent on others.
8. Chair/bed transfer	15 = Independent, including locking the wheelchair and raising footrests. 10 = Minimal assistance or supervision. 5 = Able to sit but requires maximum assistance for transfers. 0 = Completely unable.
9. Walking	15 = Independently walks 50 meters. May use assistive devices, excluding rolling walkers. 10 = Able to walk up to 50 meters with assistance. 5 = If unable to walk, independently uses a wheelchair to walk 50 meters. 0 = Completely unable, cannot walk independently, even with a wheelchair.
10. Going upstairs	10 = Independent. May use assistive devices. 5 = Requires some assistance (such as support) or supervision. 0 = Unable to complete even with assistance (such as support).

BI measures ten basic activities of daily living for patients, including eating, transferring, independent toileting, bathing, walking, or dressing. Based on the difficulty of each task, grade each item on a scale of 0, 5, 10, 15 points to assess the patient. If the patient is unable to complete an activity, the score for each item will be determined by the actual time and amount of assistance required. If the patient requires assistance, even if it's minimal or just supervision, full points cannot be awarded. When the patient cannot meet the specified criteria, it is recorded as 0 points. If a patient scores the maximum points (100 points), they should be able to control bowel movements, feed themselves, get out of bed or chairs, independently bathe, walk at least 50 meters, and go up and down stairs. However, this only means that he can be alone and does not imply that he can live independently (he may be unable to cook or clean the room).

Assessment Guidelines

·This indicator is used to record what the patient has done, rather than what the patient is able to do.

·Its primary purpose is to determine the level of independence of the patient in situations where there is no assistance, whether verbal or physical, regardless of how minimal or for what reason.

·In each tested item, the patient is considered not independent when supervision is required.

·The patient's performance should be based on the most reliable evidence. Typically derived from the patient's friends, relatives, and nurses, but direct observation and consensus are also crucial.

·Generally, the patient's performance in the preceding 24 to 48 hours is crucial, but occasionally it may also be related to a longer duration (such as last week's bowel movements).

·Unconscious patients should be scored 0, even if there is no urinary and fecal incontinence.

·Intermediate level implies that the patient's effort exceeds 50%.

·If the patient can control urination, an intermediate score implies only occasional urinary incontinence (≤1 episode per 24 h).

·Use of assistive tools (such as a cane) is permitted for independence.

Use Guide

1. Eating: Independent feeding means the patient is able to eat prepared food independently within a reasonable time. The food includes any regular diet (not just soft food), and it can be prepared or served by others. If the patient can independently handle tasks such as picking up food, serving rice, stirring, cutting food, a score of 10 is given. If some assistance is needed for tasks like picking up foods, serving rice, stirring, cutting food, a score of 5 is given; otherwise, a score of 0 is given.

2. Bathing: If the patient can enter and exit the bathroom without guidance, supervision, or assistance, wash independently, and shower without assistance or supervision, a score of 5 is given; otherwise, a score of 0 is given.

3. Grooming: Within the last 24 to 48 hours, the patient can independently complete personal hygiene activities such as washing face, combing hair, brushing teeth, and shaving. If caregivers help squeeze toothpaste and prepare water, a score of 5 is given; otherwise, a score of 0 is given.

4. Dressing: If the patient can independently put on and take off various clothes, shoes, etc.,

including the ability to fasten buttons, zip, and put on shoes, a total score of 10 is given. If the patient performs complex tasks such as fastening buttons, tying shoelaces, and zipping with assistance, but can independently perform simple functions such as putting on outerwear and shoes, a score of 5 is given; otherwise, a score of 0 is given.

5. Bowel control: Refers to the situation over one week. Full control is scored 10 points. Occasional incontinence (less than or equal to once per week) is scored 5 points. Incontinence more than once per week or in cases of unconsciousness is scored 0 points.

6. Bladder control: Refers to the situation within the last 24 to 48 hours. Full control is scored 10 points. Occasional incontinence (less than or equal to once every 24 h, more than once per week) is scored 5 points. Frequent incontinence (more than once every 24 h) is scored 0 points. Categorizing urinary incontinence in catheterized patients.

7. Toileting: If the patient is able to independently enter and exit the bathroom or use a commode, without the need for assistance in dressing or hygiene, a score of 10 is given. If assistance is needed for some aspects of these activities, a score of 5 is given. If assistance is required for major functions such as dressing and hygiene, a score of 0 is given.

8. Chair/bed transfer: The patient can independently and safely move from the bed to the chair and back, a score of 15 is given. If one person is needed to assist or provide verbal guidance for safety, a score of 10 is given. If assistance from two persons or one strong and skilled person is required, a score of 5 is given. If the patient cannot sit up or requires assistance from two or more persons, a score of 0 is given.

9. Walking on level surface: If the patient can move independently within the home, ward, or hospital premises using assistive tools (including canes, excluding rolling walking aids such as wheelchairs), and can walk without supervision or caregiving for 50 meters, a score of 15 is given. If assistance is needed from an untrained person (physical or verbal guidance), including under supervision and caregiving, and the patient can walk 50 meters, a score of 10 is given. If the patient can independently move using a wheelchair and walk 50 meters, a score of 5 is given. If the patient cannot accomplish this, a score of 0 is given.

10. Stair climbing: The patient can independently go up and down stairs, including the use of assistive devices (such as a cane), a score of 10 is given. If the patient can go up and down stairs

with partial assistance from others (such as support) or under supervision, a score of 5 is given; otherwise, a score of 0 is given.

Appendix 4: National Institutes of Health Stroke Scale (NIHSS)

Investigators at the University of Cincinnati Stroke Center developed the NIHSS by quantifying the neurological functional status of stroke patients.

Overview

Comparisons between the baseline assessment and the assessment at 3-month follow-up of acute stroke patients should be conducted by the same assessor.

Instructions for use: Assessments must be conducted by investigators holding a NIHSS usage certificate.

The examination should be conducted in the order of items on the scale. Record the results after completing each item and avoid revisiting previous items to change scores. Follow the guidelines for each examination. The score should reflect what the patient has done, not what the clinician believes the patient can do. The doctor should examine and record simultaneously for a rapid assessment. Do not instruct the patient on how to do, meaning not allowing the patient to repeat your instructions, thereby showing improvement with each repetition, and affecting the accuracy of the score.

For all examination items, except for the “Language Function” sub-item, record the patient’s initial response. Even if subsequent responses may be better, they should not be used;

In item 7 “Ataxia”, “one limb” refers to either an upper limb or lower limb, meaning each patient has four limbs, not just two on one side. For instance, if a patient exhibits limb ataxia on the right side, the patient should be scored 2 points for having ataxia in two limbs, not 1 point. This is a common misunderstanding in clinical trials in China.

In item 11 “Neglect”, clinicians in China often overlook this aspect. The neglect test primarily assesses spatial visual neglect and tactile neglect. Visual neglect can be examined simultaneously with the “Visual Fields” item. If the patient has a severe visual field deficit that hinders visual signal stimulation on both sides, proceed to examine the condition of skin tactile neglect. If it is normal, it is recorded as normal. If the patient is aphasic but can attend to both sides, it is considered normal.

For items that cannot be assessed, please record the score as the pre-defined value, commonly

set internationally as “UN” or “9”. However, in computer statistical processing, treat “UN” or “9” as the default value.

● Give the score as per table and record the results. Do not change the score, which reflects the actual situation of the patient, rather than what the doctor believes the patient should be. Quickly check and record the results. Do not train the patient unless you have the necessary instructions (e.g., repeatedly asking the patient to make some kind of effort).

● If some items are not assessed, they should be specified in the table.

Text explanation 1a Level of consciousness: The investigator selects an answer and gives a score, even if there are difficulties such as endotracheal intubation, language disorders, tracheal trauma, or bandaging. If the patient shows no response (or reflex activity) to strong external stimuli, a score of 3 is given.	Scoring criteria: 0—Conscious, able to respond quickly 1—Partially conscious, can obey, answer, and respond appropriately to mild stimuli 2—Not conscious, requires repeated stimuli to elicit a response or slow response. Requires strong or painful stimuli to elicit a response (not reflexive) 3—Only reflexive movements or vegetative effects or complete unresponsiveness, flaccid paralysis, no reflexes
1b Level of consciousness questioning: Requires the patient to answer the current month and their age. The answer must be correct—partial scoring based on approximation is not allowed. Individuals who cannot comprehend the question due to aphasia or unconsciousness are scored 2 points. Patients with severe dysarthria, language disorders, or an inability to speak due to reasons such as tracheal intubation or tracheotomy, or any other cause not secondary to, are scored 1 point. It is crucial to note that scoring is based solely on the initial response, and the examiner must not provide additional	Scoring criteria: 0—Correct responses to both questions 1—Correct response to a question 2—Incorrect responses to both questions.

linguistic or non-linguistic cues.	
1c Level of consciousness command: Instruct the patient to open and close their eyes, and then to grip and release with the unaffected hand. If hand cannot be used, replace it with an alternative command. If the patient has a clear intention to fulfill the request but is unable to do so due to physical weakness, the assessment should reflect this. If the patient does not respond to these requests, the examiner should demonstrate the tasks to them (using gestures), and then score based on the results (e.g., completing 0, one, or both commands). Patients with trauma, recent limb surgery, or other physical impairments should be given a single appropriate command. Draw the corresponding answer based on their initial response.	Scoring criteria: 0—Responsive to both commands 1—Responsive to one command 2—Non-responsive to both commands
2. Gaze: Test only horizontal eye movement function. Score voluntary or reflexive (oculocephalogyric reflex) eye movements, but there is no need for caloric test. If the patient can overcome binocular gaze with voluntary or conditioned reflexes, score 1 point. If the patient has peripheral nerve paralysis (cranial nerves III, IV, VI), still score 1 point. The gaze test is applicable to all aphasic patients. For patients who have undergone ophthalmic surgery, are bandaged, are already blind, or have visual field impairments for various reasons, the examiner should conduct a gaze test through conditioned eye reflex. For example, instruct the patient to fix their gaze on an object and then have them walk from one side to the other, which may reveal partial gaze palsy in the patient.	Scoring criteria: 0—Normal 1—Partial gaze palsy, impaired gaze function in one or both eyes, but not complete paralysis of all gaze abilities 2—Compulsive strabismus or complete gaze palsy that cannot be overcome by oculocephalogyric reflex
3. Visual field: The testing of visual fields (upper and lower quadrants)	Scoring criteria:

involves the examiner having the patient judge the number of fingers or an appropriate object in front of them to assess their visual capacity. If the patient can perceive the direction of moving fingers, it can be considered normal. If one eye is blind, or if one eyeball has been removed, the visual field test should be performed on the other eye. Visual field asymmetry or quadrant blindness is scored 1 point. Bilateral blindness, regardless of the cause, is scored 3 points. Patients with loss of light sensitivity should answer question 11.	0—Normal visual field, no hemianopia 1—Partial hemianopsia 2—Complete hemianopia 3—Bilateral hemianopia (including cortical blindness).
4. Facial paralysis: The examiner gives verbal commands or gestures, asking the patient to show teeth, frown, or close their eyes. For patients with poor response or lack of comprehension, judgment is made based on whether facial expressions produced under stimulation are symmetrical. If there is facial injury, bandaging, a tracheal strap, or other physical disorders hindering facial expressions, they should be moved aside as much as possible.	0—Able to make facial expressions normally 1—Slight paralysis (nasolabial fold becomes shallow, asymmetry on both sides when smiling) 2—Partial paralysis (lower half of the face completely or nearly completely paralyzed) 3—One or both sides of the face completely paralyzed (no facial expressions can be made on the upper and lower face)
5 & 6. Upper and lower limb motor function: Place the four limbs in the appropriate position, extending the arms (palms down) at a 90 degree angle from the body (if sitting) or at a 45-degree angle (if lying down), and extending the legs at a 30 degree angle from the body (if lying diagonally). If the arms can be held for more than 10 seconds and the legs for more than 5 seconds, a judgment can be made based on this condition. For aphasic patients without other stimuli, encouragement through language or gestures can be used to help them complete the movement of the arms and legs. Begin by testing the non-paralyzed arm, and then alternate with the other limbs. If the patient has an amputation or	0—The arms remain at 90 degree or 45 degree without movement for 10 seconds 1—Shaking observed; although the arm could be maintained at 90 degree or 45 degree, there is some shaking before the full 10 seconds, and it does not fall to the bed or other support. 2—Although able to lift the arm against gravity, it cannot be maintained at 90 degree or 45 degree and quickly fall back to the bed 3—Arm is unable to lift against gravity

joint fusion at the shoulder or hip joint, it should be recorded as unable to test (marked as UN or a predetermined value such as "9"), and the reason should be specified.	4—No response Unable to test (marked as UN or a predetermined value such as "9") = Amputee or individuals with joint fusion at the shoulder or hip joint
5a: Left arm 5b: Right arm 6a: Left leg 6b: Right leg	0—The leg can be maintained at 30 degree without shaking for 5 seconds 1—Shaking observed; the leg can be maintained at 30 degree, but it moves downward before reaching 5 seconds, without falling to the bed or other support 2—The patient has strength to lift the leg but cannot maintain it at 30 degree, and when putting down, seek support from the bed or another surface 3—The patient has no strength to lift the leg; the leg immediately falls onto the bed 4—No response UN or "9" = Amputee or individuals with joint fusion at the shoulder or hip joint
7. Ataxia: This item tests the degree of impairment in unilateral cerebellar function. During the test, keep both eyes open. If there is visual impairment, ensure testing is done within the intact visual field. Perform the finger-to-nose test and heel-knee-tibia test on both sides. Unless the arm is extremely weak during testing, assess for ataxia in all other cases. If the patient cannot comprehend or has limb paralysis, record as 0 points. If the patient is an amputee or has joint fusion, it should be recorded as untestable, with the reason	Scoring criteria: 0—No ataxia 1—Ataxia on one side of the body 2—Ataxia on both sides of the body Cannot be tested = Amputation or joint fusion

specified. Testing blind patients involves lightly touching their nose with a finger to determine if there is any ataxia.	
8. Sensation: Inspect for the sensation and painful expression caused by needle pricks; observe for avoidance of noxious stimuli in comatose or aphasic patients (muscle contraction). If there is no sensation, it is pathological; only sensory loss caused by stroke is considered abnormal. To accurately assess complete sensory loss throughout the body, it is important to involve as many body regions as possible. The examiner should accurately test certain areas of the patient's body, such as the arms (not just the hands), legs, trunk, and face, to determine whether there is a loss of sensory function on one side of the body. "Severe or complete sensory loss" refers to patients with significantly impaired or completely lost sensory function, scored 2 points; comatose or aphasic patients may also be scored 1 or 0 points; brainstem stroke patients with bilateral limb sensory loss are scored 2 points; if the patient shows no response at all or has quadriplegia, a score of 2 is given; comatose patients (scored 3 points in 1a) should be scored 2 points.	Scoring criteria: 0—Normal; No sensory loss 1—Mild to moderate sensory loss; the patient has a delayed response to needle pricking or lacks pain sensation on the affected side, and only being aware that the body is being touched (has tactile sensation) 2—Severe or complete sensory loss; when pricked with a needle on the patient's face, arm, and leg, the patient feels no sensation
9. Language expression ability: During the testing process, brief greetings can provide information about the patient's language expression ability and condition. The patient is asked to describe what is happening in the picture, give a name to the picture, and read any text present in the picture. The patient's comprehension and language expression abilities can be assessed based on their performance in executing the test commands. If visual issues hinder the test, the patient is asked to distinguish objects placed in their hands through touch. Repeat	Scoring criteria: 0—No Aphasia: Normal 1—Mild or moderate aphasia: Fluent language expression and comprehension with minor thought and grammatical errors. However, due to reduced comprehension and/or language expression ability, it is difficult or impossible to engage in a conversation based on provided materials. Nevertheless, through discussion with

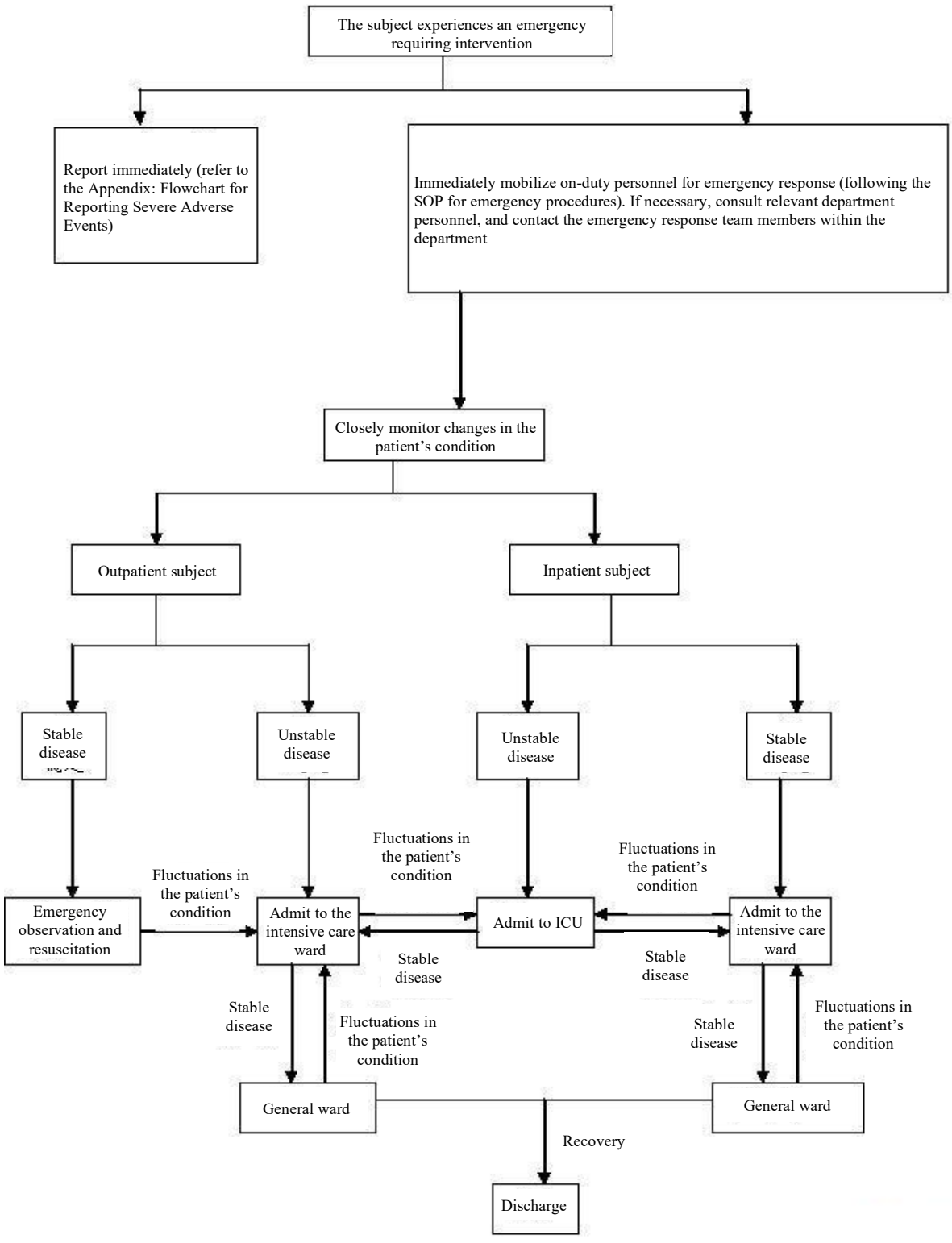
the process multiple times and instruct the patient to verbalize their findings. For patients with tracheal intubation, instruct them to write down the corresponding information. For patients in a coma (as indicated in 1a = 3), record the answer as 3. For patients in a drowsy state or with limited cooperation, the examiner should choose an appropriate score for the patient. However, a score of 3 should only be assigned for patients who cannot speak and cannot execute any commands.	the patient about a particular object, the examiner can infer the specific picture or card the patient is referring to from their responses. 2—Severe aphasia: All expressions consist of disjointed words or phrases. Listeners must exert considerable effort to understand, inquire, and guess. The scope of communication between the patient and others is very limited and challenging. It places a significant burden on listeners, and the examiner cannot discern the specific object the patient is referring to from their responses. 3—Aphasia: Unable to speak or completely aphonic, with no language or auditory, speaking, or comprehension abilities.
10. Dysarthria: If a patient is able to repeatedly read a specified sentence, they should be considered as having normal speech expression. In cases of severe aphasia, judgment can be made by assessing the patient's unconscious articulation of syllables. If the patient has tracheal intubation or other physical disorders that impede pronunciation, score UN or "9". The examiner must clearly explain why no score is given. Do not tell the patient why they are being tested.	Scoring criteria: 0—Normal 1—Mild to moderate: The patient speaks indistinctly and can articulate some sentences or words intermittently. Although there is some difficulty, the meaning expressed can be generally understood. 2—Severe: The patient's speech is so unclear that it cannot be understood, but there is no aphasia or the aphasia is disproportionate, or there is aphonia. UN or "9" = Intubation or caused by physical

	disorders.
11. Resolution and inattention (neglect): The information about neglect has been adequately obtained in the above examinations. If the patient has severe visual impairment to the extent that simultaneous visual stimulation on both sides is not possible, and skin stimulation is normal, it is recorded as normal. If there is aphasia but definite attention to both sides, it is recorded as normal. Spatial neglect or anosognosia can also be considered as evidence. Because only abnormalities are recorded, this item must be measurable.	0—Normal 1—Vision, touch, hearing, and spatial stimuli: Able to recognize one of these sensory stimuli when two are presented simultaneously. 2—Almost no sensation when stimulated, with no recognition of one's own hands and spatial orientation

Chinese-adapted words and sentences for assessing speech disorders and dysarthria:

Please read the following sentences:	Please read the following words:
Know	Mom
Go down stairs	Earth
Go home and cook	Airplane, airplane
Review at school	Silk
Deliver an impressive speech	Start work on time
	Eat grapes without spitting out the grape skin

Appendix 5: Flowchart for Emergency Response to Severe Adverse Events



Appendix 6. Overview of the Radiology Subgroup Study

The Radiology Subgroup Study involves conducting baseline and endpoint head MRI examinations on the patients enrolled in this study.

Study objective

The primary objective of this study is to collect patients' radiological data, objectively assess the efficacy of the drug, assist in diagnosis and treatment, and determine endpoint events.

Study time point

The study is divided into two time points: baseline MRI examination and endpoint examination.

Baseline examination (prior to randomization)

Prior to randomization, screen acute stroke patients (within 72 h after onset).

Exclude lesions such as cerebral hemorrhage, vascular malformation, tumor, and abscess.

Endpoint examination (Day 90 of randomized treatment)

Compare with the baseline examination and observe the continuous changes in the radiological presentation of patients.

Identify new infarctions or hemorrhagic lesions (primary endpoints).

Identify other changes (such as alterations in large cerebral vessels).

Examination equipment requirements

Above 1.5 T

Equipped with echo planar imaging for conducting DWI.

Capable of performing T2*GRE sequence scans.

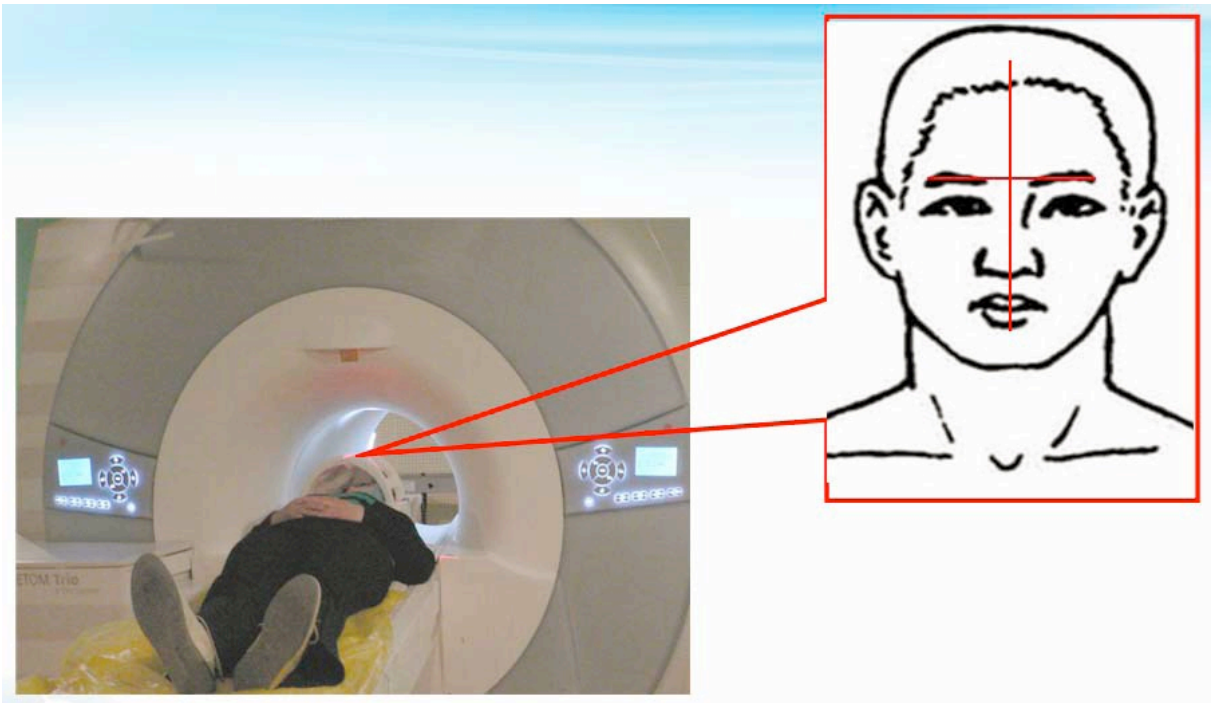
Capable of ensuring the use of the same equipment for both baseline imaging examinations and imaging examinations at the 90 day follow-up.

Examination requirements

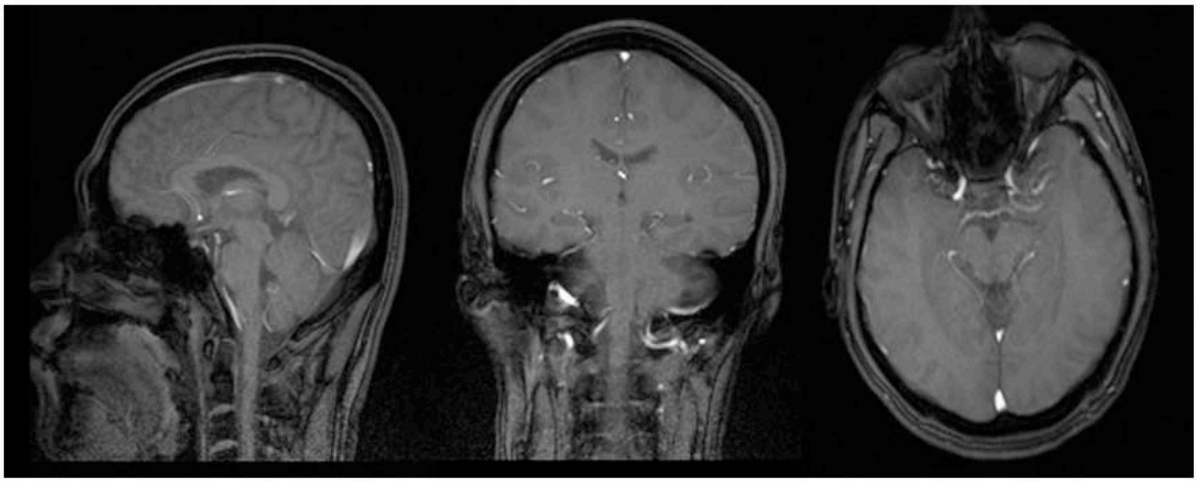
The patient's position and orientation should strictly adhere to the requirements outlined in this manual.

Endpoint examinations should ensure consistency in cross-sectional scanning planes and slice thickness with baseline examinations.

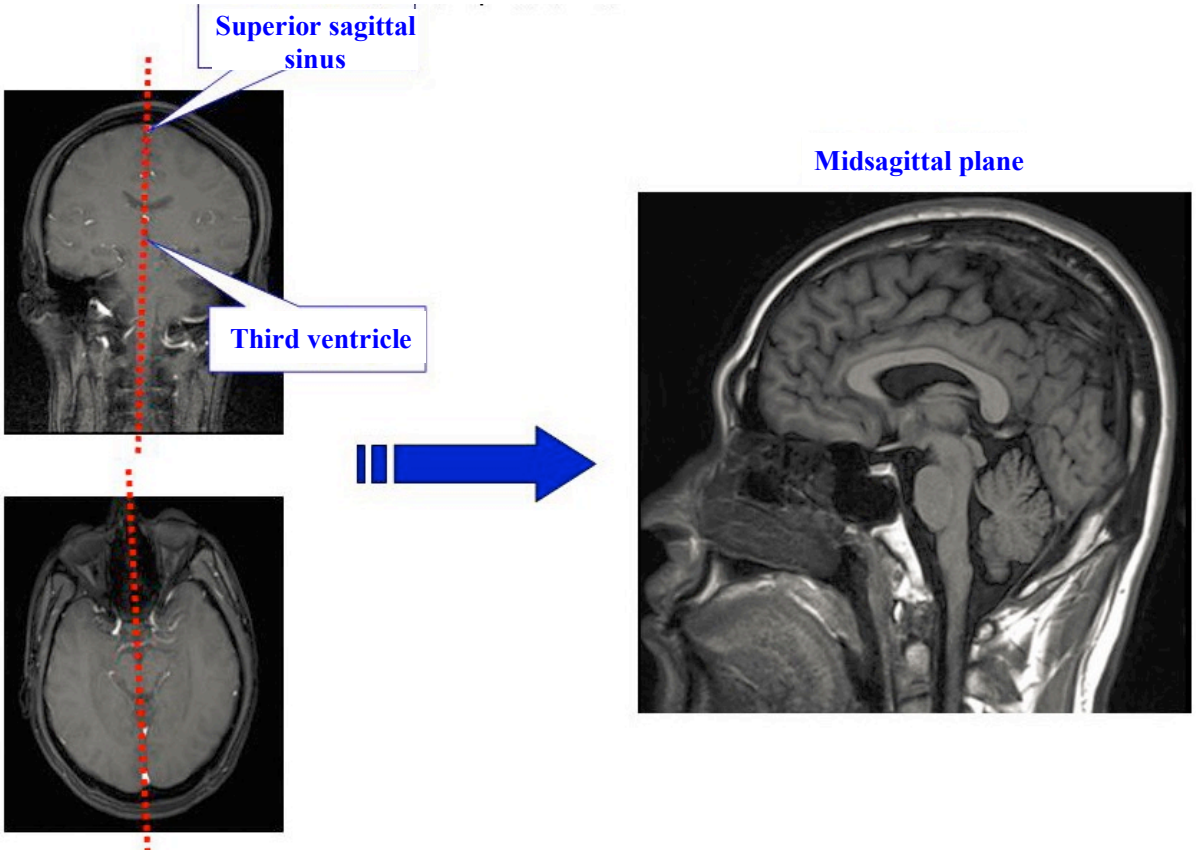
1. Patient positioning requirements: The horizontal line passes through both eyebrows, and the vertical line passes through the midline of the nose. As shown in the figure below.



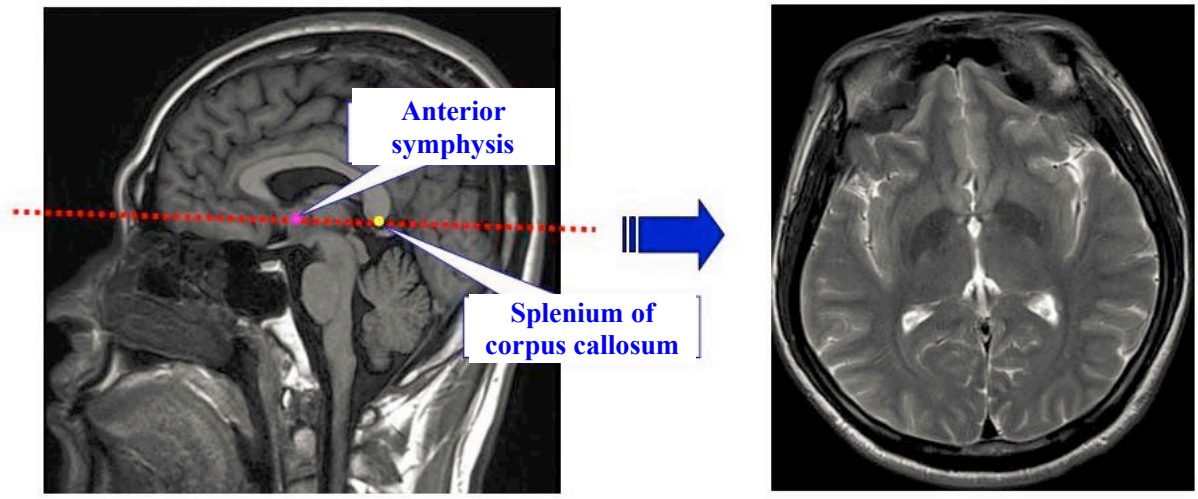
2. Three-axis orientation: As shown in the figure below.



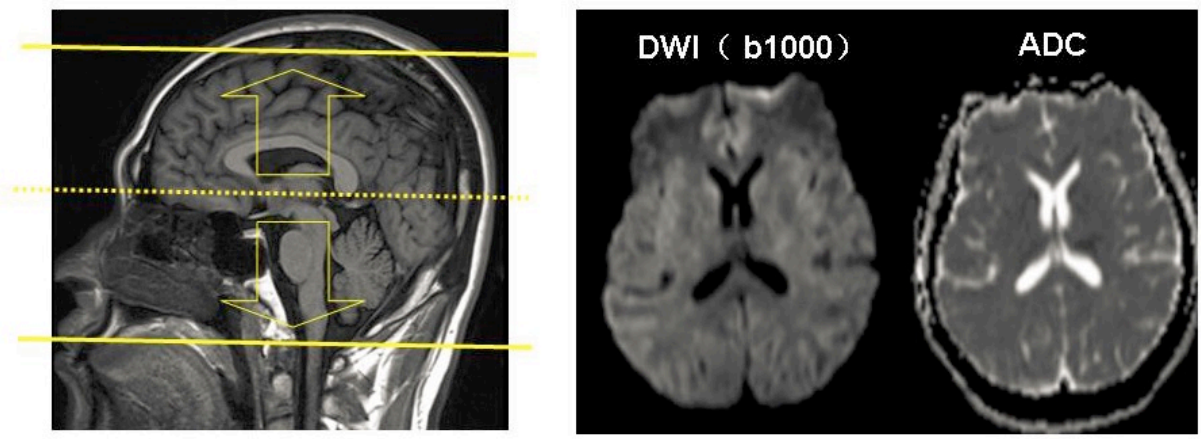
3. Coronal T1WI: As shown in the figure below.



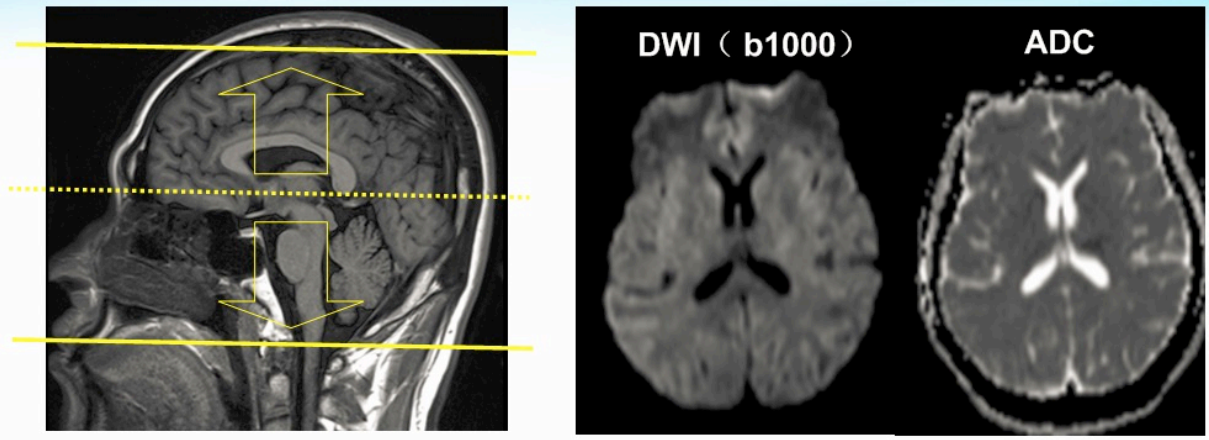
4. Cross-sectional orientation: As shown in the figure below.



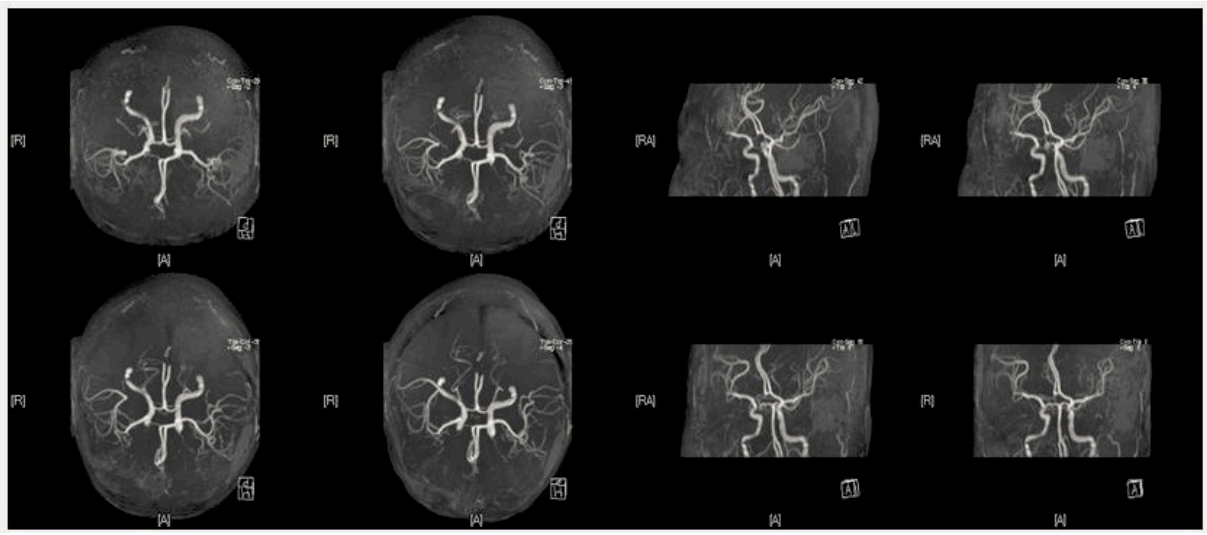
5. Cross-sectional DWI: The scanning range covers the entire brain, and scans with b-values of 0 and 1,000 should be performed separately. The slice thickness is 5 mm, with an interslice gap of 30% (i.e., 1.5 mm).



6. Cross-sectional T2WI + FLAIR + T2*GRE: The scanning range, orientation lines, slice thickness, gap, and center for each cross-sectional scan should be consistent with those for DWI scans.



7. MRA: Utilizing the Time-of-Flight (TOF) technique, scan the entire brain. Image post-processing: MIP reconstruction, left-right and top-bottom rotation, with a reconstruction angle of 12 degree. As shown in the figure below



8. Collection of radiological data

The collected radiological images are saved in DICOM format, and the digitized images are stored on rewritable magneto-optical disks provided by the project team. Periodically, the

collected disks are sent to the Central Imaging Evaluation Laboratory based on the specific circumstances of each center.

Appendix 7: Guidelines for the Diagnosis and Treatment of Acute Ischemic Cerebrovascular Disease in China 2010

Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke in China 2010

Acute ischemic stroke (cerebral infarction) is the most common type of stroke, accounting for 60% to 80% of all strokes. The time division for its acute phase is not yet unified, generally referring to the first two weeks after onset. The management of acute ischemic stroke should emphasize early diagnosis, early treatment, early rehabilitation, and early prevention of recurrence. The Chinese Stroke Society initiated the compilation of the Chinese Guidelines for the Prevention and Treatment of Cerebrovascular Diseases at the end of 2002. In early 2005, it was officially approved by the Ministry of Health for nationwide promotion. In early 2007, the People's Medical Publishing House formally published the first edition of the Chinese Guidelines for the Prevention and Treatment of Cerebrovascular Diseases. It played a positive role in standardizing the diagnosis and treatment of cerebrovascular diseases in China. Due to the continuous publication of new study evidence in recent years, the first edition of the guidelines has also received multiple suggestions for improvement during its usage. Therefore, the Chinese Society of Neurology entrusted the Chinese Stroke Society to revise the first edition of the guidelines. For clinical convenience, this edition of the guidelines includes the entire diagnostic and treatment process for acute ischemic stroke after onset. The writing group, after reviewing relevant study evidence, soliciting opinions from various sources, and engaging in thorough discussions to reach a consensus, has formulated recommendations, with the aim to assist clinicians in choosing the currently more favorable diagnostic and treatment strategies for stroke patients. In clinical practice, physicians should tailor individualized treatments based on the principles of these guidelines, new developments, and specific conditions of the patients.

I. Revision Principles

1. Guided by the principles of evidence-based medicine, the revision is made by referencing international standards, and considering national conditions, feasibility, the experience of using the first edition, and new study evidence. The strength of recommendation and evidence grade are based on international guidelines and common standards, taking into account national conditions and practicality.

2. For each treatment measure or clinical issue, a summary and analysis of current study evidence (literature search up to November 2009) are conducted first. Recommendations are then provided based on the evidence grade and consensus.

3. Recommendations are based on the most reliable evidence whenever possible (such as Grade A evidence). In the absence of high-level evidence, the best available evidence is considered, and consensus is reached through thorough discussion.

4. For commonly used therapies in China, guided by the principles of evidence-based medicine, consensus is reached by fully considering national conditions and experience. Attention is paid to balancing efficacy, risks, cost, and ease of use, among other factors.

II. Standards for Strength of Recommendations and Evidence Grade (including therapeutic and diagnostic measures)

1. Strength of recommendation (divided into 4 levels, with Level I being the strongest and Level IV being the weakest): Level I: Based on Grade A evidence or expert consensus with high consistency; Level II: Based on Grade B evidence and expert consensus; Level III: Based on Grade C evidence and expert consensus; Level IV: Based on Grade D evidence and expert consensus.

2. Evidence grade for therapeutic measures (divided into 4 grades, with Grade A being the highest and Grade D being the lowest): Grade A: Meta-analysis or systematic review of multiple randomized controlled trials (RCTs); multiple RCTs or one RCT with sufficient sample size (high quality); Grade B: At least one high-quality RCT; Grade C: Non-randomized but well-designed controlled trials, or well-designed cohort studies or case-control studies; Grade D: Series case analysis without concurrent control or expert opinion.

3. Evidence grade for diagnostic measures (divided into 4 grades, with Grade A being the highest and Grade D being the lowest): Grade A: Multiple prospective cohort studies or one prospective cohort study with sufficient sample size, utilizing reference (gold) standards, and blinded assessment (high quality); Grade B: At least one prospective cohort study or well-designed retrospective case-control study, utilizing gold standards and blinded assessment (higher quality); Grade C: Retrospective, non-blinded controlled studies; Grade D: Series case analysis without concurrent control or expert opinion.

I Pre-hospital Management

The key to pre-hospital management is to promptly identify suspected stroke patients and transport them to the hospital as quickly as possible.

i. Pre-hospital Identification of Stroke

If a patient suddenly experiences the following symptoms, the possibility of a stroke should be considered: ① Weakness or numbness in one side of the body (with or without facial

involvement); ② Numbness on one side of the face or distortion of commissure; ③ Slurred speech or difficulty understanding language; ④ Gaze deviation of both eyes to one side; ⑤ Loss or blurred vision in one or both eyes; ⑥ Dizziness with vomiting; ⑦ Unusual and severe headache with vomiting; ⑧ Impaired consciousness or seizures.

ii. On-site Management and Transportation

On-site emergency personnel should promptly conduct a brief assessment and necessary first aid, including: ① Managing airway, breathing, and circulation issues; ② Monitoring the heart; ③ Establishing intravenous access; ④ Administering oxygen; ⑤ Assessing for hypoglycemia.

Avoid: ① Administering sugar-containing fluids to non-hypoglycemic patients; ② Excessively lowering blood pressure; ③ Large-volume intravenous infusions.

Quickly obtain a brief medical history, including: ① Time of symptom onset; ② Recent medical history; ③ Past medical history; ④ Recent medication history.

Patients should be promptly transported to the nearest qualified hospital (with the capability of 24 h emergency CT scans).

Recommendation: For patients who suddenly experience the above symptoms and are suspected of having a stroke, a brief assessment and emergency treatment should be conducted, and they should be promptly transported to the nearest qualified hospital (Level I recommendation).

II. Emergency Room Diagnosis and Treatment

Due to the narrow treatment window for acute ischemic stroke, timely assessment of the condition and diagnosis are crucial. Hospitals should establish a rapid pathway for the diagnosis and treatment of strokes, prioritizing the handling and admission of stroke patients whenever possible.

i. Diagnosis

1. Medical history collection and physical examination: Conduct medical history collection and physical examination as soon as possible (see relevant content in Section IV).

2. Diagnostic and assessment steps: (1) Is it a stroke? Pay attention to the presentation form and onset time. Exclude brain lesions caused by conditions such as head trauma, poisoning, postictal state, tumor-related stroke, hypertensive encephalopathy, abnormal blood glucose, encephalitis, and severe dysfunction of vital organs. Conduct necessary laboratory tests (see relevant content in Section IV). (2) Is it an ischemic or hemorrhagic stroke? Unless there are special reasons preventing the examination, all suspected stroke cases should undergo prompt neuroimaging (CT or MRI) to rule out hemorrhagic stroke and establish the diagnosis of

ischemic stroke. (3) Is the patient suitable for thrombolytic therapy? Is the onset time within 4.5 or 6 h? Are there indications for thrombolysis? (See relevant content in Section IV).

ii. Management

Close monitoring of basic life functions such as airway and breathing; cardiac monitoring and treatment of cardiac abnormalities; blood pressure and temperature regulation. Emergent situations that require immediate attention: Increased intracranial pressure, severe blood pressure abnormalities, abnormal blood glucose and temperature, seizures, etc. (see relevant content in Section IV).

Recommendation: Perform a rapid diagnosis of suspected stroke patients according to the above diagnostic steps. Complete assessments such as brain CT within 60 min of arriving at the emergency room if possible and make treatment decisions promptly (Level I recommendation).

iii. Stroke Unit

A stroke unit is an organized medical management model for stroke inpatients, combining various independent methods of traditional stroke treatment such as drug therapy, physical rehabilitation, speech training, psychological rehabilitation, and health education into a comprehensive treatment system. A Cochrane systematic review (including 23 trials, 4,911 patients) has confirmed that stroke units significantly reduce the mortality and disability rates of stroke patients.

Recommendation: Hospitals admitting stroke patients should establish stroke units whenever possible. All acute ischemic stroke patients should be admitted to stroke units as early as possible (Level I recommendation, Grade A evidence) or neurology wards (Level II recommendation) for treatment.

IV Diagnosis and Treatment in the Acute Phase

i. Assessment and Diagnosis

Assessment and diagnosis of stroke include: medical history and physical examination, imaging tests, laboratory tests, disease diagnosis, and etiological classification.

(i) Medical History and Physical Examination

1. Medical history collection: Inquiring about the time of symptom onset is crucial. Other information includes the characteristics and progression of neurological symptoms, cardiovascular risk factors, medication history, drug abuse, migraines, seizures, infections, trauma, and pregnancy history.

2. General physical examination and neurological examination: After assessing airway, breathing, and circulation functions, proceed immediately with a general physical examination and neurological examination.

3. Stroke scales can be used to assess the severity of the condition. The commonly used scales include: (1) Chinese Stroke Patient Clinical Neurological Deficit Severity Scale (1995). (2) National Institutes of Health Stroke Scale (NIHSS), the most widely used scale internationally. (3) Scandinavian Stroke Scale (SSS).

(ii) Examination of Brain Lesions and Vascular Lesions

1. Brain lesion examination: (1) Plain CT scan: Emergency plain CT scan can accurately identify the majority of intracranial hemorrhages and help differentiate non-vascular lesions (such as brain tumors). It is the preferred imaging method for patients suspected of having a stroke. (2) Multi-modal CT: Perfusion CT can differentiate reversible from irreversible ischemia, thus identifying the ischemic penumbra. However, its role in guiding the treatment of acute cerebral infarction is not yet certain. (3) Standard MRI (T1-weighted, T2-weighted, and proton density) is significantly superior to plain CT in identifying acute small infarcts and posterior fossa infarcts. It can identify subclinical infarcts, does not involve ionizing radiation, and does not require contrast agents containing iodine. However, it has limitations, including higher cost, longer examination time, and contraindications in patients (with cardiac pacemakers, metal implants, or claustrophobia). (4) Multi-modal MRI includes Diffusion-Weighted Imaging (DWI), Perfusion-Weighted Imaging (PWI), Fluid-Attenuated Inversion Recovery (FLAIR), and Gradient Recalled Echo (GRE) imaging. DWI can detect ischemic lesions within minutes of symptom onset and can early determine the size, location, and time of the infarct. It is more sensitive for early detection of small infarcts compared to standard MRI. PWI can display the cerebral hemodynamic status. The mismatch between diffusion and perfusion (PWI showing a low perfusion area without a corresponding diffusion abnormality of the same size) suggests the possible presence of ischemic penumbra. However, the current evidence for routine use in selecting thrombolytic therapy patients is not yet sufficient. The gradient echo sequence can reveal asymptomatic microhemorrhage that CT cannot indicate, but the significance for thrombolytic or antithrombotic therapy is not yet clear.

2. Vascular lesion examination: Intracranial and extracranial vascular lesion examination helps to understand the pathogenesis and etiology of stroke, guiding the selection of treatment strategies. Commonly used examinations include carotid duplex ultrasonography, transcranial Doppler (TCD), magnetic resonance angiography (MRA), CT angiography (CTA), and digital subtraction angiography (DSA).

Carotid duplex ultrasonography is helpful in detecting extracranial carotid vascular lesions, especially stenosis and plaques. Transcranial Doppler (TCD) can examine intracranial blood flow and microemboli, and monitor treatment effects, but its performance is significantly influenced by the operator’s technical proficiency and the presence of bone windows.

MRA and CTA can provide information about vascular occlusion or stenosis. With DSA as the reference standard, the sensitivity and specificity of MRA for detecting stenosis in the vertebral and extracranial arteries are 70% to 100%. MRA can demonstrate proximal occlusion or stenosis in large intracranial vessels, but it may have limitations in displaying distal or branching vessels clearly.

DSA has the highest accuracy and remains the gold standard for vascular lesion examination, but its main drawbacks include invasiveness and certain risks.

(iii) Laboratory and Imaging Examination Selection

For suspected stroke patients, routine laboratory tests should be conducted to exclude stroke mimics or other etiologies.

Tests that should be conducted for all patients include: ① Plain brain CT or MRI; ② Blood glucose, blood lipid, liver and kidney function, and electrolytes; ③ Electrocardiogram and cardiac ischemia markers; ④ Complete blood count, including platelet count; ⑤ Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT); ⑥ Oxygen saturation; ⑦ Chest X-ray.

Tests that may be considered for some patients when necessary include: ① Toxicology screening; ② Blood alcohol levels; ③ Pregnancy test; ④ Arterial blood gas analysis (if hypoxia is suspected); ⑤ Lumbar puncture (suspected subarachnoid hemorrhage not visible on CT or suspicion of stroke secondary to infectious disease); ⑥ Electroencephalogram (suspected seizure).

(iv) Diagnosis

The diagnosis of acute ischemic stroke can be based on: (1) Acute onset of symptoms; (2) Focal neurological deficits, with a minority presenting with global neurological deficits; (3) Symptoms and signs lasting for several hours or longer (for thrombolysis, patients should meet specific criteria); (4) Brain CT or MRI ruling out hemorrhage and other lesions; (5) Brain CT or MRI revealing responsible infarct lesions.

(v) Etiological Classification

Classifying the etiology of acute ischemic stroke in patients helps determine prognosis, guide treatment, and select secondary prevention measures. The widely used TOAST classification system internationally categorizes ischemic stroke into five types: large-artery atherosclerosis, cardioembolic, small-vessel occlusion, other determined etiology, and undetermined etiology.

(vi) Diagnostic Process

Diagnostic process for acute ischemic stroke should include the following 5 steps: (1) Is it a stroke? Exclude non-vascular diseases. (2) Is it an ischemic stroke? Perform a brain CT or

MRI scan to rule out hemorrhagic stroke. (3) Severity of stroke? Assess based on the neurological deficit scale. (4) Is thrombolytic therapy possible? Verify indications and contraindications (refer to relevant information on thrombolysis). (5) Etiologic classification? Refer to the TOAST criteria and determine the etiology based on medical history, laboratory results, brain lesions, and vascular lesions.

Recommendation: (1) Head CT or MRI scan is recommended for all suspected stroke patients (Level I recommendation). (2) Prior to thrombolytic and other treatments, a head CT scan is recommended (Level I recommendation). (3) The aforementioned hematological, coagulation, and biochemical tests are recommended (Level I recommendation). (4) All stroke patients should undergo ECG examination (Level I recommendation). (5) Assess the severity of the condition using the neurological deficit scale (Level II recommendation). (6) Vascular lesion examination is recommended (Level II recommendation), but not overly emphasized within the first 6 h after symptom onset. (7) Follow the diagnostic process outlined in the above guidelines (Level I recommendation).

ii. General Management

Currently, there is limited high-grade study evidence on general management; consensus recommendations are as follows.

(i) Oxygen Therapy and Respiratory Support

(1) Patients with concomitant hypoxemia (oxygen saturation below 92% or arterial blood gas indicating hypoxia) should receive oxygen therapy. Those with severe airway obstruction should receive airway support (endotracheal intubation or tracheostomy) and assisted ventilation. (2) Patients without hypoxemia do not require routine oxygen therapy.

(ii) Cardiac Monitoring and Management of Cardiac Abnormalities

Routine ECG should be performed within 24 h after ischemic stroke. Cardiac monitoring may be necessary to detect cardiac abnormalities early for appropriate management. Avoid or use drugs that increase the burden on the heart with caution.

(iii) Temperature Control

(1) Patients with elevated body temperature should have the cause of fever identified. If there is an infection, antibiotic therapy should be administered. (2) Patients with a body temperature >38°C should be given antipyretic measures.

(iv) Blood Pressure Control

1. Hypertension: Approximately 70% of ischemic stroke patients experience blood pressure increased in the acute phase, mainly including pain, nausea and vomiting, increased intracranial pressure, confusion, anxiety, post-stroke stress state, pre-existing hypertension. In

the majority of patients, blood pressure spontaneously decreases within 24 h after a stroke. In patients with stable conditions and without intracranial hypertension or other serious complications, the blood pressure level after 24 h can essentially reflect their pre-illness level. Currently, there is a lack of reliable study evidence regarding whether blood pressure should be immediately lowered in the early stages after a stroke, what is the target values for blood pressure reduction, when to resume the original antihypertensive drugs post-stroke, and the choice of antihypertensive drugs. Domestic studies indicate that about 14% of patients have a systolic blood pressure ≥220 mmHg (l mmHg = 0.133 kPa), and 56% have a diastolic blood pressure ≥120 mmHg upon admission.

2. Hypotension: Possible causes of hypotension in stroke patients include aortic dissection, decreased blood volume, and reduced cardiac output. The cause should be actively investigated, and appropriate treatment should be administered.

Recommendation: (1) For candidates preparing for thrombolysis, the systolic blood pressure should be maintained at <180 mmHg and the diastolic blood pressure at <100 mmHg. (2) Patients with blood pressure increased within 24 h after ischemic stroke should be handled with caution. Anxiety, pain, nausea, vomiting, and increased intracranial pressure should be managed before addressing other issues. In cases of sustained increase in blood pressure, with systolic blood pressure ≥200 mmHg or diastolic blood pressure ≥110 mmHg, or in the presence of severe heart failure, aortic dissection, or hypertensive encephalopathy, antihypertensive treatment may be administered with caution. Blood pressure changes should be closely monitored, and if necessary, short-acting intravenous medications (such as labetalol, and nicardipine) can be used. It is preferable to use a microinfusion pump to avoid excessive lowering of blood pressure. (3) For individuals with a history of hypertension who are currently taking antihypertensive drugs, if the condition is stable, resumption of antihypertensive drug can commence 24 h after the stroke. (4) Patients with hypotension after a stroke should actively identify and address the underlying causes. If necessary, volume expansion and blood pressure support measures can be implemented.

(v) Blood Glucose Control

1. Hyperglycemia: About 40% of patients experience post-stroke hyperglycemia, which is associated with an unfavorable prognosis. It is currently recognized that control of post-stroke hyperglycemia is advisable, but there are only a few RCTs available on the specific measures and target blood glucose levels to be employed. No final conclusion has been reached yet.

2. Hypoglycemia: The incidence of hypoglycemia after a stroke is relatively low. Although there is a lack of clinical trials on its management, hypoglycemia can directly lead to cerebral ischemic injury and worsen edema, which is detrimental to the prognosis. Therefore, hypoglycemia should be corrected promptly.

Recommendation: (1) Administer insulin therapy when blood glucose exceeds 11.1 mmol/L. (2) Administer 10% to 20% glucose orally or by injection when blood glucose is below 2.8 mmol/L.

(vi) Nutritional Support

Post-stroke, dehydration and malnutrition due to vomiting and difficulty swallowing may slow down the recovery of neurological functions. Fluid and nutritional status assessment after a stroke should be emphasized. Hydration and nutritional support should be provided as needed.

Recommendation: (1) No additional nutritional supplementation is needed for those who eat normally orally. (2) Individuals who cannot eat normally can be fed nasally. For those requiring prolonged nutritional support and with the consent of the individual or family, percutaneous endoscopic gastrostomy (PEG) tube feeding is feasible.

iii. Specific Treatment

Specific treatment refers to interventions targeted at a specific link in the pathophysiological mechanisms of ischemic injury. In recent years, the research focus has primarily revolved around various measures to improve cerebral blood circulation (such as thrombolysis, antiplatelet therapy, anticoagulation, fibrinolysis reduction, volume expansion), and multiple drugs for neuroprotection.

(i) Improvement of Cerebral Blood Circulation

1. Thrombolysis: Thrombolysis is currently the most crucial measure for restoring blood flow. Recombinant tissue plasminogen activator (rtPA) and urokinase (UK) are the main thrombolytic drugs used in China. The current consensus is that the effective time window for rescuing penumbral tissue is 4.5 h or 6 h.

(1) Intravenous thrombolysis: 1) rtPA: Several clinical trials have evaluated the efficacy and safety of intravenous thrombolysis with rtPA for acute ischemic stroke. The treatment window includes within 3 h, 6 h, or 3 to 4.5 h after onset. The NINDS trial showed that within 3 h, the rtPA intravenous thrombolysis group had a significantly higher rate of complete or near-complete neurological recovery at 3 months compared to the placebo group, with similar mortality rates in both groups. The incidence of symptomatic intracranial hemorrhage was higher in the treatment group than in the control group. The ECASS III trial showed that intravenous administration of rtPA remains effective within 3 to 4.5 h after onset. Subgroup analysis from Cochrane systematic review indicated that intravenous thrombolysis with rtPA within 6 h significantly reduces long-term death or disability but significantly increases the rate of fatal intracranial hemorrhage. Treatment of 1,000 patients may result in a reduction of 55 cases of death or disability. The use of multi-modal MRI or CT to assist in selecting patients with a penumbra for thrombolysis beyond 3 h is still in the study stage. In addition to the risk of bleeding, there have been reports of rtPA causing vasogenic edema leading to

partial obstruction of the airway. 2) Urokinase: The "Urokinase Intravenous Thrombolysis in Acute Ischemic Stroke Within 6 h" trial in the 9-5 National Key Research Project in China is divided into two phases. The preliminary results of the first phase of the open-label trial confirmed the safety of domestically produced urokinase and established a dosage range of 1 million to 1.5 million IU for urokinase administration. The second phase is a multicenter, randomized, double-blind, placebo-controlled trial. A total of 465 patients with acute ischemic stroke within 6 h after onset were randomly divided into three groups: intravenous urokinase (1.5 million IU group: with 155 cases, 1 million IU group: 162 cases) and placebo group (148 cases). The results indicated that the use of urokinase thrombolysis within 6 h is relatively safe and effective. 3) Indications and contraindications for intravenous thrombolysis: ① Indications: A. Age 18 to 80 years; B. Onset within 4.5 h (rtPA) or 6 h (urokinase); C. Signs of ongoing severe brain functional impairment persisting for more than 1 h; D. Brain CT has ruled out intracranial hemorrhage, and there are no early large-scale imaging changes of brain infarction; E. Patient or family member has signed an *Informed Consent Form*. ② Contraindications: A. History of intracranial hemorrhage, including suspected subarachnoid hemorrhage; history of head trauma within the past 3 months; gastrointestinal or urinary system hemorrhage within the past 3 weeks; major surgery within the past 2 weeks; arterial puncture in a non-compressible site within the past 1 week. B. History of stroke or myocardial infarction within the past 3 months, excluding old lacunar infarctions without residual neurological signs. C. Severe cardiac, hepatic or renal insufficiency, or severe diabetes. D. Evidence of active hemorrhage or trauma (such as fractures) found during physical examination. E. Oral anticoagulant therapy with INR >15; received heparin treatment within the past 48 h (APTT exceeds the normal range). F. Platelet count $<100 \times 10^9$/L, blood glucose <27 mmol/L. G. Blood pressure: Systolic blood pressure >180 mmHg, or diastolic blood pressure >100 mmHg. H. Pregnancy. I. Non-cooperative. 4) Monitoring and management of intravenous thrombolysis: A. Monitor the patient in the intensive care unit or stroke unit whenever possible; B. Perform regular neurological assessments, every 30 min in the first hour, then every hour until 24 h; C. In case of severe headache, hypertension, nausea, or vomiting, discontinue thrombolytic drugs immediately and perform a brain CT scan; D. Monitor blood pressure regularly, every 15 min in the first 2 h, then every 30 min within the next 6 h, and then every hour until 24 h; E. If systolic blood pressure is ≥180 mmHg or diastolic blood pressure is ≥100 mmHg, increase the frequency of blood pressure monitoring and administer antihypertensive drugs; F. Delay the placement of nasogastric tubes, urinary catheters, and arterial pressure measurement catheters; G. Before administering anticoagulants or antiplatelet drugs, perform a repeat cranial CT.

(2) Arterial thrombolysis: Arterial thrombolysis delivers thrombolytic drugs directly to the site of the thrombus, theoretically resulting in a higher rate of revascularization than intravenous thrombolysis, with a reduced risk of hemorrhage. However, the benefits may be offset by the delay in the initiation of thrombolysis. A randomized, double-blind, controlled trial (n = 121) showed that in patients with severe middle cerebral artery occlusion within 6 h after onset, arterial use of recombinant urokinase resulted in better scores on the modified Rankin Scale and a higher rate of revascularization at 90 d in the treatment group compared to the control group. The differences in symptomatic intracranial hemorrhage and overall

mortality between the two groups were not statistically significant, pending further confirmation in more clinical trials.

Currently, there are limited data from small-sample studies on the time window, safety, and efficacy of thrombolytic therapy for vertebral-basilar artery ischemic stroke. There is currently no reliable study evidence on the efficacy and safety of thrombolytic therapy for ischemic stroke through intracranial artery injection.

Recommendation: (1) For patients with ischemic stroke within 3 h (Level I recommendation, Grade A evidence) and 3 to 4.5 h after onset (Level I recommendation, Grade B evidence), patient selection should be strictly based on the indications, and intravenous thrombolytic therapy with rtPA should be administered as soon as possible. Administration: rtPA 0.9 mg/kg (maximum dose 90 mg) intravenous infusion, with 10% administered as an initial bolus within the first minute, and the remaining administered as a continuous infusion within 1 h. Patients should be closely monitored during the administration and for 24 h afterward, as recommended above (Level I recommendation, Grade A evidence). (2) For patients with ischemic stroke within 6 h after onset, if rtPA cannot be used, consideration may be given to intravenous urokinase. Patient selection should be strictly based on the indications. Administration: Urokinase 1 to 1.5 million IU, dissolved in 100 to 200 mL of normal saline, administered as a continuous intravenous infusion over 30 min. Patients should be closely monitored during the administration, as recommended above (Level II recommendation, Grade B evidence). (3) Study on other thrombolytic drugs is possible, but their use outside of study is not recommended (Level I recommendation, Grade C evidence). (4) For patients with severe stroke within 6 h after onset caused by occlusion of the middle cerebral artery, and who are not suitable for intravenous thrombolysis, arterial thrombolysis may be considered after rigorous selection in qualified hospitals (Level II recommendation, Grade B evidence). (5) For patients with severe stroke within 24 h after onset caused by occlusion of the posterior circulation arteries, and who are not suitable for intravenous thrombolysis, arterial thrombolysis may be considered after rigorous selection in qualified units (Level III recommendation, Grade C evidence). (6) For patients requiring antiplatelet therapy or anticoagulation therapy after thrombolysis, initiation of such therapy should be delayed until 24 h after thrombolysis (Level I recommendation, Grade B evidence).

2. Antiplatelet therapy: Large-sample trials (China Acute Stroke Trial and International Stroke Trial) investigated the efficacy of oral aspirin within 48 h after stroke. The results showed that aspirin significantly reduced the rate of death or disability at the end of the follow-up period, decreased recurrence, and only slightly increased the risk of symptomatic intracranial hemorrhage. A preliminary trial suggested that early combination therapy with clopidogrel and aspirin is safe for patients with mild ischemic stroke or TIA. It may reduce vascular events, but the difference is not statistically significant. There is currently no large-sample RCT reporting on the clinical efficacy of other antiplatelet drugs in the acute phase of stroke.

Recommendation: (1) For ischemic stroke patients who do not meet the indications for thrombolysis and have no contraindications, oral aspirin 150 to 300 mg/d should be administered as early as possible after the onset (Level I recommendation, Grade A evidence). After the acute phase, the dose can be adjusted to a preventive dose (50 to 150 mg/d), as detailed in the secondary prevention guidelines. (2) For patients undergoing thrombolytic therapy, antiplatelet drugs such as aspirin should be initiated 24 h after thrombolysis (Level I recommendation, Grade B evidence). (3) For patients who cannot tolerate aspirin, consideration may be given to using antiplatelet therapy such as clopidogrel (Level III recommendation, Grade C evidence).

3. Anticoagulation: Although anticoagulant therapy has been used for over 50 years in the acute phase, there has been ongoing controversy. A Cochrane systematic review included 24 RCTs with a total of 23,748 patients. The drugs studied included unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, and thrombin inhibitors. Their meta-analysis showed that anticoagulant therapy did not reduce mortality at the end of follow-up, and there was no significant decrease in disability rates at the end of follow-up. Anticoagulant therapy reduced the recurrence rate of ischemic stroke and lowered the incidence of pulmonary embolism and deep vein thrombosis, but these benefits were offset by an increase in symptomatic intracranial hemorrhage. There is currently no evidence to show a net therapeutic effect of anticoagulation in special subgroups such as cardiac or arterial thrombus, arterial dissection, and vertebral-basilar artery infarction. The clinical trial of heparin anticoagulation within 3 h showed that the treatment group had better outcomes at 90 d than the control group, but symptomatic bleeding increased significantly, suggesting that ultra-early anticoagulation should not replace thrombolytic therapy. Thrombin inhibitors, such as argatroban, have potential advantages over heparin, including direct inhibition of thrombin in clots, rapid onset, short duration of action, low bleeding tendency, and lack of immunogenicity. A randomized, double-blind, placebo-controlled trial showed no significant increase in symptomatic intracerebral hemorrhage, suggesting good safety.

Recommendation: (1) For the majority of patients with acute ischemic stroke, early anticoagulation therapy is not recommended without specific selection (Level I recommendation, Grade A evidence). (2) For anticoagulation therapy in special patients, it can be used with caution after careful assessment of the risk-benefit ratio (Level IV recommendation, Grade D evidence). (3) For patients requiring anticoagulation therapy after thrombolysis in special circumstances, anticoagulants should be used 24 h after thrombolysis (Level I recommendation, Grade B evidence).

4. Defibrination: Many studies showed an increase in plasma fibrinogen and blood viscosity in the acute phase of ischemic stroke. Hemocoagulase preparations can significantly reduce plasma fibrinogen and have a mild thrombolytic and anti-thrombotic effect.

(1) Defibrase: A multicenter, randomized, double-blind, placebo-controlled trial conducted in China in 2000 (n = 2,244) showed that domestically produced defibrase can improve neurological function, reduce the recurrence rate of stroke, and is more effective when

administered within 6 h after onset. However, there is an increased risk of bleeding when fibrinogen levels drop below 1.3 g/L. In the multicenter, randomized, double-blind, placebo-controlled trial on defibrase treatment for acute ischemic stroke published in 2005 in China, 1,053 patients within 12 h after onset were included. The results indicated that the treatment group had better outcomes at 3 months compared to the control group, with a slight increase in the 3 month mortality rate compared to the control group. The treatment group showed a significantly higher rate of extracranial hemorrhage compared to the control group, with no significant increase in intracranial hemorrhage.

(2) Batroxobin: It has been used for several years in China, with a certain amount of clinical experience accumulated. A multicenter, randomized, double-blind, placebo parallel-controlled study suggested that batroxobin is effective in acute ischemic stroke with mild adverse reactions, but attention should be paid to the risk of bleeding. Another randomized, double-blind, placebo-controlled study compared the efficacy of batroxobin and urokinase within 6 h, showing no statistically significant difference in disability rates between the two groups.

(3) Ancrod: It is one of the most studied defibrination agents internationally, with 6 randomized controlled trials involving 2,404 patients. However, the results are still inconsistent.

(4) Other defibrination agents: Other defibrination agents such as lumbrokinase and acutase have also been used in clinical practice, pending further study.

Recommendation: For patients with ischemic stroke who are not suitable for thrombolysis and have undergone strict screening, especially those with hyperfibrinogenemia, defibrination therapy may be considered (Level II recommendation, Grade B evidence).

5. Vasodilation: For general ischemic stroke patients, there is currently insufficient evidence from RCTs to support the improvement of prognosis with volume expansion and blood pressure measures. A Cochrane systematic review (including 18 randomized controlled trials) indicated that early hemodilution therapy after stroke shows a tendency to reduce pulmonary embolism and lower extremity deep vein thrombosis. However, it does not have a significant impact on short-term or long-term mortality and functional outcomes.

Recommendation: (1) For general ischemic stroke patients, volume expansion is not recommended (Level II recommendation, Grade B evidence). (2) For acute ischemic stroke caused by hypotension or decreased cerebral perfusion, such as watershed infarction, volume expansion may be considered, but attention should be paid to potential complications such as increased cerebral edema and heart failure. Volume expansion is not recommended for such patients (Level III recommendation, Grade B evidence).

6. Vasodilation: Currently, there is a lack of evidence from large-sample, high-quality RCTs supporting the use of vasodilators to improve the clinical prognosis of ischemic stroke. More clinical trials are needed.

Recommendation: (1) For general ischemic stroke patients, vasodilation is not recommended (Level II recommendation, Grade B evidence).

(ii) Neuroprotection

In theory, drugs (neuroprotective agents) targeting cellular damage after acute ischemia or reperfusion can protect brain cells and enhance tolerance to ischemia and hypoxia. The clinical study status of major neuroprotective agents is as follows: The efficacy of calcium antagonists, excitatory amino acid antagonists, gangliosides, and NXY to 059 in animal experiments has not been confirmed in clinical trials. The results of an RCT on magnesium agent showed no significant reduction in the number of deaths or disability rates compared to the control. Another trial on the early use of magnesium agent in post-stroke patients (FAST to MAG) is currently underway.

Edaravone is an antioxidant and free radical scavenger. Several randomized double-blind placebo-controlled trials both domestically and internationally suggest that Edaravone can improve functional outcomes in acute ischemic stroke and is safe. Citicoline is a cell membrane stabilizer, and several randomized double-blind placebo-controlled trials have evaluated its efficacy in the acute phase of stroke. Individual trials did not show statistically significant differences, but a meta-analysis of four trials involving 1,372 patients suggested that patients who received oral citicoline within 24 h after stroke had a significantly higher likelihood of complete functional recovery at 3 months compared to the placebo group, with similar safety profiles. Cerebrolysin is a medication with neurotrophic and neuroprotective effects. Randomized double-blind placebo-controlled trials conducted abroad suggested its safety and improvement in prognosis. Clinical trial results of piracetam are inconsistent, and a definitive conclusion has not been reached at present.

Recommendation: The efficacy and safety of neuroprotective agents need further confirmation through more high-quality clinical trials (Level I recommendation, Grade B evidence).

(iii) Other Therapies

1. Butylphthalide: It is a Class I new drug recently developed in China. Several multicenter, randomized, double-blind, placebo-controlled trials evaluating the oral administration of butylphthalide in patients with acute ischemic stroke revealed that the butylphthalide treatment group exhibited significant improvement in neurological function deficits and activities of daily living scores compared to the placebo control group, with good safety. 2. Human urinary kallidinogenase: Human urinary kallidinogenase (urinary kallidinogenase) is another Class I new drug recently developed in China. A multicenter, randomized, double-blind, placebo-controlled trial evaluating intravenous administration of human urinary kallidinogenase in patients with acute ischemic stroke showed significant improvement in functional outcomes in the urinary kallidinogenase treatment group compared to the placebo group, and the treatment was deemed safe.

3. The efficacy and safety of hyperbaric oxygen and mild hypothermia still need to be confirmed through high-quality RCTs.

(iv) Traditional Chinese Medicine

1. Proprietary Chinese medicines: Proprietary Chinese medicines have been widely used in China for the treatment of ischemic stroke for many years. A systematic review of 191 clinical trials, involving 21 proprietary Chinese medicines and comprising 189 clinical trials (involving 19,180 patients), revealed in the meta-analysis that these medicines could improve neurological function deficits. Further high-quality studies are warranted to substantiate these findings.

2. Acupuncture: There are currently numerous published clinical trials on the efficacy of acupuncture in treating strokes, but the quality of the studies varies, and the results are inconsistent. A Cochrane systematic review, including 14 RCTs (comprising a total of 1,208 patients), revealed in the Meta-analysis a statistically significant reduction in the number of deaths or disabilities at the end of follow-up in the acupuncture group compared to the control group (P = 005), and a significant improvement in neurological function deficit scores. However, trials comparing acupuncture with sham acupuncture failed to replicate the above effects.

Recommendation: The efficacy of proprietary Chinese medicine and acupuncture in the treatment of acute ischemic stroke needs further confirmation through more high-quality RCTs. It is recommended to consider the use of acupuncture (Level II recommendation, Grade B evidence) or proprietary Chinese medicine (Level III recommendation, Grade C evidence) based on the specific situation and patient’s preferences.

IV. Treatment of Complications in the Acute Phase

(i) Cerebral Edema and Increased Intracranial Pressure

Severe cerebral edema and increased intracranial pressure are common complications of acute severe ischemic stroke and are major contributors to mortality.

Recommendation: (1) Bed rest, avoid and manage factors that increase intracranial pressure, such as excessive twisting or bending of the head and neck, agitation, exertion, fever, seizures, respiratory tract obstruction, coughing, and constipation (Level I recommendation). (2) Intravenous infusion of mannitol is recommended (Level I recommendation, Grade C evidence); if necessary, glycerin fructose or furosemide can also be considered (Level II recommendation, Grade B evidence). (3) For patients under 60 years old with malignant middle cerebral artery infarction, severe increased intracranial pressure within 48 h after onset, unsatisfactory response to medical treatment, and no contraindications, neurosurgical consultation is recommended to consider decompression (Level I recommendation, Grade A evidence) (4) For patients with large cerebellar infarction causing brainstem compression,

neurosurgical consultation is recommended for assistance in management (Level III recommendation, Grade C evidence).

(ii) Hemorrhagic Transformation

The incidence of hemorrhagic transformation in ischemic stroke ranges from 8.5% to 30%, with symptomatic cases accounting for 1.5% to 5%. Risk factors for hemorrhagic transformation include cardioembolism, large cerebral infarction, mass effect, early signs of low density, age over 70 years, and the use of anticoagulant drugs (especially anticoagulants) or thrombolytic drugs.

Studies indicated that the prognosis of asymptomatic hemorrhagic transformation does not statistically differ from cases without hemorrhagic transformation. Currently, there is a lack of study evidence on how to manage asymptomatic hemorrhagic transformation and when to reintroduce antithrombotic drugs (anticoagulants and antiplatelet drugs) after symptomatic hemorrhagic transformation. Currently, there are no specific treatment recommendations for patients with asymptomatic hemorrhagic transformation.

Recommendation: (1) Symptomatic hemorrhagic transformation: Discontinue antithrombotic therapy and other bleeding-inducing drugs (Level I recommendation, Grade C evidence); for bleeding associated with anticoagulation and thrombolysis, refer to the guidelines for cerebral hemorrhage. (2) When to initiate anticoagulation and antiplatelet therapy: For patients requiring antithrombotic therapy, it may be initiated 7 to 10 d after the stabilization of hemorrhagic transformation; for those with a relatively lower risk of recurrent thrombosis or poor overall health, antiplatelet drugs may be used as a substitute for warfarin.

(iii) Seizures

The early incidence of seizures after ischemic stroke ranges from 2% to 33%, while the late incidence ranges from 3% to 67%. Currently, there is a lack of evidence regarding the need for prophylactic use of antiepileptic drugs or the treatment of post-stroke seizures.

Recommendation: (1) Prophylactic use of antiepileptic drugs is not recommended (Level IV recommendation, Grade D evidence). (2) After a single isolated seizure or control of acute symptomatic seizures, long-term use of antiepileptic drugs is not recommended (Level IV recommendation, Grade D evidence). (3) For seizures recurring 2 to 3 months after a stroke, it is recommended to follow standard epilepsy treatment, involving long-term drug therapy (Level I recommendation). (4) For status epilepticus following a stroke, it is recommended to manage it according to the principles of status epilepticus treatment (Level I recommendation).

(iv) Difficulty Swallowing

About 50% of stroke patients experience difficulty swallowing upon admission, and this decreases to around 15% after 3 months. To prevent and treat pneumonia and malnutrition

after a stroke, it is important to emphasize the assessment and management of difficulty swallowing.

Recommendation: (1) It is suggested to use a water swallow test for the assessment of swallowing function before patient intake (Level II recommendation, Grade B evidence). (2) For patients with difficulty swallowing unable to recover in the short term, early nasogastric tube feeding is recommended (Level II recommendation, Grade B evidence). For those with long-term unrecoverable difficulty swallowing, PEC feeding is recommended (Level III recommendation, Grade C evidence).

(v) Pneumonia

About 56% of stroke patients develop pneumonia, with aspiration being the main cause. Disturbance of consciousness and difficulty swallowing are the primary risk factors for aspiration, while others include vomiting and immobility. Pneumonia is one of the main causes of death in stroke patients, with 15% to 25% of stroke patients dying from bacterial pneumonia.

Recommendation: (1) Early assessment and management of difficulty swallowing and aspiration are recommended, with particular attention to preventing pneumonia in patients with disturbance of consciousness (Level I recommendation, Grade C evidence). (2) Patients with suspected pneumonia and fever should receive antibiotic treatment, but prophylactic use of antibiotics is not recommended (Level II recommendation, Grade B evidence).

(vi) Urinary Dysfunction and Urinary Tract Infection

Urinary dysfunction is common in the early stages of a stroke, mainly involving urinary incontinence and urinary retention. During hospitalization, 40% to 60% of moderate to severe stroke patients experience urinary incontinence, and 29% experience urinary retention. Urinary tract infections primarily occur as a result of indwelling catheters in patients with urinary incontinence or urinary retention, with about 5% developing sepsis, which is associated with a poor prognosis in stroke.

Recommendation: (1) Early assessment and rehabilitative treatment for urinary dysfunction are recommended, including the documentation of a voiding diary (Level II recommendation, Grade B evidence). (2) Individuals with urinary incontinence should avoid indwelling catheter whenever possible and may use bedpans or urinals on a scheduled basis, with a frequency of every 2 h during the day and every 4 h at night (Level I recommendation, Grade C evidence). (3) Patients with urinary retention should measure residual urine in the bladder, and during voiding, pressure can be applied on the pubic bone to enhance urination. Intermittent urinary catheterization or indwelling catheter may be used as needed (Level IV recommendation, Grade D evidence). (4) Individuals with urinary tract infections should receive antibiotic treatment, but prophylactic use of antibiotics is not recommended (Level I recommendation).

(vii) Deep Vein Thrombosis (DVT) and Pulmonary Embolism

Risk factors for DVT include venous stasis, endothelial damage in the venous system, and a hypercoagulable state. Individuals with severe paralysis, advanced age, and atrial fibrillation have a higher proportion of developing DVT, with a symptomatic DVT incidence rate of 2%. The most significant complication of DVT is pulmonary embolism. According to relevant studies, the following recommendations are suggested for management.

Recommendation: (1) Encourage patients to engage in early mobilization and elevate their lower limbs; avoid intravenous infusions in the affected limb, especially on the paralyzed side (Level I recommendation). (2) For individuals at high risk of DVT and pulmonary embolism without contraindications, low molecular weight heparin or unfractionated heparin may be administered. In cases with contraindications to anticoagulation, aspirin treatment is recommended (Level I recommendation, Grade A evidence). (3) Combination therapy with compression (such as compression stockings or intermittent pneumatic compression devices) and pharmacological prevention of DVT is recommended. Routine use of compression treatment alone is not recommended. However, for ischemic stroke patients with contraindications to anticoagulation, the use of compression treatment alone for the prevention of DVT and pulmonary embolism is recommended (Level I recommendation, Grade A evidence). (4) For DVT or pulmonary embolism patients without contraindications to anticoagulation and thrombolysis, initial treatment with heparin is recommended. Thrombolytic therapy may be considered for patients with proximal DVT or pulmonary embolism who do not experience relief of symptoms (Level IV recommendation, Grade D evidence).

A Randomized, Double-blind, Placebo Controlled Evaluation, Multicenter Clinical Study of Tongxinluo Capsule in Ischemic Stroke Patients

Statistical Analysis Plan V1.0

Study title: A Randomized, Double-blind, Placebo Controlled Evaluation, Multicenter Clinical Study of Tongxinluo Capsule in Ischemic Stroke Patients

Statistical unit: Peking University Clinical Research Institute
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Contents

1. Abbreviations and Statistics

Abbreviations	Interpretation
AE	（Adverse Event）
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Urea nitrogen
CI	（Confidence Interval）
Cm	Centimeter
CMH	Cochran-Mantel-Haenszel Cochran-Mantel-Haenszel test
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
DRQ	DRQ
F	F-statistics (results of covariance analysis)
FAS	（Full Analysis Set）
GCP	Good Clinical Practice
ITT	Intentionality (population)
LOCF	（Last Observation Carried Forward）
Max	Maximum value
Mean	Mean
Median	Median
Min	Minimal value
P	P value
Power	Power of test
PP	Per-protocol (population)
PPS	Per-protocol Set
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard operating procedure
SS	Safety set

2. Study title

A randomized, double-blind, placebo controlled evaluation, multicenter clinical study of Tongxinluo Capsule in ischemic stroke patients

3. Study objectives

The primary objective of this study: In comparison with placebo, to evaluate the improvement of self-help ability of patient's daily living after early application of Tongxinluo Capsule with treating ischemic stroke (within 72 hours after onset) for 90 days.

The secondary objective of this study: To investigate the improvement of neurologic impairment and self-help ability of patient's daily living, differences of disability rate, incidence of combined vascular events and incidence of ischemic cerebrovascular diseases, and safety of medication between placebo and early application of Tongxinluo Capsule with treating ischemic stroke (within 72 hours after onset) for 90 days. To evaluate the safety and effectiveness of Tongxinluo Capsule at different etiological typing and randomized times, and in different imaging subgroup analyses and more exploratory analyses.

4. Study design

4.1 Overall design and summary of study preparation

4.1.1 Overall design

This is a randomized, double-blind, placebo-controlled evaluation, multicenter clinical study in ischemic stroke patients.

4.1.2 Overall arrangement

All patients are randomly divided into the treatment group and control group at a ratio of 1:1. The patient receives study drug on the basis of current routine basic therapy.

Treatment group: Basic treatment + Tongxinluo Capsules (4 capsules per time, tid, oral administration)

Control group: Basic treatment + Tongxinluo Placebo Capsules (4 capsules per time, tid, oral administration)

Other traditional Chinese medicine or Chinese patent medicine (the traditional Chinese medicine having similar functional components with Tongxinluo Capsule) is not allowed to take during treatment period.

Follow-up should be made on the 7th day, discharge day (if the hospital stay is longer than 21 days, follow-up should be made on the 21th day) and 90th day after randomization, in order to make effective and safety evaluation until the end of study.

4.1.3 Trial flow chart

Study phase	Screening/ random grouping	Double-blind treatment stage			Follow-up*
Visit	1	2	3	4	5
Number of days	3 days ago to day 0	Day 7±2	At the discharge day	Day 90±7	
Basic information					
Informed consent	●				
General data	●				
Medical history	●				
Physical examination	●	●	●	●	◎
Treatment					
Inclusion/ exclusion criteria	●				
Random allocation	●				
Distributing study	●				

drugs					
Record drug combination	●	●	●	●	
Drug recovery and counting			●	●	
Determination on compliance			●	●	
Completion				●	
Inclusion index					
CT or MRI	●		◎	●	
Pregnancy test	●				
Safety index					
Blood routine test	●		◎	●	◎
Routine urine test	●		◎	●	◎
Biochemical test	●		◎	●	◎
Four items of coagulation	●		◎	●	◎
12-led ECG	●		◎	●	◎
Evaluation on AE		●	●	●	◎
Efficacy index					
Modified Rankin scale	●	●	●	●	
NIHSS score	●	●	●	●	
BI index score	●	●	●	●	
		●	●	●	
Check					
Check by researchers				●	●
Check by supervisors	●	●	●	●	●
Check by head of sub-center				●	●

Note: Inclusion index CT or MRI*: if the patient has taken head CT or MRI in the clinical study unit within 72 hours before grouping, it is not necessary to take examination again, and the report or relevant copies can be attached in case history. MRI sequence examination (T1+T2+DWI+FLAIR+MRA+T2*) should be taken in the centre participating in imaging subgroups at baseline and last follow-up, baseline examination can be taken before or 3 days after randomization.

At discharge day*: If the hospital stay is longer than 21 days, the follow-up can be made on day 21.

Follow-up*: When there are persistent adverse events or laboratory abnormality or abnormal vital signs with clinical significance at the end of treatment, the researchers should take follow-up to obtain the measurement value, and the follow-up can be made by various means according to the specific condition, or by phone.

4.2 Randomization and implementation

All patients are randomly divided into the treatment group and control group at a ratio of 1:1. Central dynamic randomization is adopted so that each center is grouped in competition. The centralized random grouping program will be performed with Interactive Web-based Randomization System (IWRS) provided by the Peking University Clinical Research Institute. The main investigators have their own accession numbers and passwords to

ensure the security and integrity of the login system. After screening each eligible participant in each study center, the researchers should enter the randomized system with the account number and enter the information about the subject to obtain related drug package number. The researchers should deliver drugs according to the drug package number. Subjects are randomly assigned to the treatment and control groups according to stratification factors, and stratification factors include:

1、Has take thrombolytic therapy: Yes or no

2、NIHSS score: 4-7 points, 8-14 points and 15-22 points;

The randomization method is Pocock and Simon minimal randomization. Patients must start treatment within 24-48 hours after randomization. This study is treated with non-repetitive randomization.

4.3 Blind method and measures

4.3.1 Blind coding and storage of blind code

The biometric experts, who are independent of the statistical analysis, can use central stochastic system to randomly produce drug package number, and the random parameter cannot be modified or viewed after the start of project. The drug was coded according to the drug package number by statisticians unrelated to this study. After coding, the blind code should be sealed.

4.3.2 Emergency unblinding

In the event of a serious adverse event and in the need for emergency unblinding, the researchers in charge of center should login randomization system for emergency unblinding. If it fails unblinding due to speed or other reasons, the researchers can directly call the Peking University Clinical Research Institute by 24-hour hotline, and the system administrator will perform emergency unblinding. This unblinding process involves only the subject, not exposing grouping information of other subjects. Once the case is performed with emergency unblinding, he or she should be considered as off patient, but if there is any adverse reaction, these reactions should also be included in the analysis of adverse reactions.

4.3.3 Unblinding provisions

The study adopts twice unblinding. After blind check, the data is locked, main researchers, medical statisticians, data administrators and sponsor representatives will do the first unblinding, and the random number corresponding to the group will be marked with A or B, in order to make statistical analysis on all data. At the end of statistical analysis, summary report is completed, and then a second unblinding should be taken to determine the exact group of A and B.

4.4 Sample size

According to the China National Stroke Registry (CNSR), the patients with mRS≤1 at 3 months accounts for 39.59% in those with NIHSS of 4-22 at hospitalization. There is 40% of patients with mRS ≤1 at 90 days in the control group, and 47% in the treatment group. Treatment group and control group are designed in geometric proportion. Sample size is calculated by PASS 2008 (α=0.05, two-tailed test; β=0.2, power of test=80%). A total of 787 patients are enrolled in the treatment group and control group, respectively. Considering off patients in clinical study, we add another 20% of sample size that a total of 1968 cases are included in this study. The patients are divided at a ratio of 1:1 into treatment group and control group, and the study will be carried out in 50 centers.

4.5 Subjects

The enrolled patients should satisfy the following inclusion criteria, and not meet any exclusion criterion. In addition to following criteria, the patient should also be excluded if at any contraindicated medical condition or use of incompatibility drug during basic treatment period.

4.5.1 Inclusion criteria

1、Have onset of ischemic stroke within 72 hours, and be diagnosed by CT/MRI;

2、At age of 35to 75;

3、First onset or with past history of ischemic stroke, but have recovered before this onset, that is with mRS score ≤1;

4、With clear nervous system orientation sign, and national institutes of health stroke scale (NIHSS) ≥4 and ≤22;

5、The patient or his (her) legal representative has signed informed consent before the start of study.

4.5.2 Exclusion criteria

1、Head CT/MRI indicates intracranial hemorrhagic disorders: Hemorrhagic stroke, epidural hematoma, intracranial hematoma, intraventricular hemorrhage, subarachnoid hemorrhage, recurrent bleeding after cerebral hemorrhage and so on;

2、Transient ischemic attack (TIA);

3、Serious disturbance of consciousness: the patient with 1a level of consciousness scale >1; with dysphagia and unable to take oral administration of capsules; with any of upper and lower limb motor function 5a, 5b, 6a and 6b in NIHSS >2;

4、The patient with stroke that is caused by cerebral tumor, cerebral trauma, blood diseases and so on;

5、Have disorders with bleeding tendency;

6、Have received endovascular treatment after onset;

7、The one with dementia, severe Parkinson's disease, mental disorders, limb dysfunction caused by other disorders, and other diseases that may affect the judgment of efficacy;

8、The one with uncontrollable hypertension/ hypotension: Systolic blood pressure ≥ 200mmHg or diastolic blood pressure ≥ 110mmHg; or systolic blood pressure ≤ 90mmHg or diastolic blood pressure ≤ 60mmHg; the one with severe hyperglycemia / hypoglycemia: blood sugar ≥ 400mg / dl (22.2mol / L) or ≤ 50 mg / dl (2.8 mol / L);

9、The patient with liver dysfunction (transaminase level more than 2 times of the upper limit of normal), renal dysfunction (creatinine value more than 1.5 times of the upper limit of normal), cardiac dysfunction or other serious systemic disease, and the life expectancy ≤ 3 months;

10、Concomitant with malignant tumor or be taking anti-tumor treatment;

11、Have past allergic history to studying drug or control drug;

12、The patient during pregnancy or breast feeding, or the one with possibility of pregnancy or plan to get pregnant;

13、Have participated or be participating in other clinical studies in the past 3 months;

14、The one with the situation that is unsuitable for enrollment by the researcher;

4.5.3 Fall off (withdraw) standard

The subject, who has signed the informed consent and screened eligibly for the study, can be regarded as drop out case if withdraw from the program for any reason and do not complete the programme.

The patient has the right to withdraw from the study at any time for any reason. The researcher is also entitled to exclude the patient if he has a disease, an adverse event or violates the study protocol, or due to management reason or other reason. It should avoid any unnecessary withdrawal, and actively take measures to complete the final test as much as possible for the efficacy and safety of analysis. However, when the patient

decides to withdraw, the researcher should contact the patient or his / her relatives by phone or personal interview, and as far as possible confirm the reason for the withdrawal. The researcher should recover the remaining drug when the patient withdraws, finish the final assessment, complete the case report as much as possible, explain the cause of withdrawal and take follow-up on the endpoint. If the cause of withdrawal is an adverse event, the main event should be recorded in the study medical record.

Common reasons to withdraw from the study: Adverse events, lack of efficacy, taking endovascular treatment during follow-up period, violation of research programme (including poor compliance), loss of follow-up (including withdrawal due to patient's own reason), incomplete study decided by the sponsor after the judgement of researchers and other reasons;

4.5.4 Standards for suspending the study

1、Having allergic reaction clearly associated with study drugs;

2、Having adverse symptoms and signs definitely associated with study drugs, abnormal findings, or conditions in need of ending the study after judgment of researchers, which are clearly related to the medicine under study;

3、Female subjects get pregnant during the study;

4、The patients ask to end further study;

5、Take endovascular treatment during study period;

6、If there is occurrence of vascular events, it should be determined as appropriate: Discontinue study drug and terminate study, if the patient has hemorrhagic stroke, and the related condition should be recorded in appropriate part of medical records. If there is occurrence of TIA/ ischemic stroke/ myocardial infarction, the subjects do not need to discontinue taking study drug or withdraw from the study, only if concomitant drugs contraindicated by the study need to be taken.

5. Evaluation index

5.1 Primary effect index

Improvement of daily life ability 90 days after treatment (ratio of mRS score ≤1)

5.2 Secondary effect index

1、Improvement of neurological deficits (ratio of NIHSS≤1 or improve 4 score or more);

Improvement of neurological deficits (ratio of NIHSS≤1 or improve 4 score or more): It is effective for NIHSS≤1 or reducing 4 points or more; compare the ratio of efficacy and inefficacy and the continuous change of NIHSS between treatment group and control group 90 days after random treatment;

2、Improvement of daily life ability (ratio of BI index ≥85);

Ratio of patients with BI index≥85: BI score≥85 indicates the patient with ability of independent living; compare the ratio of patient with ability of independent living and continuous change of BI between treatment group and control group at 90 days after random treatment;

3、Disability rate (ratio of mRS score ≥3)

mRS≥3 indicates the patient without self-care ability; compare the disability rate between treatment group and control group at 90 days after random treatment;

4、Continuous change of mRS score

Compare change of mRS score at baseline, 7d, discharge day and 90d between treatment group and control group;

5、Incidence of ischemic cerebrovascular diseases during follow-up period;

Ratio of ischemic stroke or TIA within 90 days after random treatment, or ratio of new ischemic focus detected by MRI during the last visit, and take this kind of patients as a group for evaluation or respective evaluation;

6、Incidence of combined vascular events during follow-up period;

Accumulated ratio of patients having newly combined vascular events within 90 days after random treatment;

Definition of combined vascular events: Include any type of stroke (ischemic stroke and hemorrhagic stroke), TIA, myocardial infarction and vascular death.

Vascular death: Hemorrhagic death or fatal pulmonary embolism of any organ.

5.3 Safety index

1、Incidence of adverse events

2、Clinical laboratory index

Blood routine test (hemoglobin, red blood cells, white blood cells, platelets), routine urine test (urine protein, urinary white blood cells, urinary red blood cells), serum biochemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, glutamine, urinary nitrogen, creatinine, total bilirubin, blood glucose, total cholesterol, triglycerides, low density lipoprotein, high density lipoprotein), four items of blood coagulation (PT, APTT, TT, FIB)

3、ECG

4、Physical examination

Include: Vital signs (systolic pressure, diastolic pressure, heart rate, pulse, body temperature), examination of body systems (general condition, skin, superficial lymph nodes, head and neck, heart, lung, abdomen, nervous system, urogenital system, spine and limbs and others).

6. Statistical analysis

6.1 Analysis set

Efficacy analysis is conducted on the basis of FAS and PPS. Analysis on baseline demographic data will be performed on the basis of FAS and safety evaluation on SS.

6.1.1 Full analysis set (FAS)

Full analysis set (FAS) or modified intention-to-treat (ITT): Set of all the patients who underwent randomization, given any treatment, and underwent any posttreatment assessment. When main indexes of curative effect are missing, the set should be supplemented with last observation carried forward (LOCF) on the basis of intention to treat (ITT). Comparability analysis and the missing value of secondary effect indexes don't need data-carry-forward. Take analysis on actual data in FAS.

FAS population is the main population for curative evaluation in this study.

6.1.2 Per-protocol set

Per-protocol set (PPS): The set that conforms to inclusion criteria, does not conform to exclusion criteria and completes therapeutic schedule. Do analysis (PP analysis) to cases that are fit to experiment program, with good compliance, not taking any prohibited drug and complete required contents of CRF.

PP population is the secondary population for curative evaluation in this study.

6.1.3 Safety set (SS)

Safety set (SS): The actual data that patients accept at least one time treatment with safety indexes recording. Do not do data-carry-forward if safety is missing; the incidence of adverse events takes the number of safety set as denominator.

SS population is the main population for safety evaluation in this study.

6.2 Statistical method

6.2.1 General principle

SAS9.4 software is adopted for statistical analysis. All data are performed with two-sided test, and P value less than or equal to 0.05 (two-sided test) is considered with statistical difference. (Unlcess the special instruction)

Quantitative indexes are described with case number, mean, standard deviation, median, P25 (Q1), P75(Q3), minimum value (Min) and maximum value (Max).

Classification indexes are described with case number and percentage.

Comparison of general situation should be analyzed with appropriate method based on the type of indexes. Quantitative data should be analyzed with paired t test or Wilcoxon rank sum test; classification data with chi-square test or precise probability method, and ranked data with Wilcoxon rank-sum test or CMH test.

6.2.2 Completion of study

Summarize the number of enrollment and completion of each center, completion of enrollment in treatment group and control group, and size of different data sets; make a list of drop-out case and distribution of cases in each center.

6.2.3 Demographic description and baseline description

Describe the demographic characteristics of subjects (e.g. age, sex, marital status, body height, body weight, nationality, job category), medical history, past history, imaging examination, therapeutic condition, drug combination, and so on, according to general principles, and evaluate the comparability between the two groups with inter-group comparison.

Analysis on drug compliance: Observe the detailed record of drug distribution and recovery to determine the compliance of subjects; if the actual dosage is within 80-120% of predicted dosage, the drug compliance conforms to the requirement of programme. Compare whether the patients of the two groups take investigational medicine on time and don't taking prohibited medicine and food of the scheme.

6.2.4 Efficiency evaluation

Baseline efficiency: Describe the baseline of each curative index, and comparison between groups should be made in accordance with general condition. Modified Rankin (mRS) score is regarded as ranked data, and should be compared with Wilcoxon rank sum test. NIHSS score should be regarded as quantitative data and ranked data (4-7 points, 8-14 points and 15-22 points) for description and comparison; BI score as quantitative data and enumeration data (<85 points, ≥85 points) for description and comparison.

Primary efficiency indexes:

PP analysis and FAS analysis should be performed at the same time; evaluation on patients with modified Rankin (mRS) score≤1 should be mainly conducted ontaken at day 90 day (PP set) and the time for suspending and drop-out (FAS set). Primary indexes should be compared between the two groups with CMH-$\chi 2$ method for controlling central effect.

Superiority test is adopted for primary indexes, and the hypotheses under test are as follows:

$$H_0 : \pi_{\text{treatment group}} - \pi_{\text{control group}} \leq 0$$

$$H_1 : \pi_{\text{treatment group}} - \pi_{\text{control group}} > 0$$

$$\alpha = 0.025 \text{(one-sided)}$$

The treatment group is superior to control group, if H0 is rejected under α level, or lower limit of 95% Cl for difference of retention rate between the two groups is higher than 0. Take sensitivity analysis on primary efficiency indexes with modified Rankin (mRS) score≤2 points as the limit.

Other secondary indexes can be statistically analyzed in accordance with methods for primary indexes.

6.2.5 Safety analysis

Adverse events are described with case number, times and incidence of various adverse events, and $\chi 2$ test or Fisher's exact test is adopted for comparing the incidence between the two groups. At the same time, make a detailed list to describe the specific manifestation and extent of all adverse events and serious adverse events and their relation with drugs.

Statistically describe the vital signs at baseline and 90 days after treatment according to general principles, and make comparison between former and later times and inter-group comparison.

Make description of number of normal cases before treatment, number abnormal cases after treatment and their ratios in two groups, respectively, and $\chi 2$ test or Fisher's exact test is adopted for comparing the ratio between the two groups.

Make description of number of normal cases before treatment, number abnormal cases after treatment and their ratios in two groups, respectively, and $\chi 2$ test or Fisher's exact test is adopted for comparing the ratio between the two groups. Crosstab is adopted to describe the change of laboratory indexes before and after treatment for determining the clincial significance of these indexes.

6.2.6 Exploratory analysis

Take predicted subgroup analysis on primary indexes;

7. Results of statistical analysis

7.1 Completion of study

7.1.1 Distribution of cases

Table 7.1.1.1 Distribution and grouping of cases

Center	Group	Number of enrolled cases	Number of drop-out cases	Drop-out ratio (%)	Completion
1Center	Treatment group				
	Control group				
	Total				
2 Center	Treatment group				
	Control group				
	Total				
…	…				
Total	Treatment group				
	Control group				
	Total				

Table 7.1.1.2 Completion of study, safety analysis set and efficiency analysis set

Item	Treatment group	Control group	Total
Completion of enrollment			
Random grouping			
Completed study			
Uncompleted study			
Main reasons for suspending the study			
Inconsistent with inclusion criteria or conform to exclusion criteria			
Have adverse event			
Lack of efficacy and drop out			
Violate study programme			
Cancellation of informed consent			
Have serious concomitant disease in the course of study			
Loss to follow-up or not take follow-up in time			
Other reason			
Analysis set			
FAS			
PPS			
SS			

Table 7.1.1.3 List of drop-out and excluded patients

Center	No.	Group	FAS	PPS	SS	Reason of drop-out

Table 7.1.1.4 Distribution of population

	FAS			PPS			SS		
Center	Treatment group	Control group	Total	Treatment group	Control group	Total	Treatment group	Control group	Total
1 Center									
2 Center									
…									
Total									

7.2 Demographic description and baseline description (FAS)

Table 7.2.1.1 Demographic description (FAS)

Item	Index	Total	Treatment group	Control group
	N(Missing)			
Age (year)	Mean(SD)			
	Median			
	Q1,Q3			
	Min,Max			
	Statistics			
	P Value			
Sex	Male n(%)			
	Female n(%)			
	N (Missing)			
	Statistics			
	P value			
Marital status	Unmarried n(%)			
	Married n(%)			
	N (Missing)			
	Statistics			
	P value			
Body height (cm)	N(Missing)			
	Mean(SD)			
	Median			
	Q1,Q3			
	Min,Max			
	Statistics			
	P value			
Body weight (kg)	N(Missing)			
	Mean(SD)			
	Median			
	Q1,Q3			
	Min,Max			
	Statistics			
	P value			
BMI（Kg/m^2）	N(Missing)			
	Mean(SD)			
	Median			
	Q1,Q3			
	Min,Max			
	Statistics			

Item	Index	Total	Treatment group	Control group
	P value			
Nationality	Han n(%)			
	Others n(%)			
	N (Missing)			
	Statistics			
	P value			
Job category	Manual labor n(%)			
	Non-manual labor n(%)			
	N (Missing)			
	Statistics			
	P value			

Table 7.2.1.2 Medical history (FAS)

Item	Index	Total	Treatment group	Control group
	Cerebral infarction n(%)			
Diagnosed with Western medicine	Acute phase n(%)			
	N (Missing)			
	Statistics			
	P value			
	Atherothrombotic stroke n(%)			
TOAST type	Cardioembolism n(%)			
	Small artery occlusive stroke n(%)			
	Ischemic stroke caused by other reasons n(%)			
	Ischemic stroke of unknown causes n(%)			
	N (Missing)			
	Statistics			
	P value			
	≤12h n(%)			
Course of disease	12-48h n(%)			
	48-72h n(%)			
	N (Missing)			
	Statistics			
	P value			
	First onset n(%)			
First onset /recurrence	Recurrence n(%)			
	N (Missing)			
	Statistics			
	P value			

Table 7.2.1.3 Past history (FAS)

Item	Index	Total	Treatment group	Control group
Smoking history	With n(%)			
	Without n(%)			
	Quit smoking			
	N (Missing)			
	Statistics			
	P value			
History of alcohol intake	With n(%)			
	Without n(%)			
	n(%)			
	N (Missing)			
	Statistics			
	P value			
History of menopause	Non-menopause n(%)			
	Post-menopause n(%)			
	Not applicable n(%)			
	N (Missing)			
	Statistics			
	P value			
Drug allergy history	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			
Past history	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			

Table 7.2.1.4 Imaging examination (FAS)

Item	Index	Total	Treatment group	Control group
Cerebral infarction	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			
Hemorrhagic impression	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			

Table 7.2.1.5 Therapeutic condition (FAS)

Item	Index	Total	Treatment group	Control group
Drug for cerebral infarction	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			

Item	Index	Total	Treatment group	Control group
Thrombolytic therapy	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			
Have other disease recently	With n(%)			
	Without n(%)			
	N (Missing)			
	Statistics			
	P value			

Table 7.2.1.6 Drug combination (FAS)

Item	Index	Treatment group	Control group
New drug combination during study	With n(%)		
	Without n(%)		
	N (Missing)		
	Statistics		
	P value		

Table 7.2.1.7 Drug compliance (FAS)

Item	Index	Treatment group	Control group
Drug compliance conform to programme requirement	With n(%)		
	Without n(%)		
	N (Missing)		
	Statistics		
	P value		

7.3 Efficiency evaluation

7.3.1 Baseline effect indexes

Table 7.3.1.1 Baseline mRS score

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Baseline NIHSS score	N(Missing)				
	Mean(SD)				
	Median				
	Q1,Q3				
	Min, Max				
	Statistics				
	P value				

Table 7.3.1.2 Baseline NIHSS score – as quantitative data

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Baseline NIHSS score	N(Missing)				
	Mean(SD)				

Item	Index	FAS		PPS	
		Treatment group	Control group	Treatment group	Control group
	Median				
	Q1,Q3				
	Min, Max				
	Statistics				
	P value				

Table 7.3.1.3 Baseline NIHSS score – as ranked data

Item	Index	FAS		PPS	
		Treatment group	Control group	Treatment group	Control group
Baseline NIHSS score	4-7 points n (%)				
	8-14 points n (%)				
	15-22 points n (%)				
	N (Missing)				
	Statistics				
	P value				

Table 7.3.1.4 Baseline BI score – as quantitative data

Item	Index	FAS		PPS	
		Treatment group	Control group	Treatment group	Control group
	N(Missing)				
Baseline BI score	Mean(SD)				
	Median				
	Q1,Q3				
	Min, Max				
	Statistics				
	P value				

Table 7.3.1.5 Baseline BI score – as enumeration data

Item	Index	FAS		PPS	
		Treatment group	Control group	Treatment group	Control group
Baseline BI score	<85 points n(%)				
	≥85 points n(%)				
	N (Missing)				
	Statistics				
	P value				

7.3.2 Primary effect index - Improvement of daily life ability at 90 days after treatment

Table 7.3.2.1 Improvement of daily life ability at 90 days after treatment

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

2. Statistical description of baseline mRS score see Table 7.3.1.1

Table 7.3.2.2 Improvement of daily life ability at 90 days after treatment – take mRS=2 as limit

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤2 point n(%)				
	>2 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

2. Statistical description of baseline mRS score see Table 7.3.1.1

7.3.3 Secondary effect index - Improvement of neurological deficit

Table 7.3..3.1 Improvement of neurological deficits at 90 days after treatment

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Improvement of neurological deficits at 90 days after treatment	Efficiency n(%)				
	Inefficiency n(%)				
	Missing				
	Statistics				
	P value				

Note: It is effective for NIHSS score ≤1 or reducing 4 points or more

Table 7.3.3.2 Continuous change of NIHSS score at 90 days after treatment (FAS)

Item	Index	Treatment group	Control group
Baseline NIHSS score	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
NIHSS score at 90 days after treatment	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
Change of NIHSS score at 90 days after treatment comparing with that at baseline	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
	95%CI		
	Statistics		
	P value		

Table 7.3.3.3 Continuous change of NIHSS score at 90 days after treatment

The same as above

7.3.4 Secondary effect index - Improvement of daily life ability

Table 7.3.4.1 Inter-group comparison of improvement of daily life ability at 90 days after treatment

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
	With ability of independent living n(%)				
	Without ability of independent living n(%)				
Improvement of daily life ability at 90 days after treatment	N (Missing)				
	Statistics				
	P value				

Note: BI score≥85 points indicates the patient with ability of independent living

Table 7.3.4.2 Continuous change of BI score at 90 days after treatment (FAS)

7.4.2.2 The same as Table 7.4.2.2

Table 7.3.4.3 Continuous change of BI score at 90 days after treatment (PPS)

The same as above

7.3.5 Secondary effect index – disability rate

Table 7.3.5.1 Inter-group comparison of disability rate at 90 days after treatment

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Disability rate	Without self-care ability n(%)				
	With self-care ability n(%)				
	N (Missing)				
	Statistics				
	P value				

Note: mRS≥3 indicates the patient without self-care ability

7.3.6 Secondary effect index – continuous change of mRS score

Table 7.3.6.1 Continuous change of mRS score (FAS)

Item	Index	Treatment group	Control group
Baseline mRS score	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
mRS score at 7 days after treatment	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
Change of mRS score at 7 days after treatment comparing with baseline	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
	95%CI		
	Statistics		
	P value		
mRS score at discharge day	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P 值 P value		
Comparison of mRS score at discharge day comparing with baseline	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		

Item	Index	Treatment group	Control group
	P value		
	95%CI		
	P value		
	N(Missing)		
mRS score at 90 days after treatment	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
	N(Missing)		
Changes of mRS score at 90 days after treatment comparing with baseline	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
	95%CI		
	Statistics		
	P value		

Table 7.3.6.2 Continuous change of mRS score (PPS)

The same as above

7.3.7 Secondary effect index – incidence of ischemic cerebrovascular diseases during follow-up period

Table 7.3.7.1 Inter-group comparison of incidence of ischemic stroke within 90 days after treatment

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
	With n(%)				
	Without n(%)				
Have ischemic stroke within 90 days after treatment	N (Missing)				
	Statistics				
	P value				

Table 7.3.7.2 Inter-group comparison of TIA incidence within 90 days after treatment

The same as above

Table 7.3.7.3 Inter-group comparison of ratio of new ischemic focus detected by MRI at last visit

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
	With n(%)				
	Without n(%)				
New ischemic focus detected by MRI at the last visit	N (Missing)				
	Statistics				
	P value				

Table 7.3.7.4 Inter-group comparison of incidence of ischemic cerebrovascular disease during follow-up period

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Have ischemic cerebrovascular disease during visit	With n(%)				
	Without n(%)				
	N (Missing)				
	Statistics				
	P value				

Note: Ischemic cerebrovascular diseases during follow-up period include: Ischemic stroke or TIA within 90 days after random treatment, or new ischemic focus detected by MRI at the last visit

7.3.8 Secondary effect index – incidence of combined vascular events during follow-up period

Table 7.3.8.1 Inter-group comparison of incidence of ischemic stroke within 90 days after treatment

The same as Table 7.3.7.1

Table 7.3.8.2 Inter-group comparison of incidence of myocardial infarction within 90 days after treatment

The same as above

Table 7.3.8.3 Inter-group comparison of incidence of vascular death within 90 days after treatment

The same as above

Table 7.3.8.4 Inter-group comparison of incidence of vascular death during follow-up period

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
Combined vascular events during follow-up period	With n(%)				
	Without n(%)				
	N (Missing)				
	Statistics				
	P value				

Note: Definition of combined vascular events: Include any type of stroke (ischemic stroke and hemorrhagic stroke), TIA, myocardial infarction and vascular death.

7.4 Safety evaluation

7.4.1 Adverse event

Table 7.4.1.1 Inter-group comparison of incidence of adverse events

	Treatment group			Control group			
Item	Case times	Case number	Percentage	Case times	Case number	Percentage	P value
Adverse events							
Adverse events related to study drugs							
Serious adverse events							
Adverse events causing drop-out							
Severe adverse events							
Severe adverse events related to study drugs							

7.4.2 Physical examination

Table 7.4.2.1 Comparison of vital sign indexes between before and after treatment (SS) - systolic pressure (mmHg)

Item	Index	Treatment group	Control group
Systolic pressure at baseline (mmHg)	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
Systolic pressure at 90 days after treatment (mmHg)	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min, Max		
	Statistics		
	P value		
Changes of systolic pressure at 90 days after treatment comparing with that at baseline	N(Missing)		
	Mean(SD)		
	Median		
	Q1,Q3		
	Min,Max		
	Statistics		
	P value		
	95%CI		
	Statistics		
	P value		

Table 7.4.2.2 Comparison of vital sign indexes between before and after treatment (SS) - diastolic pressure (mmHg)

The same as above

Table 7.4.2.3 Comparison of vital sign indexes between before and after treatment (SS) – heart rate (times/minute)

The same as above

Table 7.4.2.4 Comparison of vital sign indexes between before and after treatment (SS) – pulse (times/minute)

The same as above

Table 7.4.2.5 Comparison of vital sign indexes between before and after treatment (SS) – body temperature (℃)

The same as above

Table 7.4.2.6 Numbers and percentages of normal cases before physical examination and abnormal cases after physical examination (SS)

	Treatment group		Control group		
Item	Case number	Percentage	Case number	Percentage	P value
General condition					
Skin and superficial lymph nodes					
Head and neck					
Heart					
Lung					
Abdomen					
Nervous system					
Urogenital system					
Spine and four limbs					
Others					

7.4.3 Laboratory indexes

Table 7.4.3.1 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – blood routine test

	Treatment group		Control group		
Item	Case number	Percentage	Case number	Percentage	P value
Red blood cell –abnormal but without clinical significance					
Red blood cell –abnormal and with clinical significance					
White blood cell - abnormal but without clinical significance					
White blood cell - abnormal and with clinical significance					
Hemoglobin - abnormal but without clinical significance					
Hemoglobin - abnormal and with clinical significance					
Platelet count - abnormal but without clinical significance					
Platelet count - abnormal and with clinical significance					

Table 7.4.3.2 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS)– routine urine test

The same as above

Table 7.4.3.3 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – liver funciton

The same as above

Table 7.4.3.4 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – renal function

The same as above

Table 7.4.3.5 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – blood fat and blood glucose

The same as above

Table 7.4.3.6 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – four items of blood coagulation

The same as above

Table 7.4.3.7 Numbers and percentages of cases with normal laboratory indexes before treatment and abnormal laboratory indexes after treatment (SS) – ECG

	Treatment group		Control group		
Item	Case number	Percentage	Case number	Percentage	P value
Abnormal Q wave					
Abnormal T wave					
Arrhythmia – atrial fibrillation					
Arrhythmia –ventricular premature beat					
Arrhythmia - ventricular tachycardia					
Arrhythmia - atrioventricular block / bundle branch block					
Arrhythmia – other					
Others					
Number of cases with normal ECG before treatment and abnormal ECG after treatment					

Table 7.4.3.8 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – red blood cell – treatment group

Treatment group	After treatment				
Before treatment	Normal	Abnormal but without clinical significance	Abnormal and with clinical significance	Unchecked Loss	Total
Normal					
Abnormal but without clinical significance					
Abnormal and with clinical significance					
Unchecked Loss					
Total					

Table 7.4.3.9 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – red blood cell – control group

Table 7.4.3.11 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – white blood cell – treatment group

Table 7.4.3.13 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – white blood cell – control group

Table 7.4.3.12 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test - hemoglobin –treatment group

Table 7.4.3.13 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test - hemoglobin –control group

The same as above

Table 7.4.3.14Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – platelet count – treatment group

The same as above

Table 7.4.3.15 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood routine test – platelet count – control group

Table 7.4.3.16 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – red blood test – treatment group

The same as above

Table 7.4.3.17 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – red blood test – control group

Table 7.4.3.18 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – white blood cell – treatment group

The same as above

Table 7.4.3.19 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – white blood cell – control group

Table 7.4.3.20 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – urine protein – treatment group

The same as above

Table 7.4.3.21 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) –routine urine test – urine protein – control group

Table 7.4.3.22 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – AST – treatment group

The same as above

Table 7.4.3.23 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – AST – control group

Table 7.4.3.24 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – AST – treatment group

The same as above

Table 7.4.3.25 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – AST – control group

Table 7.4.3.26 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – ALP – treatment group

The same as above

Table 7.4.3.27 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – ALP – control group

Table 7.4.3.28 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – TBIL – treatment group

The same as above

Table 7.4.3.29 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – TBIL – control group

Table 7.4.3.30 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – GGT – treatment group

The same as above

Table 7.4.3.31 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – liver function – GGT – control group

Table 7.4.3.32 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – BUN/UREA – treatment group

The same as above

Table 7.4.3.33 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – BUN/UREA – control group

Table 7.4.3.34 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – Cr – treatment group

The same as above

Table 7.4.3.35 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – Cr – control group

Table 7.4.3.36 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – UA – treatment group

同上 The same as above

Table 7.4.3.37 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – renal function – UA – control group

Table 7.4.3.38 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – TC – treatment group

The same as above

Table 7.4.3.39 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – TC – control group

Table 7.4.3.40 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – LDL-C – treatment group

The same as above

Table 7.4.3.41 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – LDL-C – control group

Table 7.4.3.42 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – HDL-C –treatment group

The same as above

Table 7.4.3.43 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – HDL-C – control group

Table 7.4.3.44 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – TG – treatment group

The same as above

Table 7.4.3.45 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – TG – control group

Table 7.4.3.46 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – GLU – treatment group

Table 7.4.3.47 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – blood lipid and blood glucose – GLU – control group

Table 7.4.3.48 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – PT – treatment group

Table 7.4.3.49 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – PT – control group

Table 7.4.3.50 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – APPT – treatment group

Table 7.4.3.51 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – APPT – control group

Table 7.4.3.52 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – TT – treatment group

Table 7.4.3.53 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – TT – control group

The same as above

Table 7.4.3.54 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – FIB – treatment group

The same as above

Table 7.4.3.55 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – four items of blood coagulation – FIB – control group

The same as above

Table 7.4.3.56 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – ECG-treatment group

Treatment group	After treatment			
Before treatment	Normal	Abnormal	Loss	Total
Normal				
Abnormal				
Loss				
Total				

Table 7.4.3.57 Crosstab for determining clincial significance of laboratory indexes before and after treatment (SS) – ECG-control group

The same as above

7.5 Exploratory analysis

7.5.1 Predicted subgroup analysis on primary indexes –subgroup with or without thrombolytic therapy

Table 7.5.1.1 Improvement of daily life ability at 90 days after treatment –subgroup with thrombolytic therapy

		FAS		PPS	
item	index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.1.2 Improvement of daily life ability at 90 days after treatment – subgroup without thrombolytic therapy

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.2 Predicted subgroup analysis on primary indexes –baseline NIHSS score subgroups

Table 7.5.2.1 Improvement of daily life ability at 90 days after treatment –baseline NIHSS score 4-7 points subgroup

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.2.2 Improvement of daily life ability at 90 days after treatment–baseline NIHSS score 8-14 points subgroup

		FAS		PPS	
项目 Item	指标 Index	试验组 Treatment group	对照组 Control group	试验组 Treatment group	对照组 Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.2.3 Improvement of daily life ability at 90 days after treatment –baseline NIHSS score 15-22 points subgroup

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.3 Predicted subgroup analysis on primary indexes – TOAST type subgroups

Table 7.5.3.1 Improvement of daily life ability at 90 days after treatment – atherothrombotic stroke subgroup

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.3.2 Improvement of daily life ability at 90 days after treatment – cardioembolism subgroup

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.3.3 Improvement of daily life ability at 90 days after treatment – small artery occlusive stroke subgroup

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.3.4 Improvement of daily life ability at 90 days after treatment – subgroup with ischemic stroke caused by other reasons

		FAS		PPS	

Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.3.5 Improvement of daily life ability at 90 days after treatment – subgroup with ischemic stroke of unknown causes

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.4 Predicted subgroup analysis on primary indexes –subgroups for course of disease

Table 7.5.4.1 Improvement of daily life ability at 90 days after treatment – subgroup for course of disease≤12h

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.4.2 Improvement of daily life ability at 90 days after treatment – subgroup for course of disease of 12-48h

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.4.3 Improvement of daily life ability at 90 days after treatment – subgroup for course of disease of 48-72h

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.5 Predicted subgroup analysis on primary indexes –subgroups for course of disease – imaging subgroups

Table 7.5.5.1 Improvement of daily life ability at 90 days after treatment – subgroup with cerebral infarction diagnosed by imaging examination

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.5.2 Improvement of daily life ability at 90 days after treatment - subgroup without cerebral infarction diagnosed by imaging examination

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.5.3 Improvement of daily life ability at 90 days after treatment – subgroup with hemorrhagic impression diagnosed by imaging examination

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.5.4 Improvement of daily life ability at 90 days after treatment - subgroup without hemorrhagic impression diagnosed by imaging examination

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.6 Predicted subgroup analysis on primary indexes –subgroups for course of disease – random time subgroups

Table 7.5.6.1 Improvement of daily life ability at 90 days after treatment - subgroup for random time earlier than median random time

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference 95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

Table 7.5.6.2 Improvement of daily life ability at 90 days after treatment - subgroup for random time later than median random time

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group

		FAS		PPS	
Item	Index	Treatment group	Control group	Treatment group	Control group
mRS score at 90 days after treatment	≤1 point n(%)				
	>1 point n(%)				
	N (Missing)				
	Statistics				
	P value				
	Rate difference				
	95%CI				

Note: 1. Take CMH-χ^2 test to control central effect

7.5.7 Other exploratory analysis

8. Attached tables

Include: List of drug combination, have other disease recently, drug treatment, adverse events, severe adverse events, etc.