Title

A Prospective, Multicenter, Open-Label, Randomized Controlled Study of Early Intensive Lipid-Lowering in Endovascular Treatment for Acute Ischemic Stroke

Early Aggressive Strategy for Treatment of Lipid-Lowering in Acute Ischemic Stroke Delivered with Endovascular Therapy for Large Artery Occlusion (EAST-LDL)

Study Protocol

Protocol Design Institution: East Hospital Affiliated to Tongji University

Principal Investigator Institution: East Hospital Affiliated to Tongji University

MA-CVD-Ⅱ-001

Version Number: 2.1

Version Date: April 25, 2025

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I. Protocol Synopsis

Protocol Title	A Prospective, Multicenter, Open-Label, Randomized Controlled Study of Early Intensive Lipid-Lowering in Endovascular Treatment for Acute Ischemic Stroke
Version No./Version Date	V2.1/April 25, 2025
Study Subjects	Patients with acute ischemic stroke with anterior circulation large vessel occlusion undergoing endovascular treatment
Study Objectives	Primary Objective: To compare the rate (%) of good functional outcome at 90 days (modified Rankin Scale [mRS] score 0-2) in patients with acute ischemic stroke undergoing endovascular treatment between preoperative intensive lipid-lowering therapy with PCSK9 inhibitor (PCSK9i) and guideline-recommended standard of care (SoC). Secondary Objectives 1) mRS ordinal score at 90 days; 2) NIHSS score at 14±3 days or before discharge; 3) Change from baseline in NIHSS score at 14±3 days or before discharge; 4) LDL-C target attainment rate at 14±3 days or before discharge; 5) Change from baseline in LDL-C at 14±3 days or before discharge; 6) Change from baseline in inflammatory markers at 14±3 days or before discharge; 7) Rate of severe disability (mRS score 3-5) at 90 days; 8) Mortality rate (mRS score of 6) at 90 days; 9) Incidence of recurrent ischemic stroke events within 90 days; 10) Incidence of symptomatic intracranial hemorrhage transformation within 24-48h; 11) Incidence of new hemorrhagic stroke within 90 days; 12) Incidence of major adverse cardiovascular events (MACEs) within 90 days; 13) Safety assessment within 90 days; 14) Quality of life scale (EQ-5D) at 90 days.
Study Design	This study adopts a prospective, national multicenter, open-label, randomized controlled clinical trial design. Patients meeting eligibility criteria will be allocated 1:1 to the PCSK9i intensive lipid-lowering treatment group or the guideline-recommended SoC group, with the proportion of patients with modified Rankin Scale (mRS) (0-2) at 90 days as the primary endpoint. A total of 652 patients are planned for enrollment. This study will use a stratified block randomization method, with stratification factors as follows: 1) Medical center (stratified into 2 subgroups based on the number of patients who received endovascular treatments for acute ischemic stroke at the center in the previous year: 50-99 patients/year; ≥100 patients/year) 2) Time from onset to randomization (0-6h [inclusive]; 6-24h)

Study Population	Patients with acute ischemic stroke with anterior circulation large vessel occlusion undergoing endovascular treatment
Inclusion/Exclusion Criteria	**Inclusion Criteria** (1) Adults (age 18 years and older); (2) Imaging diagnosis of acute ischemic stroke with anterior circulation large vessel occlusion (including: internal carotid artery, middle cerebral artery M1 and M2, anterior cerebral artery A1 and A2); (3) Planned to undergo endovascular intervention within 24 hours of symptom onset (or last known well time) according to local guidelines; (4) Provision of informed consent by the patient or his/her legally authorized representative (or by an appropriate agent according to local requirements). **Exclusion Criteria** (1) ASPECTS score ≤5 on cranial CT imaging; (2) Pre-existing functional impairment, with mRS score >2; (3) Patients who are allergic to PCSK9 inhibitors; (4) Patients who have received PCSK9 monoclonal antibody within 1 month prior to enrollment or PCSK9 siRNA therapy within 6 months prior to enrollment; (5) Severe renal insufficiency, defined as estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2 at final screening; (6) Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal; (7) Severe, concomitant non-cardiovascular disease expected to reduce life expectancy to less than 3 months; (8) Pregnant or lactating women; (9) Patients who are participating in other clinical trials; (10) Other conditions deemed unsuitable for inclusion in the clinical study by the investigator.
Study Drugs	**Investigational Product:** **Drug Name:** Recaticimab Injection **Drug Strength:** 150mg Recaticimab lyophilized powder for injection

Method of Administration	[Investigational Group] Recaticimab is added to the guideline-recommended SoC. After randomization and before endovascular treatment, patients will receive a subcutaneous injection of Recaticimab. The specific method is: Recaticimab 450mg (3 vials) as a single subcutaneous injection, until the end of the follow-up for this study. [Control Group] Guideline-recommended SoC.
Evaluation Measures	1. Baseline: NIHSS score; LDL-C level; blood inflammatory markers (white blood cell count, CRP); 2. 24-48 hours: NIHSS score; cranial CT assessment for symptomatic intracranial hemorrhage; 3. 14±3 days or at discharge: NIHSS score; LDL-C level; blood inflammatory markers (white blood cell count, CRP); 4. 90 ± 7 days: mRS score; recurrent ischemic stroke events within 90 days; new-onset hemorrhagic stroke events within 90 days; MACEs within 90 days; adverse events (AEs); EQ-5D scale.
Sample Size	This is a randomized controlled study. According to previous study reports, the proportion of patients with mRS (0-2) in patients with acute ischemic stroke receiving endovascular treatment from the control group is approximately 45%. Based on early study data of the investigational treatment regimen, the proportion of patients with mRS (0-2) in the investigational group in this study is expected to reach 58%, with an inter-group difference of approximately 13%. The significance level α is set at 0.05 (two-sided). Using the Z-test (pooled) module of NCSS PASS 21 (LLC. Kaysville, Utah, USA, ncss.com/software/pass) software, it is calculated that approximately 309 subjects need to be enrolled in each group to provide at least 90% power (1-β) to detect a difference in the proportion of patients with mRS (0-2) between the investigational treatment regimen and the control treatment regimen. Considering 5% dropout and protocol violations, a total of 326 subjects need to be enrolled in each group for this study, meaning a total of 652 subjects need to be enrolled for both groups.
Statistical Methods	**General Analysis** For continuous data, statistics such as number, mean, standard deviation, median, minimum, and maximum will be summarized; for categorical data, statistics such as frequency and percentage will be summarized; for

	time-to-event data, the Kaplan-Meier method will be used to estimate the survival function and the median time to event occurrence, and survival curves will be plotted. Efficacy analyses of primary and secondary endpoints will be conducted in the intent-to-treat (ITT) population, i.e., all randomized patients. Safety analysis will be performed in the as-treated safety set (SS). All statistical analyses will be performed using SAS 9.4 software. **Efficacy Analysis** The study's primary efficacy endpoint is the percentage of patients with mRS (0-2), and a logistic regression model adjusted for stratification factors will be used to estimate the odds ratio of mRS (0-2) between the investigational group and the control group, along with the corresponding 95% confidence interval (CI) and *p*-value. For the ordinal mRS endpoint among the secondary endpoints, a proportional-odds logistic regression model adjusted for stratification factors will be used to estimate the common odds ratio and its corresponding 95% CI and *p*-value. Other binary endpoints will be analyzed using the same regression model as the primary endpoint. For event endpoints, the Kaplan-Meier method will be used to estimate the median value, and the Brookmeyer-Crowley method will be used to estimate the 95% CI for the median time to event. Survival curves will be plotted, and the stratified Logrank test will be used to compare survival differences between groups; **Safety Analysis** Safety analysis will primarily be descriptive statistical analysis. All AEs will be coded using MedDRA and graded according to the NCI-CTCAE version 5.0 grading system. All treatment-emergent AEs, drug-related AEs, serious adverse events (SAEs), and drug-related SAEs will be listed by the highest severity. Laboratory test results, vital signs, electrocardiogram (ECG) data, etc. will be analyzed using conversion tables to compare the baseline and post-baseline conditions.

II. Table of Contents

III. Management Algorithm

Protocol History Record

Version No.	Version Date	Revision Summary
1.0	January 20, 2025	Initial Version
2.0	March 12, 2025	1. Added quality of life assessment at 90 days using the EQ-5D scale. 2. Added lipid profile testing at 90 days. 3. Adjusted PCSK9i administration time to before endovascular treatment.
2.1	April 25, 2025	Added supplementary explanation for the selection of study drug administration regimen

IV. Study Background

1. Epidemiology

Stroke is a global health problem and the second leading cause of death worldwide. Furthermore, there are currently over 80 million stroke survivors globally. Among these survivors, half are left with moderate to severe neurological deficits, and one-quarter require assistance from others in their daily lives. Stroke is now the third leading cause of disability in adults worldwide[1]. China also faces the world's largest stroke challenge. Results from the global burden of disease (GBD) study show that in 2019, there were 3.94 million new stroke cases in China, the number of stroke patients reached 28.76 million, and the number of stroke deaths was 2.19 million[2]. Furthermore, in the coming decades, the family and societal burden of stroke is expected to increase further due to population aging, the continued high prevalence of risk factors (such as hypertension), and inadequate management[3].

Stroke can be divided into ischemic stroke and hemorrhagic stroke based on its nature, with approximately 80% of strokes being ischemic stroke[2]. Acute ischemic stroke (AIS) refers to a clinical syndrome characterized by acute cerebral blood supply disorders due to various causes, leading to local brain tissue ischemia, hypoxic necrosis, and corresponding neurological deficits. It is mostly caused by thrombosis or embolism obstructing cerebral blood vessels supplying specific brain regions. Particularly, acute ischemic stroke with large vessel occlusion (LVO) accounts for about 30% of all AIS. Due to the large area supplied by the occluded vessel, ischemia can lead to extensive cerebral infarction, resulting in higher mortality and disability rates than other ischemic stroke subtypes[3]. In recent years, endovascular interventional treatment, by rapidly opening occluded large arteries early and

quickly restoring blood flow to brain tissue, has been proven to benefit some patients with ischemic stroke with large artery occlusion[4]. Endovascular interventional treatment has become the preferred treatment for selected patients with stroke with anterior circulation large vessel occlusion. Data from the CNIS China Thrombectomy Quality Control Registry show that the number of emergency thrombectomies in China reached 88,131 in 2023. Combined with 77,299 cases in 2022 and 67,147 cases in 2021, the national number of emergency thrombectomies is expected to maintain an annual growth rate of around 10,000 cases in the next 2-3 years. However, even with this effective treatment, only about 40% of patients who successfully achieve vascular recanalization through reperfusion therapy achieve a good prognosis[5]. This phenomenon, where functional recovery is poor despite vascular recanalization, is known in the medical field as "futile recanalization"[6], and its causes are currently unclear. In recent years, growing evidence suggests that neuroinflammation and the presence of microthrombi may be among the key mechanisms underlying futile recanalization after reperfusion therapy for ischemic stroke[7,8]. However, effective drugs for targeted treatment are currently lacking. Therefore, medical researchers and clinicians urgently need to find effective solutions.

2. Application of PCSK9i in Lipid Management for Acute Ischemic Stroke

Therapies to lower low-density lipoprotein cholesterol have been proven to reduce the risk of recurrence after acute ischemic stroke, and statins are the main representative drugs for lowering LDL-C levels, forming the cornerstone of secondary prevention therapy for ischemic stroke[4,9]. Although the mainstream clinical drugs for lowering LDL-C are statins (cholesterol synthesis inhibitors). Moderate statin therapy can reduce LDL-C levels by 25% ~ 50%, but doubling the dose only increases the LDL-C lowering effect by an additional 6%, while increasing potential side effects such as liver damage, myopathy, and new-onset diabetes[31]. LDL-C control in China is not ideal. Among individuals with established ASCVD, the LDL-C control target achievement rate is only 6.8%[31]. Furthermore, the Chinese population has poorer tolerance to high-dose statins compared to European and American populations, further exacerbating the treatment dilemma. In recent years, the emergence of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has ushered in a new era of lipid-lowering therapy. The 2023 "Chinese Guidelines for Lipid Management" recommend, on the basis of lifestyle intervention, initiating treatment with moderate-intensity statins, and if necessary, using a treat-to-target strategy by combining cholesterol absorption inhibitors and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors[31].

PCSK9 is the 9th member of the proprotein convertase subtilisin/kexin family, is a serine protease encoded by the PCSK9 gene, mainly produced in liver cells, and is expressed in various cells throughout the body. In 2003, Abifadel et al. first revealed the correlation between PCSK9 gene mutations and autosomal dominant familial hypercholesterolemia[10]. Subsequent studies further found that loss-of-function mutations in PCSK9 can enhance the liver's lipid metabolism capacity, thereby lowering blood LDL-C levels[11]. Further exploration of its mechanism revealed that PCSK9 protein can participate in the degradation of the low-density lipoprotein receptor (LDLR). When LDLR on the cell surface binds to free LDL-C in the blood and mediates its endocytosis into the cell, it is further degraded and metabolized intracellularly, while LDLR is transported back to the cell membrane for recycling. The PCSK9 molecule can bind to LDLR extracellularly, forming a PCSK9-LDLR-LDL-C complex. This complex is transported to lysosomes for degradation, blocking the process of LDLR returning to the cell membrane for recycling, thereby inhibiting the cell's clearance of LDL-C and leading to abnormally elevated LDL-C levels in the blood. [12]

Drugs targeting PCSK9 have been a research hotspot in recent years, including monoclonal antibodies, antisense nucleotides, small interfering RNAs, and small molecule inhibitors. Their function is to neutralize or inhibit the PCSK9 protein, block its mediated LDLR degradation process, and upregulate cell surface LDLR levels, thereby enhancing the body's ability to metabolize LDL-C. Among these, PCSK9 monoclonal antibody (PCSK9 mAb), as a representative drug of PCSK9i, was the first to enter clinical application and is characterized by strong targeting, high specificity, and low toxic side effects. During 2017-2018, two high-quality clinical studies demonstrated that when used in combination with statins, PCSK9 inhibitors can further reduce low-density lipoprotein (LDL) cholesterol levels and decrease the incidence of vascular events, including ischemic stroke and myocardial infarction[13,14]. Precisely because of the evidence from these two pivotal trials, authoritative guidelines both domestically and internationally, such as the 2019 European Society of Cardiology (ESC) dyslipidemia management guidelines, recommend the combined use of PCSK9 inhibitors for secondary prevention in high-risk atherosclerotic cardiovascular disease (ASCVD) patients if lipid levels remain poorly controlled despite high-dose statin and ezetimibe combination therapy[15].

However, in the early management of acute ischemic stroke, the correlation between lipid levels and patients' neurological functional prognosis remains unclear. In recent years, there has been increasing attention on the impact of lipid levels and intensive lipid-lowering

therapy on neurological functional outcomes in acute ischemic stroke. Observational studies have found that among patients with acute ischemic stroke, those whose LDL-C levels increased during hospitalization had a higher proportion of unfavorable outcomes at discharge compared to those whose LDL-C levels decreased[16]. The latest high-quality RCT study found that in patients with acute ischemic stroke, early initiation of intensive statin therapy within 72 hours, compared to delayed intensive statin lipid-lowering therapy, can reduce the risk of recurrent stroke within 90 days and improve patients' neurological functional prognosis without increasing the risk of hemorrhage[17]. Another retrospective clinical study found that for patients with ischemic stroke with large artery occlusion undergoing mechanical thrombectomy, those who received early PCSK9i lipid-lowering therapy had lower NIHSS scores at discharge and a higher proportion of mRS ≤3 compared to the control group. Although there was no significant statistical difference in the proportion of good prognosis at 3 months between the two groups, there was no risk of early neurological deterioration or hemorrhage[18]. Preliminary analysis from a small-sample observational study previously conducted at our center also found that patients with large vessel occlusion who received PCSK9 inhibitors after thrombectomy had better mRS scores at 3 months compared to the control group. In summary, the use of intensive lipid-lowering therapy in the early stage of acute ischemic stroke may be safe and has the potential value of improving neurological functional outcomes. As a novel lipid-lowering drug that has emerged in recent years, PCSK9i achieves a greater degree of intensive lipid-lowering than statins and other oral lipid-lowering drugs. Therefore, its impact on neurological function when used for early lipid-lowering therapy in patients with acute ischemic stroke is highly worthy of further exploration, and the underlying mechanisms also warrant further investigation.

3. Pleiotropic Effects of PCSK9 Inhibitor Drugs Beyond Lipid Lowering

In fact, in addition to regulating lipid components such as LDL-C, PCSK9 inhibitors may also be involved in processes such as anti-inflammatory immune regulation, and antithrombotic effects in arteries and veins, exerting pleiotropic effects.

Studies have found that PCSK9 can lead to the upregulation of receptors such as SR-A, CD36, and LOX-1 on the surface of macrophages, activating downstream inflammation-related pathways and promoting the occurrence of inflammatory responses[19]. PCSK9 siRNA, by regulating inflammation-related transcription factors, can inhibit nuclear factor-kappa B (NF-kB) and suppress the secretion of inflammatory factors such as interleukin-1α (IL-1α), IL-6, and tumor necrosis factor α (TNF-α) induced by oxidized low-density lipoprotein (ox-LDL), exerting anti-inflammatory functions in mice[20]. In PCSK9 gene knockout mice,

while plaque volume and intimal thickness were reduced, the levels of inflammatory factors within the plaques also decreased[21]. There is also evidence that inhibiting PCSK9 can eliminate ox-LDL-mediated inflammatory responses in pro-inflammatory T cells and dendritic cells, including downregulation of co-stimulatory molecules (CD83, CD86, and HLA-DR) and scavenger receptors (LOX-1 and CD36) on the cell membrane, as well as inhibition of T cell polarization towards Th1 and Th17 subsets[22]. After PCSK9 mAb treatment, the expression of chemokine (C-C motif) receptor 2 (CCR2) on the surface of monocytes can be reduced, thereby significantly decreasing monocyte infiltration in the vascular wall[23]. Previous studies at our center found that after injecting PCSK9 inhibitor into ischemia-reperfusion model mice, neurological dysfunction was alleviated compared to the control group, and it was also found that the GPNMB/CD44 pathway-mediated inflammatory response was inhibited[24]. In summary, a large amount of cellular and animal experimental data currently supports the anti-inflammatory effects of PCSK9 inhibitors, but corresponding clinical data to confirm this is still lacking. Although there has been some exploration in studies of acute cardiovascular events, research on patients with ischemic stroke is still almost nonexistent.

In addition to inflammatory responses, PCSK9 may also be involved in the formation of arterial and venous thrombi. Studies have found that in in vitro experiments, after activation by agonists, indicators of platelet interaction from human and mouse sources, such as P-selectin and glycoprotein IIb/IIIa, are further elevated[25,26]. Additionally, in a carotid artery injury mouse model with PCSK9 knockout, using ferric chloride to stimulate thrombus formation, it was found that compared to wild-type mice, PCSK9 knockout mice took longer to form arterial thrombi, and the volume of the thrombi formed was also smaller[26]. These findings all suggest a correlation between PCSK9 and platelet activation reactivity. Similar findings have also been observed in human populations. Navarese et al. found that in patients with acute coronary syndrome, those with higher PCSK9 concentrations exhibited stronger platelet aggregation responses after activation by adenosine diphosphate[27]. Barale et al. found that after treating hypercholesterolemia patients with PCSK9i, their platelet activity significantly decreased and their responsiveness to aspirin increased. Factors reflecting platelet function, such as P-selectin and platelet factor 4, showed a significant decline[28]. A meta-analysis including the FOURIER and ODYSSEY studies found no significant correlation between baseline LDL-C levels and the extent of reduction in venous thromboembolism risk. However, the use of PCSK9 inhibitors significantly reduced the risk of venous thromboembolism (HR=0.69, 95% CI: 0.53~0.90, P=0.007)[29].

In summary, PCSK9 can directly activate platelets on the one hand, and on the other hand, it can lead to abnormal lipid and inflammatory states, indirectly causing a hypercoagulable state in the body. Both of these enhance platelet function when PCSK9 levels are elevated. This also suggests that, in addition to lowering lipid levels, PCSK9 inhibitors have the potential for combined use with traditional drugs such as aspirin in patients requiring antiplatelet or even anticoagulant therapy, thereby enhancing patients' responsiveness to antiplatelet drugs and improving prognosis[30].

V. Study Objectives

1. Primary Objective

To explore the effect of preoperative early intensive lipid-lowering therapy with PCSK9 inhibitor on good functional outcome at 90 days (modified Rankin Scale [mRS] score 0-2) in patients with acute ischemic stroke with anterior circulation large vessel occlusion undergoing endovascular treatment.

2. Secondary Objectives

Compared to the control group receiving guideline-recommended SoC, the effects of adding PCSK9 inhibitor on the following aspects in patients with acute ischemic stroke with anterior circulation large vessel occlusion undergoing endovascular treatment: mRS ordinal score at 90 days; NIHSS score at 14±3 days or before discharge; change from baseline in NIHSS score at 14±3 days or before discharge; LDL-C target attainment rate at 14±3 days or before discharge; change from baseline in LDL-C at 14±3 days or before discharge; change from baseline in inflammatory markers (white blood cell count, CRP) at 14±3 days or before discharge; rate of severe disability (mRS 3-5) at 90 days; mortality rate (mRS 6) at 90 days; incidence of recurrent ischemic stroke events within 90 days; incidence of symptomatic intracranial hemorrhage transformation within 48h; incidence of new-onset hemorrhagic stroke within 90 days; incidence of MACEs within 90 days; incidence of SAEs within 90 days; European quality of life scale (EQ-5D) at 90 days.

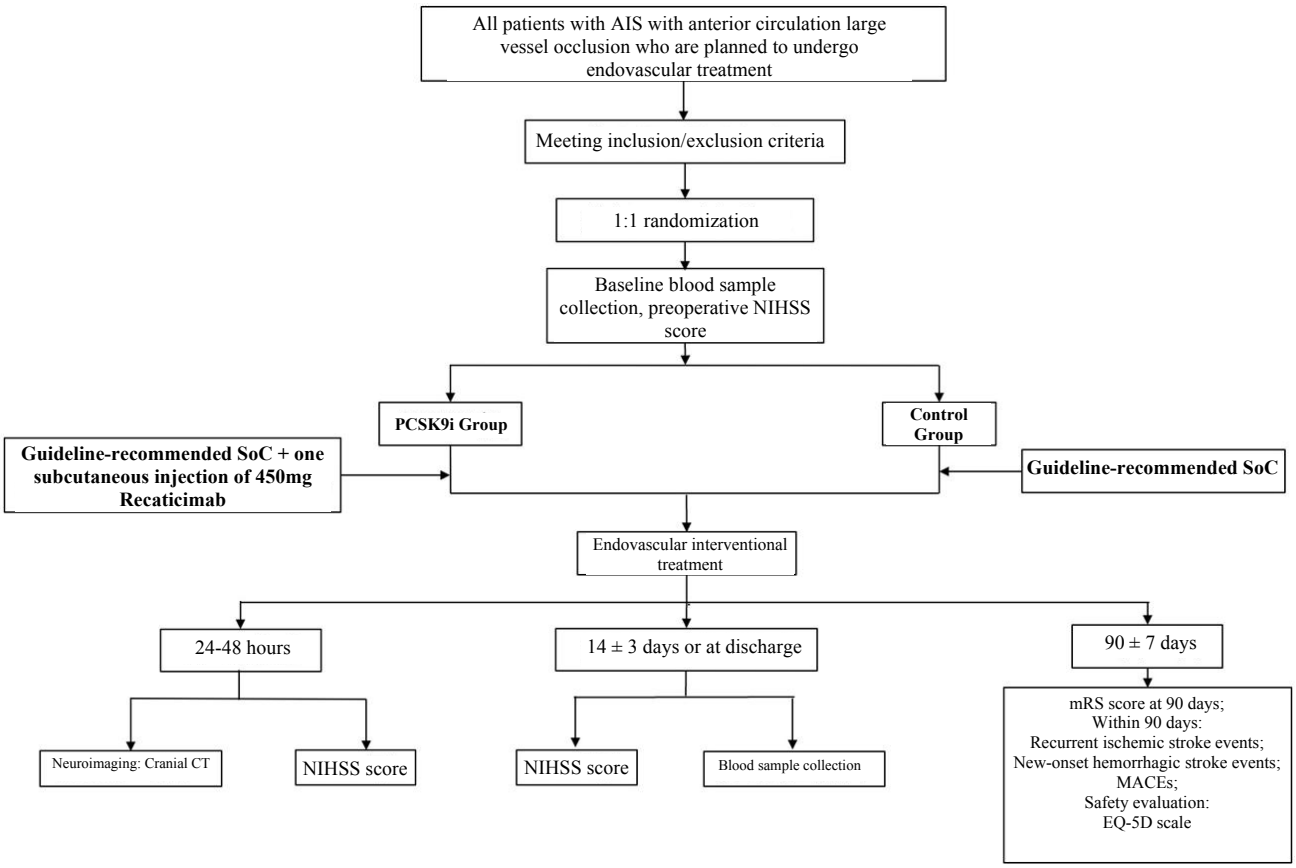
VI. Study Methods

1. Overall Design:

This is a prospective, multicenter, open-label, randomized controlled clinical study. This study will enroll 652 patients with acute ischemic stroke with anterior circulation large vessel

occlusion undergoing endovascular treatment from approximately 10+ clinical sites in China. Patients will be randomly assigned 1:1 to the PCSK9 inhibitor treatment group and the SoC control group. The study design is shown in the figure below (Study Design Flowchart).

2. Study Design (Flowchart)



3. Study Population

All patients with acute ischemic stroke with anterior circulation large vessel occlusion who are planned to undergo endovascular reperfusion therapy at participating sites can be considered for this study. The principal investigator at each site bears the primary responsibility for patient enrollment. Because enrollment is recommended before stroke patients receive endovascular treatment, successful enrollment is expected to require the active participation of relevant physicians at each site. The following reasons are expected to limit the enrollment rate:

- The absolute number of patients receiving endovascular treatments;
- Compliance with inclusion/exclusion criteria;
- Obtaining informed consent, and conducting baseline assessments.

4. Inclusion and Exclusion Criteria

To meet the inclusion criteria for this study, patients must meet the local standard criteria for endovascular treatment of acute ischemic stroke with anterior circulation large vessel occlusion, and the attending physician must consider the clinical uncertainty for each patient, weighing the potential benefits and risks of neuroprotective therapy, as follows:

4.1 Inclusion Criteria

[1] Adults (age 18 years and older);

[2] Imaging diagnosis of acute ischemic stroke with anterior circulation large vessel occlusion (including: internal carotid artery, middle cerebral artery M1 and M2, anterior cerebral artery A1 and A2);

[3] Planned to undergo endovascular intervention within 24 hours of symptom onset (or last known well time) according to local guidelines;

[4] Provision of informed consent by the patient or his/her legally authorized representative (or by an appropriate agent according to local requirements).

4.2 Exclusion Criteria

[1] ASPECTS score ≤5 on cranial CT imaging;

[2] Pre-existing functional impairment, with mRS score >2;

[3] Patients who are allergic to PCSK9 inhibitors;

[4] Patients who have received PCSK9 monoclonal antibody within 1 month prior to enrollment or PCSK9 siRNA therapy within 6 months prior to enrollment;

[5] Severe renal insufficiency, defined as estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m2 at final screening;

[6] Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal;

[7] Severe, concomitant non-cardiovascular disease expected to reduce life expectancy to less than 3 months;

[8] Pregnant or lactating women;

[9] Patients who are participating in other clinical trials;

[10] Other conditions deemed unsuitable for inclusion in the clinical study by the investigator.

5. Ethical Issues

This study adheres to the principles outlined in the Declaration of Helsinki of the World Medical Association.

5.1 Ethics Committee Approval

Before patient enrollment begins, each participating site must obtain written approval from the Ethics Committee (e.g., Institutional Review Board [IRB]). The principal investigator at each study site is responsible for any amendments to the study protocol, reporting of serious adverse events (SAEs), and routine reports to the IRB.

5.2 Informed Consent

Most patients presenting with acute ischemic stroke with large artery occlusion require emergency treatment, including endovascular interventional therapy. However, the acute nature of this condition means that patients may be unable to understand the information that must be conveyed during the informed consent process due to their medical condition. To avoid delays in emergency treatment, informed consent needs to be obtained promptly. The optional informed consent procedures for this study are detailed below, and local Ethics Committee regulations should be adhered to.

5.2.1 Patient Informed Consent

Whenever possible, the patient should provide written informed consent. A clinician familiar with the study protocol will explain the situation to the patient and the implications of consenting to participate in this study.

5.2.2 Legally Authorized Representative Informed Consent

If the patient is unable to provide informed consent, for example, due to a decreased level of consciousness or confusion, the patient's legally authorized representative may provide informed consent on his/her behalf.

5.2.3 Withdrawal of Informed Consent

The informed consent information provided to the patient and/or his/her legally authorized representative will clearly state that the patient may withdraw from the study at any time without explanation, and the patient will not be prejudiced or disadvantaged as a result. This should be documented in the patient's file. If the patient withdraws consent only related to the

use of PCSK9i, data collection may continue, and this situation will be recorded in the patient's file.

5.2.4 Confidentiality and Privacy

Patient privacy should be respected during the conduct of the study. To ensure patient privacy, submitted data will be de-identified. However, during the monitoring of data quality and adherence to the study protocol, clinical research associates (CRAs) may access medical records at participating hospitals.

6 Randomization

6.1 Randomization Procedure

Eligible patients will be randomly assigned 1:1 according to a stratified block randomization method to ensure balance between groups and within groups over time.

Stratification Factors:

1) Medical center (stratified into 2 subgroups based on the number of patients who received endovascular treatments for acute ischemic stroke at the center in the previous year: 50-99 patients/year; ≥100 patients/year)

2) Time from onset to puncture (0-6h [inclusive]; 6-24h)

Procedure for Handling Patients Incorrectly Enrolled or Randomly Assigned

Under no circumstances should patients who do not meet the eligibility criteria be enrolled in this study or undergo randomization. This principle must be adhered to in all situations.

If a patient who does not meet the eligibility criteria has already been enrolled in this study, the following procedure should be followed:

1) The investigator or CRA should immediately notify the study team physician, with patient safety as the top priority.

2) If continuing the study treatment may jeopardize the patient's safety, the study treatment must be discontinued. After discussion between the study team physician and the investigator, a decision will be made on whether to discontinue the study drug. The reason for discontinuing study treatment must be clearly documented. The patient should undergo follow-up according to the prescribed study procedures, including follow-up for endpoint events, until the end of the study. This is consistent with the intention-to-treat principle.

3) If continuing the study is deemed not to pose a safety risk to the patient and not to affect the treatment of the disease, the reason for continuing the study should be clearly documented.

The patient should continue to undergo follow-up according to the prescribed study procedures.

6.2 Blinded Follow-up

Follow-up assessment scales, event occurrences, and imaging evaluations, etc., will be analyzed, assessed, and recorded by a trained professional designated by each site or arranged by the study coordinating site, who is unaware of the patient's treatment group assignment.

6.3 Blinded Review

After blinded review and confirmation of the correctness of the established database, the data will be locked by the principal investigator and statistical analysts. Locked data files will not be modified further.

7 Interventions

7.1 Study Drugs

7.1.1 PCSK9i Drug Selection

Drug Name: Recaticimab

Drug Strength: Lyophilized powder for injection, 150 mg/vial

7.2 Dosage and Method of Administration

Investigational Group: Recaticimab is added to the guideline-recommended SoC. After randomization and before endovascular interventional treatment, patients will receive a subcutaneous injection of Recaticimab. The specific method is: Recaticimab 450mg (3 vials) as a single subcutaneous injection, until the end of the follow-up for this study.

The Phase III registration studies of Recaticimab, REMAIN-1 and REMAIN-2, have confirmed good lipid-lowering efficacy and safety of Recaticimab 450mg SC Q12W (every 12 weeks). Considering that most acute stroke patients have limited mobility, to improve subject follow-up compliance and ensure study quality, the 450mg SC Q12W dosing regimen is chosen.

Control Group: Guideline-recommended SoC, including but not limited to oral lipid-lowering drugs, antiplatelet aggregation drugs, anticoagulant drugs, antihypertensive drugs, etc. It is to be determined by the investigator based on the subject's treatment needs.

7.3 Drug Management

Drug management will be carried out in accordance with the package insert and the standard operating procedures for pharmacy management at each hospital.

7.4 Surgical Method:

The surgical method for endovascular interventional reperfusion therapy is not restricted.

7.5 Prohibited Medications in the Study:

Any drugs targeting PCSK9 (including PCSK9 mAb or PCSK9 siRNA) or non-drug lipid-lowering therapies (such as lipid filtration, etc.) are prohibited.

8. Withdrawal and Removal Criteria

8.1 Withdrawal at the Investigator's Discretion

If a situation arises during the study where it is inappropriate for an enrolled subject to continue, the investigator will decide to withdraw the case from the study.

1) Occurrence of allergic reactions or SAE, where the physician judges that the subject should be withdrawn from the study.
2) The patient's symptoms worsen after medication for which, to protect the subject, he/she will be withdrawn from the study to receive other effective treatments.
3) During the study, the subject develops certain comorbidities, complications, or special physiological changes that affect the assessment of efficacy and safety.
4) During the study, the subject has poor compliance, with drug usage less than 70% or more than 130% of the prescribed amount.
5) During the study, cases of unblinding for any reason;
6) Other situations where the investigator deems it inappropriate to continue the study.

8.2 Withdrawal at the Subject's Discretion

According to the provisions of the informed consent form (ICF), subjects have the right to withdraw from the study midway, or if a subject, although not explicitly withdrawing, is lost to follow-up by no longer accepting medication and assessments, this is also considered "withdrawal" (or "dropout").

Patients are free to withdraw from the study at any time (e.g., permanently discontinuing study medication and withdrawing from study assessments) without affecting their further treatment (withdrawal of informed consent). Withdrawal of informed consent from this study must be confirmed by the investigator and recorded on the case report form (CRF) and the

ICF. If possible, the patient and the investigator should re-sign and date the ICF. These patients should be asked the reason for withdrawal and whether any AEs are present. The reason for permanent discontinuation of study drug treatment and the date of the last dose of study drug must be recorded in the CRF.

Patients who permanently discontinue study medication should receive standard treatment, if applicable, and should be asked to continue participating in visits. If the patient refuses any additional study follow-up and formally withdraws informed consent (including whether they consent to the continued use of collected de-identified clinical data), the study coordinating site should be notified. If the patient and his/her family refuse the use of any clinical data for the study, after notifying the study coordinating site, the database will be contacted to delete all data for that patient.

At the end of the planned follow-up period for all patients (90 days ± 7 days post-randomization), for patients who have withdrawn informed consent, their survival status will be collected from public data sources to the extent permitted by local regulations after their withdrawal of consent.

To ensure the validity of study data, it is important to collect as much data as possible during the study period, especially survival status (dead or alive). Therefore, investigators should attempt at the end-of-treatment visit and study closure visit to collect survival status information for all patients who have withdrawn informed consent from public data sources. Withdrawn subjects cannot be replaced.

8.3 Criteria for Case Removal

Subjects who should not have been enrolled but are enrolled, or who, although completing the study, have violated certain provisions of the study protocol during the process and are deemed by the investigator to warrant removal, include:

1) Those who have never received study medication;

2) Those with no assessment records after study medication;

3) Those for whom efficacy and safety evaluation is impossible due to the use of a prohibited medication.

At the blinded review meeting, the principal investigator and statisticians will decide whether a case is to be removed and into which dataset it will be entered. The reasons for removing cases should be stated, and their study medical records should be retained for inspection.

9. Study Endpoints:

Primary Endpoint:

1) To compare the rate (%) of good functional outcome at 90 days (mRS 0-2) in patients with acute ischemic stroke undergoing endovascular treatment between preoperative intensive lipid-lowering therapy with PCSK9 inhibitor (PCSK9i) and guideline-recommended standard of care (SoC).

Secondary Endpoints:

1) mRS ordinal score at 90 days;
2) NIHSS score at 14±3 days or before discharge;
3) Change from baseline in NIHSS score at 14±3 days or before discharge;
4) LDL-C target attainment rate at 14±3 days or before discharge;
5) Change from baseline in LDL-C at 14±3 days or before discharge;
6) Change from baseline in inflammatory markers at 14±3 days or before discharge;
7) Rate of severe disability (mRS score 3-5) at 90 days;
8) Mortality rate (mRS score of 6) at 90 days;
9) Incidence of recurrent ischemic stroke events within 90 days;
10) Incidence of symptomatic intracranial hemorrhage transformation within 24-48h;
11) Incidence of new hemorrhagic stroke within 90 days;
12) Incidence of MACEs within 90 days;
13) Safety assessment;
14) Quality of life scale (EQ-5D).

10. Data Collection and Follow-up

Study sites need to collect all patient and study-related information at the following time points: Baseline (after randomization, before treatment); treatment period (Day 0, day of randomization); 24-48 hours post-randomization, Day 14±3 days or at discharge, and Day 90±7 days follow-up. Assessments at each follow-up time point will be conducted face-to-face or by telephone by a trained physician designated by each study site or the study

coordinating site, who is blinded to the patient's treatment group assignment. The content of the follow-up conversations must be audio-recorded and saved. For results of blood test indicators at baseline and each follow-up time point, laboratory reports should be collected for retention. Brain imaging data will be collected by each site. The study coordinating site will assist each site with uploading imaging data. After uploading, a trained professional designated by the study coordinating site, who is blinded to the patient's treatment group assignment, will be responsible for imaging analysis. All data must be entered into the database or recorded on paper CRFs and retained as source data.

All randomized patients will be followed up for 90 days ± 7 days. If death occurs before 90 days ± 7 days, follow-up will be performed until patient death. Patients who do not adhere to the protocol and/or discontinue their assigned treatment regimen also need to be followed up for 90 days ± 7 days, as their data will be analyzed according to the "intention-to-treat" principle. The study flowchart lists the types of data to be collected and the schedule during the study. The study coordinating site will provide paper versions of the CRFs and an operations manual for reference, as well as CRF completion guidelines and definitions of terms.

10.2 Randomization Assessment

For all patients undergoing endovascular treatment for acute ischemic stroke, the attending physician will use an inclusion/exclusion criteria checklist to assess the patient's suitability for enrollment in this study. This checklist needs to be kept with the patient's study file in a locked filing cabinet at each participating study site.

Specifically, it includes:

- Inclusion and exclusion criteria.
- Medical center information: Name; Number of patients who underwent endovascular treatments for acute ischemic stroke at the center in the previous year.
- Patient information: Initials, sex, date of birth, time of onset (last known well time), pre-stroke mRS score.
- Imaging information: ASPECTS score on cranial CT, responsible vessel indicated by CTA/MRA imaging.
- Randomization stratification information: Hospital stratification, time from onset to randomization.
- Randomization result: Investigational group or control group.

10.3 Baseline Data

(1) Patient basic information and general condition: Height, body weight.

(2) History of present illness and physical examination: Time of arrival at hospital, blood pressure on admission, heart rate, blood glucose, NIHSS score on admission, GCS score,

(3) Acute phase drug treatment information:

a) Whether intravenous thrombolysis is performed, name of thrombolytic drug (rtPA, TNK, other, time of administration, dose);

b) Antithrombotic drugs used in the acute phase: Drug names: Aspirin, Clopidogrel, Ticagrelor, Cilostazol, and Tirofiban, other, specific time of administration, dose.

(4) Past medical history: Hypertension, diabetes mellitus, stroke or TIA, cerebral hemorrhage, ischemic heart disease, hyperlipidemia, arrhythmia, valvular heart disease, history of smoking, history of alcohol consumption.

(5) Prior medications: Anticoagulant drugs, antiplatelet drugs, lipid-lowering drugs, including statins, ezetimibe, etc. Whether PCSK9i-related drugs have been used previously, record name and time of use.

(6) Hematological parameters:

a) Lipids: Total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipoprotein (a), apolipoprotein B;

b) Hematology: Red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count;

c) Blood chemistry: Renal function: Creatinine, uric acid; Liver function: Aspartate aminotransferase, alanine aminotransferase; Glucose;

d) Coagulation function tests: APTT, INR;

e) Blood inflammatory response markers: CRP;

(7) Brain imaging: Study sites with necessary capability may complete brain tissue perfusion assessment (record the time): Cranial CTP or PWI, etc., record core infarct volume, hypoperfusion volume, and name of assessment software.

(8) ECG: Record the time, presence of atrial fibrillation.

10.4 Medication Information (Preoperative)

(1) PCSK9i use information, including drug information for PCSK9i (Recaticimab) (e.g., number), time of subcutaneous injection, and dose injected; Ensure patient adherence to the assigned PCSK9i use regimen. If the dose deviates from the protocol, record the reason.

(2) Other lipid-lowering therapy information, including oral lipid-lowering drugs such as statins, fibrates, ezetimibe, etc. Record drug name, dose, time of administration, time of discontinuation.

10.5 Interventional and Perioperative Treatment Information

(1) Endovascular treatment information: Arterial puncture time, time of first angiography, number of thrombectomy attempts, mTICI grade of blood flow status before and after thrombectomy, end of procedure time, whether angioplasty is performed (if yes, select: simple balloon angioplasty, or balloon angioplasty + stent implantation).

10.6 Follow-up Data

10.6.1 24-48 Hours

(1) Neurological function assessment: GCS score and NIHSS score;

(2) Brain imaging:

Plain cranial CT: Assess for intracranial hemorrhage.

(3) Record presence of symptomatic intracranial hemorrhage transformation (Yes/No):

Symptomatic intracranial hemorrhage is defined as any apparent intracerebral or intracranial hemorrhage associated with clinical deterioration. Specifically, it refers to hemorrhage that leads to neurological deterioration, indicated by an increase of 4 points or more on the NIHSS score compared to baseline or the lowest value, or hemorrhage that leads to death and is identified as the primary cause of neurological deterioration.

10.6.2 Assessment Form at Day 14±3 or Discharge

On Day 14±3 postoperatively or on the day of discharge, confirm and record the detailed contact information of the patient or his/her caregiver to facilitate future follow-up assessments.

The following needs to be recorded:

(1) Assessment time, discharge (death) time

(2) Neurological function assessment: NIHSS score, mRS score, GCS score

(3) Ischemic stroke type (TOAST classification)

(4) Information on other treatments received during hospitalization:

a) Whether decompressive craniectomy is performed

b) Whether mechanical ventilation >24h is received

c) Whether infection requiring antibiotics occurs

(5) Hematological parameters:

a) Lipids: Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, lipoprotein (a), apolipoprotein B;

b) Hematology: Red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count;

c) Blood chemistry: Renal function: Creatinine, uric acid; Liver function: Aspartate aminotransferase, alanine aminotransferase; Glucose;

d) Coagulation function tests: APTT, INR;

e) Blood inflammatory response markers: CRP;

(6) Calculate and record whether current LDL-C is <1.8 mmol/L (70 mg/dL).

10.6.3 Day 90±7

The following needs to be recorded:

(1) mRS score

(2) Clinical events

a) Recurrent ischemic/hemorrhagic stroke events

Adjudication of recurrent stroke events requires confirmation based on patient-provided medical history, signs and symptoms, and imaging examinations, such as head CT or MRI, to confirm the presence of new infarcts (ischemic stroke) or hemorrhages (hemorrhagic stroke). All cases of suspected recurrent stroke should be confirmed by imaging whenever possible to ensure the accuracy of new stroke events. The above will be adjudicated by an Event Adjudication Committee, and original materials will be

collected and retained.

b) Major adverse cardiovascular events (MACEs)

MACE is defined as a composite endpoint, including:

a) Recurrent stroke (ischemic or hemorrhagic)

b) Acute coronary syndrome

c) New-onset or worsening peripheral vascular disease

d) Cardiovascular death

Adjudication of MACEs requires confirmation based on patient-provided medical history, signs and symptoms, imaging examinations, etc., adjudicated by the Event Adjudication Committee, and original materials will be collected and retained.

(3) Safety assessment: Record potentially common adverse reactions, such as injection site reactions, abnormal biochemical indicators, etc., and the investigator's determination of their relevance to the study.

(4) Quality of life scale (EQ-5D).

(5) Lipids: Total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipoprotein (a), apolipoprotein B.

10.6.4 Death

If a patient dies before the planned follow-up time points listed above, documents regarding the cause of death, including the date and time of death, must be collected. Copies of autopsy reports, admission records, or death certificates should be kept with the subject contact information form for monitoring by the study coordinating site.

10.7 Discontinuation of Assigned Treatment and Protocol Deviations

The study coordinating site will provide a form to record the date and specific circumstances of protocol deviations or missed assessments.

10.8 Informed Consent

The informed consent process should be recorded in the patient's medical record and CRF, and the type of informed consent obtained should be recorded in the database.

10.9 Serious Adverse Events

All SAEs should be recorded on the SAE form and reported to the study coordinating site via fax or email within the specified timeframe. Supplementary information regarding the event

and outcome may be requested.

VII. Study Flow Chart

Assessment Contents	Baseline (Screening and Enrollment)	Administration	Within 24-48 hours	Day 14±3 or at discharge	Day 90±7 (Endpoint Visit)
Signing ICF	X				
Demographic characteristics	X				
Current medical history	X				
Past medical history	X				
Concomitant medications	X				X
Vital signs	X		X	X	X
Laboratory tests	X			X	X
Check inclusion/exclusion criteria	X				
Randomization	X				
Imaging examinations	X		X		
PCSK9i medication information		X			
Information on lipid-lowering drugs in standard treatment		X	X	X	X
Endovascular treatment information	X				
mRS score	X			X	X
NIHSS score	X		X	X	
Stroke or TIA events					X
MACE events					X
AEs		X	X	X	X X

VIII. SAEs

1. Definition:

The mechanism for notifying and reporting SAEs is based on guidelines adopted by the

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) - Good Clinical Practice (GCP) (ICH-GCP). According to the definition made by WHO International Drug Monitoring Centre (1994), an SAE refers to any untoward medical occurrence that:

1) Results in death;
2) Is life-threatening (i.e., the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
3) Requires inpatient hospitalization or prolongation of existing hospitalization;
4) Results in persistent or significant disability or incapacity;
5) Results in a congenital anomaly or birth defect (please note, women in the study population may be postmenopausal);
6) Is a medically important event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Since the primary endpoint of this study includes hemorrhagic transformation for any reason, all post-infarction hemorrhagic transformations (any definition) in this study are considered medically important events by the investigator and must be reported as SAEs.

Note: The following situations are not reported as SAEs:
1) Elective surgery planned before signing the ICF for this study;
2) Hospitalization required for routine health check-ups (e.g., routine colonoscopy, etc.);
3) Hospitalization solely for the purpose of neurological rehabilitation.

Unexpected adverse reaction (UAR) is an adverse reaction inconsistent with the package insert. Suspected unexpected serious adverse reaction (SUSAR) is any unexpected adverse reaction at any dose that:

1) Results in death
2) Is life-threatening (the patient is at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe)
3) Requires hospitalization or prolongation of current hospitalization
4) Results in persistent or significant disability or incapacity
5) Results in a congenital anomaly or birth defect

2. Recording and Reporting of Serious Adverse Events

Details of the event must be recorded on the SAE form, including a complete description of the event, classification of the event according to the definitions above, the principal

investigator's judgment of the causal relationship between the randomized treatment group and the SAE, and the onset time of the SAE. All SAEs must be reported to the study coordinating site as soon as possible within 24 hours of becoming aware of them. To obtain further information, the principal investigator may need to submit follow-up reports to document the outcome of the SAE. The principal investigator is responsible for reporting SAEs to the Ethics Committee according to local regulations.

Details of the event must be recorded on the SUSAR form, including a complete description of the event, classification of the event according to the definitions above, the principal investigator's judgment of the causal relationship between the SUSAR and the suspected drug, and detailed information about the suspected drug. All SUSARs must be reported to the study coordinating site as soon as possible within 24 hours of becoming aware of them. The principal investigator may need to provide additional detailed information to supplement the initial report of the SAE, and the outcome of the SUSAR must also be recorded. The principal investigator is responsible for reporting SUSARs to the IRB or regulatory authorities according to local regulations or administrative requirements.

3. Monitoring of Serious Adverse Events

The study coordinating site will closely monitor all SAEs to understand the relationship between SAEs and study procedures and protocol, or the occurrence of clusters of similar events at a specific site. If an excessive number of special SAEs related to the protocol occur, the study protocol may need to be revised or the study terminated prematurely. In addition, outside of planned interim analysis meetings, the study coordinating site will submit all SUSARs to the Data Safety Monitoring Board (DSMB) for review.

4. Monitoring of Suspected Unexpected Serious Adverse Reactions

The study coordinating site will closely monitor all SUSARs to understand the relationship between SUSARs and study procedures and protocol, or the occurrence of clusters of similar events at a specific clinical study site. In addition, the study coordinating site will report according to the requirements of the Ethics Committees of each participating site.

IX. Quality Assurance

The study will be conducted in hospitals with acute stroke units that can perform thrombectomy and have experience in thrombectomy. CRAs will conduct data verification at each study site and monitor the execution of the study. The first monitoring visit will take

place after the first few patients have been randomized at the study site, followed by monitoring at least twice a year based on the number of enrolled patients. Monitoring will ensure that investigators strictly adhere to the protocol and GCP requirements, guarantee the authenticity and reliability of data, and ensure that all conclusions in the clinical study are derived from source data.

1. Preservation and Monitoring of Source Documents/Files

Source documents are the basis for verifying the actual existence of subjects and the credibility of collected data. Source documents should be kept at each study site.

Data on the CRF are derived from source documents and should be consistent with them. Any discrepancies should be explained.

All other data (i.e., written or electronic text records without data) can be directly recorded on the CRF and are recognized as source data.

Investigators must allow the sponsor to conduct monitoring and audits, the Ethics Committee to review, and relevant regulatory authorities to conduct inspections, and allow the aforementioned personnel to access all relevant source documents/files.

The CRF and all source data, including photocopies of laboratory tests and other medical examination results, must be readily available for review by the clinical monitor designated by the sponsor. CRAs should verify all CRFs and ICFs to confirm the accuracy of the data in the documents.

2. Pre-Study Activities

Before the first subject is enrolled in the study, a representative of the study sponsor should visit the study site to:

(1) Determine if the study site's facilities are adequate;

(2) Determine if the study site has suitable patients for enrollment;

(3) Discuss with the investigator/head of the study site (and other study-related personnel) their responsibilities regarding the study protocol and the responsibilities of the study sponsor or its representative, and document this in the clinical study agreement between the study sponsor and the investigator/head of the study site.

3. Site Staff Training

Before the first study subject is enrolled, the leading site will provide standardized training and assessment for the principal investigators and all investigators at the sub-sites. Sub-site study initiation can only proceed after passing the assessment. The principal investigator must ensure that all study personnel receive study-related training and that training records are maintained.

The principal investigator will maintain a record of all study-related personnel (doctors, nurses, and other staff).

4. Study Monitoring

During the study, the study sponsor will regularly contact the study site, including:

(1) Visiting the study site to provide information and support for the study to the investigators

(2) Confirming that facilities still meet requirements

(3) Confirming that all study-related personnel are adhering to the study protocol, data on the CRF are recorded promptly and accurately, and study drug accountability has been verified

(4) Conducting source data verification (SDV) (comparing data on the CRF with the subject's hospital records and other study-related records), which includes reviewing the informed consent of study subjects. Direct access to all source records (e.g., inpatient medical records) for each patient is required

If investigators or other staff at the study site require information or advice regarding study implementation, they may contact the study sponsor during follow-up intervals.

Upon study completion, CRAs must ensure that each site has a plan for long-term (15 years) retention of relevant materials and source documents.

5. Audits and Inspections by Government Regulatory Agencies

Additionally, the study may be audited by third-party organizations and by auditors dispatched by government regulatory agencies. During and after the study, all study sites must ensure that CRFs, source documents, and other study documents are accessible during audits

and inspections.

6. Source Data

The leading site will retain all original records and source data.

7. Archiving of Study Documents

Investigators should adhere to the principles outlined in the clinical study agreement.

8. Study Progress

If study procedures at an individual study site are not conducted according to the study protocol, or if the recruitment period is excessively long, this study at that site may be terminated. The study sponsor may also prematurely terminate this study due to safety concerns in this study or other studies of PCSK9 inhibitor injections.

X. Data Management

Data entry will be completed by each participating site via a password-protected internet-based data management system developed under commission by the study coordinating site. Paper CRFs will be provided to sites that wish to use them for initial data collection.

XI. Statistical Plan

1. Statistical Analysis

General Analysis

For continuous data, statistics such as number, mean, standard deviation, median, minimum, and maximum will be summarized; for categorical data, statistics such as frequency and percentage will be summarized; for time-to-event data, the Kaplan-Meier method will be used to estimate the survival function and the median time to event occurrence, and survival curves will be plotted. Efficacy analyses of primary and secondary endpoints will be conducted in the intent-to-treat (ITT) population, i.e., all randomized patients. Safety analysis will be performed in the as-treated safety set (SS). In addition, a per-protocol set (PPS) will be also established in this study: including all subjects who have completed the protocol-specified treatment or do not have serious violations of the study protocol. The exact definition of serious protocol violations will be finalized during data review and may generally include

(but is not limited to) the following situations: serious violation of eligibility criteria, presence of treatment that seriously interferes with efficacy evaluation after enrollment, serious violation of the medication regimen, lack of evaluation of primary efficacy endpoints, etc.

All statistical analyses will be performed using SAS 9.4 software or a later version.

Efficacy Analysis

The primary efficacy endpoint of this study is the percentage of mRS (0-2). A logistic regression model adjusted for stratification factors will be used to estimate the odds ratio of mRS (0-2) between the investigational group and the control group, along with the corresponding 95% CI and *p*-value.

For the ordinal mRS endpoint among the secondary endpoints, a proportional-odds logistic regression model adjusted for stratification factors will be used to estimate the common odds ratio and its corresponding 95% CI and *p*-value. Other binary endpoints will be analyzed using the same regression model as the primary endpoint.

For event endpoints, the Kaplan-Meier method will be used to estimate the median value, and the Brookmeyer-Crowley method will be used to estimate the 95% CI for the median time to event. Survival curves will be plotted, and the stratified Logrank test will be used to compare survival differences between groups;

Safety Analysis

Safety analysis will primarily be descriptive statistical analysis. All AEs will be coded using MedDRA and graded according to the NCI-CTCAE version 5.0 grading system. All treatment-emergent AEs, drug-related AEs, serious adverse events (SAEs), and drug-related SAEs will be listed by the highest severity.

Laboratory test results, vital signs, electrocardiogram (ECG) data, etc. will be analyzed using conversion tables to compare the baseline and post-baseline conditions.

2. Sample Size Estimation

This study is a randomized controlled trial. According to previous study reports, the proportion of patients with mRS (0-2) in patients with acute ischemic stroke receiving endovascular treatment from the control group is approximately 45%. Based on early study data of the investigational treatment regimen, the proportion of patients with mRS (0-2) in the investigational group in this study is expected to reach 58%, with an inter-group difference of approximately 13%. The significance level α is set at 0.05 (two-sided). Using the Z-test

(pooled) module of NCSS PASS 21 (LLC. Kaysville, Utah, USA, ncss.com/software/pass) software, it is calculated that approximately 309 subjects need to be enrolled in each group to provide at least 90% power (1-β) to detect a difference in the proportion of patients with mRS (0-2) between the investigational treatment regimen and the control treatment regimen. Considering 5% dropout and protocol violations, a total of 326 subjects need to be enrolled in each group for this study, meaning a total of 652 subjects need to be enrolled for both groups.

XII. Publication and Reporting

The main report will be published in the name of the principal investigator of this study. A writing committee approved by the steering committee will fully manage the writing of the report.

Investigators have the right to publish or present the study results. However, given that this is a multicenter academic study, investigators agree not to publish or publicly report any interim results of this study without the prior written consent of the steering committee. Investigators agree to provide the steering committee with a copy of any abstract or manuscript reporting study results (including but not limited to, text and slide presentations, any other dissemination manuscripts or media presentations) for review at least 30 days prior to submission.

The steering committee has the right to review and evaluate publications, abstracts, slides, and manuscripts from the perspectives of information accuracy, protection of individual rights, and ensuring that presentations are appropriately balanced and comply with relevant regulations.

If there is disagreement among parties regarding the appropriateness of data analysis and presentation, and/or confidentiality, investigators agree to meet with members of the steering committee at the clinical site or an agreed-upon location before submission for publication, to make every effort to discuss and resolve any such issues or disagreements in good faith.

The writing committee will be composed of members from various committees, statisticians, researchers, and investigators, with credit attributed to collaborating investigators and other study personnel.

Authors of publications must meet the following guidelines for authorship from the International Committee of Medical Journal Editors:

1 Authors must have made substantial contributions to the conception and design of the study, the acquisition of data, or the analysis and interpretation of results;

2 Authors must have drafted the publication or contributed to important revisions of the manuscript (data analysis, interpretation, or other important intellectual content) during the manuscript review process and received approval from other authors;

3 Authors must provide approval of the final draft manuscript before the article is submitted to a journal for publication.

In accordance with the ICMJE guidelines for acknowledgments, if the journal permits, all contributors who do not meet the above 3 criteria for authorship will be listed in the acknowledgments section of the publication.

XIII. Organizations

This study is an investigator-initiated and executed study, managed by Shanghai East Hospital as the study coordinating site.

Participating Sites

Neurology Ward / Department of Neuroscience / Acute Stroke Unit / Neurosurgery

Responsibilities: Overall management of the study at their respective hospitals, ensuring adherence to the study protocol; recruiting and training study nurses; introducing the protocol to colleagues, enrolling patients, collecting data, resolving data queries, liaising with the local hospital EC/IRB in accordance with local ethical guidelines and relevant reporting requirements, and reporting adverse events to the local hospital EC/IRB and the study coordinating site according to the protocol.

Data Safety Monitoring Board

This study will establish a DSMB, which will periodically review unblinded data during study follow-up and monitor dropout rates and event incidence. A detailed statistical analysis plan will be completed and archived before the enrollment of 50 patients, which will detail the stopping rules to be used.

XIV. Funding

Partial funding is provided by the New Clinical Medicine Specialty (Special Disease) under the Construction of Peak and Plateau Disciplines in Pudong New Area in 2024 (2024-PWXZ-17) and the Key Discipline of Shanghai East Hospital (2024-DFZD-003). Jiangsu Hengrui Pharmaceuticals Co., Ltd. provides partial funding, details as specified in the contract.

XV. Timeline

Central ethics submission: April 2025

Kick-off meeting, screening and enrollment: May 2025

End of follow-up: June 2028

Statistical analysis, publication: December 2028

XVI. References

1. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18**(5): 459-80.

2. Wang Y-J, Li Z-X, Gu H-Q, et al. China Stroke Statistics: an update on the 2019 report from the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol* 2022; **7**(5): 415-50.

3. Wang Y, Zhao X, Liu L, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* 2014; **45**(3): 663-9.

4. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019; **50**(12): e344-e418.

5. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *The Lancet* 2016; **387**(10029): 1723-31.

6. Aguiar de Sousa D, von Martial R, Abilleira S, et al. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. *Eur Stroke J* 2019; **4**(1): 13-28.

7. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nature Medicine* 2011; **17**(7): 796-808.

8. Xu S, Lu J, Shao A, Zhang JH, Zhang J. Glial Cells: Role of the Immune Response in Ischemic Stroke. *Front Immunol* 2020; **11**: 294.

9. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021; **52**(7): e364-e467.

10. Abifadel M, Varret M, Rabès J-P, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nature Genetics* 2003; **34**(2): 154-6.

11. Benn M, Nordestgaard BG, Grande P, Schnohr P, Tybjaerg-Hansen A. PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses. *Journal of the American College of Cardiology* 2010; **55**(25): 2833-42.

12. Barale C, Melchionda E, Morotti A, Russo I. PCSK9 Biology and Its Role in Atherothrombosis. *Int J Mol Sci* 2021; **22**(11).

13. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England Journal of Medicine* 2017; **376**(18): 1713-22.

14. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *The New England Journal of Medicine* 2018; **379**(22): 2097-107.

15. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* 2019; **290**: 140-205.

16. Yuan HW, Yang YN, Chen HF, et al. Rise in Low-Density Lipoprotein Cholesterol during Hospitalization is Related with Poor Outcome at Discharge in Patients with Acute Ischemic Stroke. *Cerebrovasc Dis* 2020; **49**(1): 88-96.

17. Gao Y, Jiang L, Pan Y, et al. Immediate- or Delayed-Intensive Statin in Acute Cerebral Ischemia: The INSPIRES Randomized Clinical Trial. *JAMA Neurol* 2024; **81**(7): 741-51.

18. Kim J, Hong U, Yoon CW, Bae JW, Rha J-H, Park H-K. PCSK9 inhibitor in acute ischemic stroke patient receiving mechanical thrombectomy: early outcomes and safety. *Front Neurol* 2024; **15**: 1375609.

19. Ding Z, Liu S, Wang X, et al. PCSK9 regulates expression of scavenger receptors and ox-LDL uptake in macrophages. *Cardiovasc Res* 2018; **114**(8): 1145-53.

20. Tang Z, Jiang L, Peng J, et al. PCSK9 siRNA suppresses the inflammatory response induced by oxLDL through inhibition of NF-κB activation in THP-1-derived macrophages. *Int J Mol Med* 2012; **30**(4): 931-8.

21. Ferri N, Marchianò S, Tibolla G, et al. PCSK9 knock-out mice are protected from neointimal formation in response to perivascular carotid collar placement. *Atherosclerosis* 2016; **253**: 214-24.

22. Liu A, Frostegård J. PCSK9 plays a novel immunological role in oxidized LDL-induced dendritic cell maturation and activation of T cells from human blood and atherosclerotic plaque. *J Intern Med* 2018.

23. Bernelot Moens SJ, Neele AE, Kroon J, et al. PCSK9 monoclonal antibodies reverse the pro-inflammatory profile of monocytes in familial hypercholesterolaemia. *European Heart Journal* 2017; **38**(20): 1584-93.

24. Zheng Y, Zhu T, Li G, Xu L, Zhang Y. PCSK9 inhibitor protects against ischemic cerebral injury by attenuating inflammation via the GPNMB/CD44 pathway. *Int Immunopharmacol* 2024; **126**: 111195.

25. Akram ON, Bernier A, Petrides F, Wong G, Lambert G. Beyond LDL cholesterol, a new role for PCSK9. *Arterioscler Thromb Vasc Biol* 2010; **30**(7): 1279-81.

26. Camera M, Rossetti L, Barbieri SS, et al. PCSK9 as a Positive Modulator of Platelet Activation. *Journal of the American College of Cardiology* 2018; **71**(8): 952-4.

27. Navarese EP, Kolodziejczak M, Winter M-P, et al. Association of PCSK9 with platelet reactivity in patients with acute coronary syndrome treated with prasugrel or ticagrelor: The PCSK9-REACT study. *International Journal of Cardiology* 2017; **227**: 644-9.

28. Barale C, Bonomo K, Frascaroli C, et al. Platelet function and activation markers in primary hypercholesterolemia treated with anti-PCSK9 monoclonal antibody: A 12-month follow-up. *Nutr Metab Cardiovasc Dis* 2020; **30**(2): 282-91.

29. Marston NA, Gurmu Y, Melloni GEM, et al. The Effect of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibition on the Risk of Venous Thromboembolism. Circulation 2020; 141(20): 1600-7.

30. Deoker A, Lehker A, Mukherjee D. Updates in Anti-anginal and Anti-ischemic Therapies for Acute Coronary Syndromes. *Curr Cardiol Rep* 2020; **22**(10): 126.

31. Joint Expert Committee for the Revision of Chinese Guidelines for Lipid Management. Chinese Guidelines for Lipid Management (2023). [J]. Chinese Circulation Journal, 2023,38(3):237-271.

XVII. Appendices

1. Modified Rankin Scale (mRS)

The modified Rankin scale is used to measure the status of neurological function recovery in patients after stroke. Bold text shows the formal definition of each level, while italicized text provides further guidance to reduce potential errors between different observers, but there are no requirements for the structure of the interview. Please note to consider only symptoms that have occurred since the stroke. If the patient does not require external help and can walk with the aid of certain assistive devices, they are considered able to walk independently.
If two levels seem equally applicable to the patient, and further questioning is unlikely to lead to an absolutely correct choice, the more severe level should be chosen.

0 No symptoms at all
Although there may be minor symptoms, the patient has not noticed any new functional limitations or symptoms since the stroke.

1 No significant disability despite symptoms; able to carry out all usual duties and activities
The patient has some symptoms caused by the stroke, whether physical or cognitive (e.g., affecting speech, reading, writing; or physical movement; or sensation; or vision; or swallowing; or emotions), but can continue to perform all work, social, and leisure activities they engaged in before the stroke. The key question to distinguish between level 1 and level 2 (see below) can be, "Are there some things you used to do regularly that you can no longer do since the stroke?" Activities with a frequency of more than once a month are considered usual activities.
2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Certain activities that could be performed before the stroke (such as driving, dancing, reading, or working) can no longer be performed by the patient after the stroke, but they can still take care of themselves daily without assistance from others. The patient is able to dress, walk, eat, go to the toilet, prepare simple food, shop, and travel locally without the help of others. The patient does not require supervision in their daily life. It is envisioned that patients at this level can live alone at home for a week or longer without care.
3 Moderate disability; requires some help, but able to walk without assistance
At this level, the patient can walk independently (possibly with the aid of assistive walking

devices), and can independently dress, go to the toilet, eat, etc., but more complex tasks require assistance from others. For example, requiring others to do shopping, cooking, or cleaning, and visiting the patient more than once a week to ensure these activities are completed. Assistance needed is not only for physical care but also for advice, for example: patients at this level will require supervision or encouragement to manage finances.

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

The patient requires help from others to manage daily life, whether it is walking, dressing, going to the toilet, or eating. The patient needs to be looked after at least once a day, usually twice or more, or must live very close to a caregiver. To distinguish between level 4 and level 5 (see below), consider whether the patient can routinely live alone for an appropriate period during the day.

5 Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

Although a trained nurse is not required, someone needs to look after them throughout the day and several times at night.

6. Dead

2. NIH Stroke Scale

Instructions	Scale Definition	Score
1a Level of Consciousness (LOC): The examiner must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert, keenly responsive 1 = Drowsy, arousable by minimal stimulation to obey commands, answer questions, or respond 2 = Stuporous or obtunded, requires strong or repeated stimulation or painful stimulation to make non-stereotyped responses 3 = Responds only with reflex motor or autonomic effects or is totally unresponsive, flaccid, and areflexic	
1b LOC Questions: (Score only the first answer, examiner should not prompt) The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1.	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly or unable to speak	
1c LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command (e.g., stick out tongue) if the hands cannot be used. Only the first attempt is scored. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated, and then the score is recorded. Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	

2 Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, score 1. If the patient has an isolated peripheral nerve paresis (Cranial Nerve (CN) III, IV, V), score 1. Gaze is testable in aphasic patients. In patients with ocular trauma, bandages, blindness, or other disorder of visual acuity or fields, the examiner should choose a reflexive movement to test. Establish eye contact and then move from one side to the other, which may occasionally reveal gaze palsy.	0 = Normal 1 = Partial gaze palsy (gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present) 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver	
3 Visual Fields Test upper and lower quadrant visual fields by confrontation, using finger counting or visual threat, as appropriate. If the patient can see fingers in the lateral fields, score as normal. If one eye is blind or enucleated, test the other eye. Score 1 if there is clear-cut asymmetry, including quadrantanopia. If patient is bilaterally blind (any cause), score 3. Stimulate both eyes simultaneously. If the patient is moribund, score 1; the result is used for question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind, including cortical blindness)	
4 Facial Palsy: Ask patient, or use pantomime, to show teeth, raise eyebrows, and close eyes. In the poorly responsive or non-comprehending patient, score symmetry of grimace to noxious stimuli. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible for assessment.	0 = Normal 1 = Minor (flattened nasolabial fold, asymmetry on smiling) 2 = Partial (total or near-total paralysis of lower face, central palsy) 3 = Complete (paralysis of one or both sides, absence of facial movement in the upper and lower face, peripheral palsy)	

5 Motor Arm Arm extension: 90º if sitting, 45º if supine. Ask to hold for 10 seconds; encourage aphasic patients with language or gestures, do not use noxious stimuli. The assessor can lift the patient's upper limb to the required position and encourage the patient to hold it.	0 = Arm holds required position for 10 seconds with no drift 1 = Arm can be lifted but cannot be maintained for 10 seconds, drifts down without hitting bed or other support 2 = Some effort against gravity, but arm cannot reach or maintain 90º (sitting) or 45º (supine), drifts down to bed fairly quickly 3 = No effort against gravity, arm falls rapidly 4 = No movement 9 = Amputation or joint fusion 5a Left Arm 5b Right Arm	
6 Motor Leg Leg raised 30º in supine position, hold for 5 seconds; encourage aphasic patients with language or gestures, do not use noxious stimuli. The assessor can lift the patient's upper limb to the required position and encourage the patient to hold it.	0 = Holds required position for 5 seconds, no drift 1 = Drifts down by end of 5 seconds, does not hit bed 2 = Falls to bed fairly quickly within 5 seconds, but some effort against gravity 3 = Falls to bed immediately, no effort against gravity 4 = No movement 9 = Amputation or joint fusion 6a Left Leg 6b Right Leg	
7 Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. If there is visual loss, ensure testing is done in intact visual field. Bilateral finger-nose and heel-shin tests. Score if ataxia is present and out of proportion to weakness. Do not score if patient cannot understand or limb is paralyzed. Blind patients touch nose with extended arm. If amputation or joint fusion, score 9 (untestable [UN]) and explain clearly.	0 = Absent 1 = Present in one limb 2 = Present in two limbs If ataxia is present; Left arm 1 = Yes 2 = No 9 = Amputation or joint fusion Right arm 1 = Yes 2 = No 9 = Amputation or joint fusion Left leg 1 = Yes 2 = No 9 = Amputation or joint fusion Right leg 1 = Yes 2 = No 9 = Amputation or joint fusion	
8 Sensory: Examine with a pin. During testing, observe sensation and facial expression in	0 = Normal, no sensory loss 1 = Mild to moderate; pinprick sensation is less sharp or dull on the affected side, or patient is	

stuporous or aphasic patients by pinprick stimulation and withdrawal. Score only sensory loss attributed to stroke. Patients with hemisensory loss require precise examination; test multiple body areas: arms (not hands), legs, trunk, face. Severe or total sensory loss, score 2. Aphasic patients can be scored 1 or 0. Bilateral sensory loss in brainstem stroke, score 2. Unresponsive and quadriplegic patients, score 2. Comatose patients (1a=3), score 2.	aware of being touched 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg	
9 Best Language Naming, reading tests. Ask patient to name items, read listed sentences. Judge comprehension from patient's responses and responses to commands in the general neurological examination. If visual impairment interferes with testing, have the patient identify items placed in the hand, repeat, and articulate. Intubated patients should write answers. For comatose patients (1a=3), score 3. Choose a score for stuporous or uncooperative patients, but score 3 only for patients who are mute or do not follow commands at all.	0 = Normal, no aphasia 1 = Mild to moderate aphasia: some loss of fluency or comprehension, but expression is not significantly limited. 2 = Severe aphasia; communication is through fragmented expression; listener must infer, question, and guess. Range of information that can be exchanged is limited; examiner feels communication is difficult. 3 = Mute or global aphasia; no usable speech or auditory comprehension	
10 Dysarthria: Do not tell the patient why this test is being done. Read or repeat words from the attached list. If the patient has severe aphasia, assess clarity of articulation during spontaneous speech. If patient is intubated or has other physical barriers preventing speech, score 9 (UN). Also note the reason.	0 = Normal 1 = Mild to moderate; at least some slurring but can be understood with some difficulty 2 = Speech is so slurred as to be unintelligible 9 = Intubated or other physical barrier	
11 Extinction and Inattention (formerly Neglect): If severe visual loss interferes with bilateral visual simultaneous examination, and cutaneous stimuli are normal, score as normal. If the patient is aphasic but does	0 = No neglect 1 = Visual, tactile, auditory, spatial, or personal inattention; or extinction to bilateral simultaneous stimulation in any sensory modality 2 = Profound hemi-inattention; more than one modality of hemi-inattention; does not recognize	

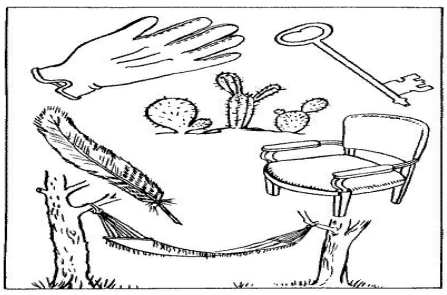
demonstrate attention to both sides, score as normal. Assess for neglect by testing the patient's ability to recognize simultaneous cutaneous sensory and visual stimuli on the right and left sides. Show the standard picture to the patient and ask them to describe it. If the patient cannot recognize parts of the picture on one side, it is considered abnormal. Then, the physician asks the patient to close their eyes and tests bilateral cutaneous sensation by pinprick on the upper or lower limbs separately. If the patient has unilateral sensory neglect, it is abnormal.	own hand or orients to one side of space only	
Total		

Notes:
Score according to the table, record the results. Do not change the score; the score reflects the patient's actual condition, not what the physician thinks the patient should be. Perform a rapid examination and record the results simultaneously. Unless necessary for pointing, do not train the patient (e.g., by repeatedly asking the patient to make an effort).
If some items are not assessed, explain in detail in the form.

Appendix: Chart for Items 9 and 10 Examination

Reading Test Picture 1

Reading Test Picture 2



Reading Test Picture 3

Please read the following sentences:
Know
Go downstairs
Go home to cook
Review at school
Deliver a wonderful speech

Reading Test Picture 4

Please read the following words:
Mama
Earth
Airplane
Silk
Start work on time
Eat grapes but do not spit out grape skins

Basic Principles and Precautions for NIHSS Scoring

Basic Principles for NIHSS Scoring:

Record the patient's first response, even if subsequent responses may be better;

Note to record only what the patient does, not what you think they are capable of doing;

Record while examining, and try to avoid leading the patient;

For items that cannot be evaluated, please record the score as "9"; computer statistical processing will automatically treat it as a missing value;

"Consistency" principle: Maintain consistent evaluation criteria during multiple follow-ups.

How to Assess NIHSS Score in Comatose Patients?

For patients with a score of less than 3 on item 1a, each item should be assessed individually. Item 1a is scored 3 only when the patient has no response to any noxious stimuli (sternal rub, supraorbital pressure, etc.), only reflex activity.

If 1a = 3 points, other items should be assessed as follows:

1b - LOC Questions: 2 points

1c - LOC Commands: 2 points

2 - Best Gaze: Assessed based on whether it can be overcome by the oculocephalic maneuver. If it can be overcome, score 1 point; if not, score 2 points.

3 - Visual Fields: Assessed using visual threat.

4 - Facial Palsy: 3 points

5, 6 - Limb Movement: 4 points for each limb

7 - Limb Ataxia: Score only if ataxia is present. If the patient's muscle strength is reduced and they cannot complete tests like finger-nose or heel-shin, score 0 points.

8 - Sensory: 2 points

9 - Best Language: 3 points

10 - Dysarthria: 2 points

11 - Extinction and Inattention: Coma implies loss of all cognitive abilities, so score 2 points.

How to Calculate the Total NIHSS Score?

When calculating the total score, the following items should not be included in the total score:

Items 5 and 6 - Limb Movement: "9 = amputation or joint fusion"

Item 7 - Limb Ataxia: The items for determining the location of ataxia, i.e., "Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain:" (not required for registration).

3. European Quality of Life Scale (EQ-5D)

The following are various descriptions of your health today. Please tick the most accurate and appropriate item in each group:

1. Mobility

Thinking carefully about your health today, which of the following best describes your mobility?

☐ I have no problems in walking about

☐ I have some problems in walking about

☐ I am confined to bed

2. Self-Care

Thinking carefully about your health today, which of the following best describes your self-care?

☐ I have no problems with self-care

☐ I have some problems washing or dressing myself

☐ I am unable to wash or dress myself

3. Usual Activities

Thinking carefully about your health today, which of the following best describes your usual activities (e.g., work, study, housework, family or leisure activities)?

☐ I have no problems performing my usual activities

☐ I have some problems performing my usual activities

☐ I am unable to perform my usual activities

4. Pain/Discomfort

Thinking carefully about your health today, which of the following best describes any pain or discomfort you may be currently experiencing?

☐ I have no pain or discomfort

☐ I have moderate pain or discomfort

☐ I have extreme pain or discomfort

5. Anxiety/Depression

Thinking carefully about your health today, which of the following best describes any anxiety or depression you may be currently experiencing?

☐ I am not anxious or depressed

☐ I am moderately anxious or depressed

☐ I am extremely anxious or depressed

The best health you can imagine

The worst health you can imagine

To help you indicate how good or bad your health is, we have drawn a scale (rather like a thermometer).

On this scale, 100 represents the best health you can imagine, and 0 represents the worst health you can imagine.

Please mark an "×" on the scale to indicate how your health is today.

Please write the number you marked on the scale in the l

ine below: _____

4. Specific Criteria for Glasgow Coma Scale (GCS) Scoring:

Eye Opening Response: Spontaneous: 4 points

To speech: 3 points

To pain: 2 points

No response to any stimuli: 1 point

Eyes cannot be opened due to swelling, fracture, etc.: C

Verbal Response: Oriented (correctly oriented, can clearly state name, etc.): 5 points

Confused (disoriented, answers incorrectly): 4 points

Inappropriate words: 3 points

Incomprehensible sounds: 2 points

No response: 1 point

Endotracheal intubation or tracheostomy preventing normal speech: T

Motor Response: Obeys commands: 6 points

Localizes pain: 5 points

Withdraws from pain: 4 points

Flexion to pain (decorticate posturing): 3 points

Extension to pain (decerebrate posturing): 2 points

No response: 1 point