Endovascular Treatment For Mild Ischemic Stroke With Acute Anterior Circulation Large Vessel Occlusion：

A Multicenter Prospective Randomized Controlled Clinical Trial：MILD-MT

STUDY PROTOCOL

(Version 1.0, 08 Nov 2023)

Principal investigator

Wenhuo Chen

Zeguang Ren

Pengfei Yang

The MILD-MT protocol,
Version number: V1.0
Date: 08th November, 2023

INVESTIGATOR AGREEMENT

I have read the following protocol:

Protocol Title: Endovascular treatment for mild stroke with acute anterior circulation large vessel occlusion：a multicenter randomized controlled trail

Version and Date: Version 1.0, Nov 08 2023

I have read this protocol and associated procedure manuals and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

_____

Investigator's Signature Date (Day / Month / Year)

_____

Name of Investigator (Printed)

_____

Name of Institution (Printed)

Principal Investigator

Co-Principal Investigator
Professor Wenhuo Chen
Zhangzhou Affiliated Hospital of Fujian Medical University, China

2023.11.8 *Date* *Signature*

Co-Principal Investigator
Professor Zeguang Ren
Affiliated Hospital of Guizhou Medical University, China

2023.11.8 *Date* *Signature*

Co-Principal Investigator
Professor Pengfei Yang
Changhai Hospital, Shanghai, China

2023-11-8 *Date* *Signature*

Contents

ADMINISTRATIVE INFORMATION

Protocol History

Version Number	Version Date	Summary of Revisions Made:
1.0	Oct 8 2023	Original

Trial Funding

The study is funded by Beijing Health Promotion Association(BHPA2021N002) and MicroPort NeuroTech Company(Shanghai).

Study Management & Oversight

Endovascular treatment for mild stroke with acute anterior circulation large vessel occlusion: a multicenter randomized controlled trail (MILD-MT) is an investigator initiated and conducted study. The study will be overseen by a committee of international experts in the fields of neurology, neurosurgery, radiology, epidemiology, and clinical trials.

General Consultant: The general consultant will be responsible for the overall direction and design of the study to ensure the orientation of the study protocol. The General Consultant will be chaired by Professor Jianmin Liu.

Steering Committee (SC): The SC is responsible for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The SC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. The SC will be co-chaired by Professor Wenhuo Chen、Professor Zeguang Ren and Professor Pengfei Yang

Glossary of Abbreviations and Terms

AIS	Acute ischemic stroke
AIS-LVO	Acute Ischemic Stroke with Large Vessel Occlusion
ASPECTS	Alberta Stroke Program Early CT Score
ADC	Apparent Diffusion Coefficient
BMM	Best Medical Management
CEC	Clinical Events Committee
CI	Confidence Interval
CRF	Case Report Form
CT	Computer Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
CRC	Clinical Research Coordinator
DWI	Diffusion Weighted Imaging
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
EVT	Endovascular Treatment
END	Early Neurological Deterioration
GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
GPI	Glycoprotein IIb/IIIa Receptor
ICA	Internal Carotid Artery
ICAS	Intracranial Artery Atherosclerosis
ICH	Intracranial Hemorrhage
ITT	Intention To Treat
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
eTICI	Extended Thrombolysis in Cerebral Infarction
NCCT	Non-contrast computed tomography
NIHSS	National Institute of Health stroke scale

NMPA	National Medical Products Administration
PPS	Per-Protocol Set
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
sICH	Symptomatic Intracranial Haemorrhage
SS	Safety Set

PROTOCOL SYNOPSIS

Main Sponsor: Zhangzhou Affiliated Hospital of Fujian Medical University
Title: Endovascular treatment for mild stroke with acute anterior circulation large vessel occlusion: a multicenter randomized controlled trail
Study Duration: Jan 2024 - Dec 2027
Objectives: To explore the efficacy and safety of endovascular treatment in patients with mild ischemic stroke caused by acute anterior circulation large vessel occlusion based on perfusion imaging screening.
Number of Planned Participants: 300 patients to be recruited at 40 Comprehensive Stroke Center in China
Study Design: Prospective, multicenter, blinded endpoint, randomized, superiority design test
Inclusion Criteria 1. Age 18-80 years old; 2. Symptoms onset or last known well to randomization is within 24 hours. 3. Clinical diagnosis of acute ischemic stroke due to anterior circulation intracranial large vessel occlusion (LVO) (including intracranial internal carotid artery [ICA], middle cerebral artery [MCA] M1 segment, MCA M2 segment, with or without ipsilateral extracranial ICA occlusion) confirmed on Computerized tomography angiography (CTA) or Magnetic resonance imaging angiography (MRA) ; 4. Baseline NIHSS score <6 before randomization (including cases with NIHSS ≥6 at onset but improves before randomization); 5. ASPECTS score ≥6 based on Non-contrast CT (NCCT) before randomization, and computerized tomography perfusion (CTP) or magnetic resonance imaging perfusion (MRP) imaging presented infarct core volume (relative cerebral blood flow (rCBF) <30%/DWI-ADC < 620) ≤50ml, and mismatch volume (Tmax>6 seconds volume - rCBF <30% /DWI-ADC < 620) ≥50mL; 6. The patient or their legal representatives voluntarily signed the informed consent form.
Clinical Exclusion Criteria 1. Premorbid Rankin Scale (mRS) score ≥ 1; 2. Known allergy to iodine, heparin, anaesthesia, or other definite contraindication to receiving endovascular treatment (EVT) procedure; 3. Patient has severe or fatal co-morbidities that could interfere with outcome assessments and follow-up (such as malignant tumour, severe heart failure, or renal failure, or life expectancy less than 6 months); 4. Poorly controlled hypertension (systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg); 5. Baseline blood glucose <50mg/dL (2.78 mmol/L) or >400mg/dL (22.20 mmol/L); **6.** Known bleeding tendencies, including but not limited to platelet count <100×109/L; received heparin treatment within 48 hours with an activated partial thromboplastin time (APTT) ≥35s; recent oral anticoagulant therapy with international normalized ratio (INR) >3; ***Note: Patients without a history of coagulation abnormalities or without suspicion of coagulation abnormalities do not need to wait for laboratory test results before enrollment;*** 7. Seizures at stroke onset or during the course, hard to accurately judge the baseline NIHSS score; 8. Female who is known to be pregnant, lactation, or tested positive for pregnancy at time of admission; 9. Currently participating in another investigational drug study or medical device treatments that may interfere with the results of this study; 10. Other conditions deemed unsuitable for participation, in the opinion of the investigator, or that may pose significant risks to the patient if participating the study.

Imaging Exclusion Criteria:

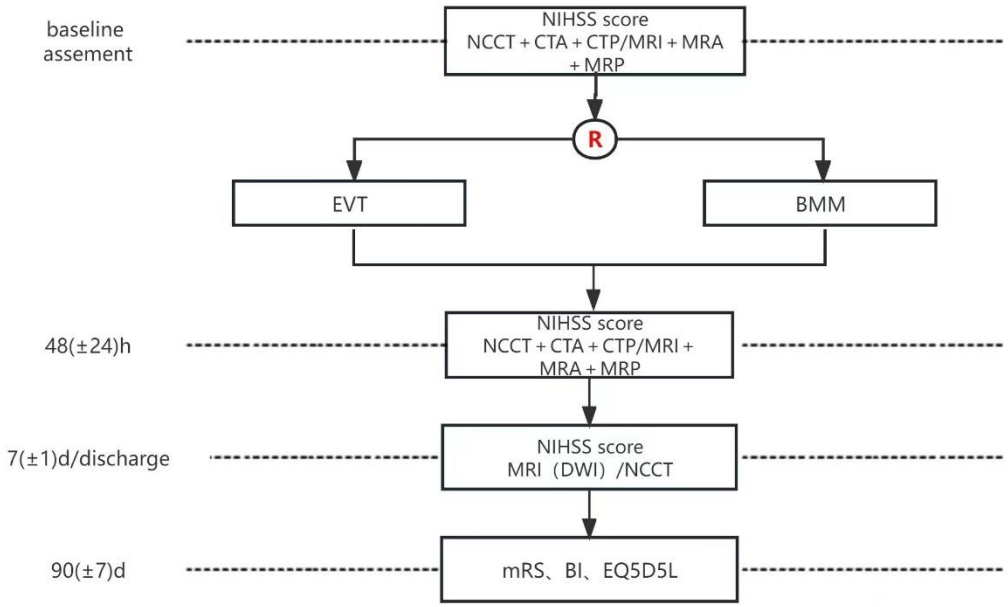
1. Evidence of intracranial haemorrhage on CT/MRI, including cerebral parenchymal haemorrhage, intraventricular haemorrhage, subarachnoid haemorrhage, and subdural/extradural haemorrhage;
2. Significant midline displacement, hernia of brain, or ventricular mass effect with midline displacement confirmed on CT/MRI;
3. Anticipated impossibility to complete endovascular treatment, such as vascular tortuosity, severe vascular wall calcification, etc.;
4. Aortic dissection;
5. Multiple intracranial large vessel occlusions confirmed by CTA or MRA, unable to clearly identify the symptomatic vessel, such as bilateral MCA occlusions or occlusions involving both the MCA and basilar artery;
6. Suspected or confirmed occluded artery is non-acute occlusion.

Randomisation and intervention:

Each center will screen patients according to the above inclusion and exclusion criteria. Based on the randomization results, patients will be divided into the Endovascular Treatment group (intervention group) and the Best Medical Treatment group (control group). Central static block group randomization was used and the stratification factors were:1) Research center; 2) Occlusion site (intracranial ICA; MCA M1; MCA M2).

- Endovascular Treatment group (Intervention group): Patients assigned to the endovascular treatment group will receive EVT immediately, combining with best medical treatment according to the local guidelines. Interventionists choose the optimal EVT strategy and device based on the patient's condition and local guidelines. This may include, but not limited to, stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, balloon angioplasty, stent implantation or combined therapy.

- Best Medical Management group (Control group): Patients will receive the best medical treatment according to local guidelines, including antiplatelet agents, anticoagulants, thrombolysis, etc., but not any EVT. In the control arm, rescue EVT is allowed within 24 hours from stroke onset based on local guidelines, if patients with disease progression leading to an increase in NIHSS≥4 and excluding the cause of non-stroke factors The rescue EVT included, but not limited to, stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, balloon angioplasty, stent implantation and combined therapy.



Brief Plot of the flow

BMM indicated best medical management.

Visiting Plan

On the randomization day, 48±24 hours, 7±1 days/discharge, and 90±7 days.

Outcome measures

Primary efficacy outcome: The rate of excellent outcome at 90±7 (mRS score 0-1) days

Secondary efficacy outcome:

1. NIHSS score change at 7±1 days or discharge;
2. Distribution of mRS scores at 90±7 days (mRS shift);
3. Proportion of subjects with good neurological function prognosis (mRS 0-2) at 90±7 days;
4. EQ-5D-5L score at 90±7 days;
5. Proportion of subjects with Barthel Index score of 95 or 100 at 90±7 days;

Primary Safety outcome:

1. Proportion of subjects with symptomatic intracranial hemorrhage within 48 hours (according to the Heidelberg criteria);
2. Proportion of subjects with early neurological deterioration (END) within 7 days (defined as an increase in NIHSS≥4 or an increase of ≥2 in any individual item within 7 days);
3. Overall mortality rate at 90±7 days.

Secondary Safety outcome:

1. Proportion of subjects with any type of intracranial hemorrhage post-randomization (according to the Heidelberg criteria);
2. Rate of secondary endovascular treatment;

Note: The safety endpoints are calculated for the control group;

3. Complications related to endovascular treatment;

Statistical analysis

MILD-MT is designed as a parallel-group randomized controlled trial with a superiority design test. The primary outcome measure is the rate of subjects with excellent prognosis (mRS 0-1) at 90 days. Based on the literature, the proportion in the intervention group with mRS 0-1 is expected to be 67.5%, and in the control group, it is expected to be 51.0%. The false positive rate (I class error, α) is two-side 0.05 and the power (1-β) is 0.8. The ratio of sample size between the two groups is 1:1. The interim analysis is planned during the 90-day follow-up of 50% of the subjects. The O'Brien-Fleming consumption function is used to ensure that the overall false positive rate (I class error) did not exceed two-side 0.05, Using PASS 2023, the calculated sample size is 135 for the intervention group and 135 for the control group. Considering a 10% loss to follow-up, the final sample size is 150 for both the intervention and control groups, totaling 300 participants. And approximately two-side 0.003 of α will be spent at the interim analysis and approximately two-side 0.048 of α will remain at the final analysis. The interim analysis plan will be conducted during the 90d follow-up after completing 50% (150 cases) of randomized subjects.

1.BACKGROUND AND RATIONALE

1.1 EVT is the standard treatment for AIS-LVO with NIHSS score≥6

Acute ischemic stroke (AIS) is a common disease, with a high morbidity, disability and mortality [1]. According to the 2019 Global Burden of Disease (GBD) report, ischemic stroke is the leading cause of death and disability in China [2,3]. Early restoration of perfusion into the ischemic area, salvaging the ischemic penumbra, promoting neural function recovery, reducing disability, and improving long-term survival are the key goals for the treatment of AIS. Several multicenter randomized controlled trials (RCTs) on Endovascular Treatment (EVT) in acute ischemic stroke with large vessel occlusion (AIS-LVO) have yielded positive results since 2015,confirming that EVT is the standard treatment for patients with AIS-LVO within 24 hours of onset [4-11].Among the numerous considerations for EVT in AIS-LVO, the severity of neurological impairment at the time of AIS onset, measured by the National Institutes of Health Stroke Scale (NIHSS) score, is a crucial focal point. Current guidelines recommend EVT for AIS-LVO patients with NIHSS score ≥6 [12,13].

1.2 AIS Population with Low NIHSS score

The severity of neurological deficits in AIS is related to the occlusion site, occlusive degree, collateral circulation establishment, blood pressure, blood glucose and the other factors. Consequently, some AIS-LVO patients may present with low NIHSS score. Definitions of mild AIS-LVO vary in different studies. However, since NIHSS score≥6 is EVT enrollment criteria of large clinical trials and guideline, the definition of mild AIS-LVO is usually based on the NIHSS scores＜6 [11-13].Currently ,only MR CLEAN[4] and EXTEND-IA[5] included some patients with mild AIS-LVO, all of the other studies excluded mild stroke. However, in clinical practice, there are substantial proportion of AIS-LVO patients with low NIHSS scores. An analysis conducted by the Michigan State Epidemiology Center revealed that over 50% of AIS patients had an NIHSS scores <6[14].A large-scale study conducted at the Massachusetts General Hospital found that nearly one-third of AIS-LVO patients had an NIHSS scores <6 [15].Moreover, intracranial artery atherosclerosis (ICAS) are more common in Asian countries and the proportion of mild strokes caused by ICAS may be high [2,3].

1.3 Medical treatment for mild AIS-LVO is unsatisfactory, reperfusion therapy can improve the prognosis

Currently, the treatment for mild AIS-LVO is controversial. Reperfusion treatments including intravenous thrombolysis and EVT is not recommended for mild AIS-LVO in many guidelines. And thrombolysis is recommended for disabling mild strokes [12,16,17]. It is also necessary to fully evaluate the treatment risks and benefits before EVT [12,13]. Studies showed high rate of neurological deterioration and poor outcomes was observed in AIS-LVO patients with low NIHSS scores who receive medical treatment. In a cohort study, approximately 30%-50% of AIS-LVO patients with a NIHSS score <6 who receive medical treatment was independent ambulation at discharge [18]. Additionally, a large study performed at the University of Bern which analyzed 184 patients with low NIHSS scores found 41.2% of patients who receive conservative treatment had an increase NIHSS scores at discharge, while this proportion was less than 20% in patients who treated with thrombolysis or EVT. The percentage of patients with an mRS score ≤1 at 90 days was 30.8% in the conservative treatment group, compared with 54.5% and 54.7% in the thrombolysis and EVT groups [19]. Two cohort studies also found that patients undergoing EVT for mild AIS-LVO with successful reperfusion (mTICI ≥2b) had significantly better outcomes at 90 days than those who did not achieve successful reperfusion [20,21].Furthermore, in the European Stroke Organization (ESO) guidelines, experts voted that thrombolysis could be beneficial for mild AIS-LVO [17] and mentioned two ongoing RCT studies targeting mild AIS-LVO ["ENDOLOW (Endovascular Therapy for Low NIHSS

Ischemic Strokes); NCT 04167527" and "MOSTE (Minor Stroke Therapy Evaluation); NCT 03796468" [22]] which both involving a treatment group receiving the best medical treatment plus endovascular therapy and a control group receiving the best medical treatment, including thrombolysis. Therefore, we believe that mild AIS-LVO can benefit from reperfusion therapy, but further research is needed to determine the optimal reperfusion therapy.

1.4 Uncertain Efficacy of EVT for Mild AIS-LVO

Although reperfusion therapy offers benefits to patients with mild AIS-LVO compared to conservative treatment, there is still significant debate about whether EVT should be the preferred option. A comprehensive systematic review published in 2021 on EVT for mild AIS-LVO [23] provides a more comprehensive summary of the relevant literature. Six single-arm studies discussing the feasibility and safety of EVT in mild AIS-LVO were included, with sample sizes ranging from 20 to 138 cases. The main safety and efficacy endpoints reported included: the proportion of postoperative vessel recanalization rate (mTICI ≥2b) ranging from 78% to 97% which indicating good vessel recanalization rate; the proportion of perioperative symptomatic hemorrhage ranging from 0% to 10%, suggesting a low postoperative bleeding risk. Additionally, two of the six studies reported Modified Rankin Scale (mRS) scores at 90 days,one study showed 95% of patients with mRS scores ≤1 at 90 days; and the other showed 75% of patients with 90 days' mRS scores≤2, indicating favorable neurological outcomes. Thus, the preliminary conclusion is that EVT is safety and feasible for mild AIS-LVO. Furthermore, the systematic review analyzed ten studies comparing the efficacy of EVT with Best Medical Management (BMM), all of which were prospective or retrospective cohort studies with sample sizes ranging from 50 to 300 cases (Figure1). Among these studies, 4 of the 10 studies suggested that EVT resulted in greater benefits than BMM for patients, while 6 studies found no significant difference in the efficacy of EVT and BMM treatments. The primary endpoints of these studies were changes in mRS scores at 90 days or at discharge. In 4 studies suggesting that EVT versus BMM could benefit patients, 3 had a sample size of more than 100 cases. Haussen et al included two cohort studies of patients with mild stroke (NIHSS score ≤5) due to acute occlusion of the intracranial artery, middle cerebral artery M1/M2, and basilar artery, with a median time from onset to admission of 5 hours. The proportion of patients with mRS score ≤2 at 90 days was 96.7% in EVT group and 72.7% in BMM group, with a significant difference (P=0.01) [24]. Nagel et al retrospectively analyzed the data from a multicenter perspective cohort study, including patients with mild stroke (NIHSS score ≤5) due to acute occlusion of the intracranial artery, middle cerebral artery M1/M2, anterior cerebral artery, and basilar artery. The average time from onset to treatment was approximately 6.5 hours. The proportion of patients with mRS score ≤2 at 90 days was 85% in EVT group and 70% in BMM group, with a significant difference (P=0.01) [25]. Shang et al retrospectively analyzed a population with mild stroke (NIHSS score ≤8) due to anterior circulation occlusion of intracranial artery, middle cerebral artery M1/M2 within 24 hours of onset. Although the initial analysis showed no significant difference between EVT group (58.2% with mRS score≤1) and BMM group (46.9% with mRS score≤1) at 90 days(P=0.13).After logistic regression adjusting for factors such as gender, age, medical history, thrombolysis, and occlusion location, patients with good prognosis were significantly associated with EVT (OR, 95% CI, 3.23 [1.35-7.73], P=0.008).

Moreover, the EVT group had a significantly higher proportion of patients with mRS score≤1 at 90 days compared to the BMM group (60% vs. 35%, P=0.02) after propensity score matching for baseline factors[26].In the six studies that considered EVT treatment had similar effects to BMM treatment, one showed a trend towards better efficacy of EVT if baseline data such as occlusion location were corrected[27].Given the limitations of previous studies such as early study periods, limited experience with clot retrieval and device use, further well-designed studies are needed to rigorously analyze the safety and efficacy of EVT in mild AIS-LVO.

Table 2 Results of studies investigating endovascular therapy versus best medical management

Year	Author	IVT in EVT arm	EVT mRS≤1		EVT mRS≤2		NIHSS shift with EVT		sICH		aICH	
			aOR	P	aOR	P	Shift	P	EVT %	BMM %	EVT %	BMM %
2014	Urra *et al*[4]	47%	NS	NS	NS	NS	–	–	11.8*	0*	–	–
2018	Haussen *et al*[5]	31%	–	–	−21%	<0.01	−3.74	0.016	6.7	0	–	–
2018	Nagel *et al*[6]	51%	NS	NS	3.1	NR*	–	–	5.2	2.6	–	–
2020	*Goyal *et al*[3]	54%	0.72	0.47	0.73	0.64	–	–	4.4	0.9	22*	3*
2017	Haussen *et al*[7]	60%	–	–	–	–	−2.5	0.01	0	0	–	–
2018	Sarraj *et al*[8]	31%	1.3	0.47	0.9	0.77	–	–	5.8*	0*	5.3	10
2020	Saito *et al*[9]	9.1%	NS	NS	1.65	0.25	–	–	NS	NS	NS	NS
2020	Wolman *et al*[10]	35%	–	–	–	–	−0.8	0.62	NS	NS	35*	10*
2017	Dargazanli *et al*[11]	61%	1.15	NS	NS	NS	–	–	NS	NS	16.5*	6.1*
2019	*Shang *et al*[12]	29%	NS	NS	3.2	0.008	–	–	10*	2*	–	–

Figure 1

1.5 Study development of EVT for mild AIS-LVO

With the continuous advancement of EVT technique and the increasing sophistication of EVT devices, there is a growing consideration of EVT for mild AIS-LVO in clinical practice. A 2020 international survey indicated that countries worldwide are considering EVT for AIS-LVO patients with NIHSS scores ≤5[28].Thus, focusing on EVT for mild AIS-LVO is the current clinical research hotspot. Currently, there are two ongoing multicenter randomized controlled trials internationally investigating the safety and efficacy of EVT for low NIHSS score of AIS-LVO:"ENDOLOW (Endovascular Therapy for Low NIHSS Ischemic Strokes); NCT 04167527" and "MOSTE (Minor Stroke Therapy Evaluation); NCT 03796468" [22].Of two studies include patients with NIHSS score≤5 and acute occlusion of the proximal anterior circulation (ICA, MCA-M1). The ENOLOW study is being conducted in North America, planning to recruit 200 patients within 8 hours of onset, with the experimental group receiving endovascular treatment using the EmboTrap II device and the control group receiving best medical management. The overall sample size is small, the aim of this study is to clarify the efficacy of EVT in the population with low NIHSS score. The MOSTE study is being conducted in Europe, planning to recruit 825 patients within 24 hours of onset with a larger sample size aiming to identify subgroups within the low NIHSS score population that can benefit from EVT. Currently, there are no relevant RCT studies in China. Additionally, the proportion of ICAS in AIS-LVO population in China is higher than that in Western countries, emphasizing the urgent need for further research in China to explore the best treatment for mild AIS-LVO.

1.6 Design considerations for the MILD-MT study

Given the unclear efficacy of EVT for mild AIS-LVO, further exploration of EVT strategies for these patients and the design of clinical studies require the identification of patients who would benefit most from EVT based on factors influencing the prognosis of mild AIS-LVO. The previous studies have shown that in the mild AIS-LVO patients, EVT is more effect in patients with more proximal large vessels occlusion and the presence of brain penumbra , but the effect is limited in patients with small to medium-sized vessels occlusion [29,30]. Additionally, current researches indicate penumbra tissue auto-calculated by cerebral perfusion software by Tmax >6s was independent predictor of neurological deterioration in AIS-LVO patients [31,32],especially in patients with mismatch penumbra volume >50ml, early neurological deterioration (END) and poor prognosis are likely to occur in such group of patients [33].Therefore, brain perfusion imaging could be applied in selection mild AIS-LVO to receive EVT, a single-center prospective cohort study was to investigated the efficacy of mechanical thrombectomy versus BMM in patients with mild stroke patients (NIHSS ≤5) due to acute occlusion of the intracranial artery, middle cerebral artery M1/M2, vertebral artery, posterior cerebral artery P1 and whom presentation time was within 24 hours of onset, in this study only patients with the core infarction volume (rCBF<30%) ≤50ml, and the mismatch ratio of the

ischemic penumbra was >1.8 selected by brain imaging were included. After propensity score matching and baseline factor adjustment, the percentage of patients with mRS score≤1 at 90 days in the mechanical thrombectomy group was 76.7%, compared to 51.2% in the control group, showing that mechanical thrombectomy was superior to BMM [34].In another exploratory study that combined data from three RCTs (EXTEND-IA and EXTEND-IA TANK I/II) investigating mild stroke due to acute occlusion of large proximal vessels within 24 hours of onset, the larger the volume of the ischemic penumbra mismatch (Tmax>6 seconds, rCBF≥30%) is, the more significant the benefit of EVT would get. Furthermore, after propensity score matching analysis for patients with larger mismatch volumes (median mismatch volume, 64.5ml in the EVT and 56ml in the BMM group), the EVT group had a significantly better efficacy than that in the BMM group, with 65.7% of patients in the EVT group and 51.2% in the control group achieving mRS scores ≤1 at 90 days (P=0.016) [35]. Therefore, we believe that patients with mild AIS-LVO, EVT can be more beneficial only if there is ischemic brain tissue and a sufficiently large salvageable brain tissue volume (ischemic penumbra volume) [36].

This study aims to select suitable patients with mild AIS caused by anterior circulation LVO with mismatch volume of the ischemic penumbra based on screen of cerebral perfusion imaging. It is a prospective, multicenter, endpoint-blinded, randomized controlled trial design, and aim to explore the efficacy and safety of EVT for mild AIS patients with anterior circulation large vessel occlusion within 24 hours of onset.

2. Research objectives

The study aimed to explore the efficacy and safety of EVT in mild ischemic stroke patients caused by acute anterior circulation LVO based on perfusion imaging screening.

3.Method

3.1 Study Design

The MILD-MT trial is a multicenter, prospective, endpoint-blinded, randomized controlled clinical study (PROBE). The intervention group receives the best medical treatment plus endovascular treatment, while the control group receives the best medical treatment alone. The study will run for 4 years in intervention centers.

3.2 Study population

3.2.1 Inclusion Criteria

1. Age 18-80 years old;
2. Symptoms onset or last known well to randomization is within 24 hours
3. Clinical diagnosis of acute ischemic stroke due to anterior circulation intracranial large vessel occlusion (LVO) (including intracranial internal carotid artery [ICA], middle cerebral artery [MCA] M1 segment, MCA M2 segment, with or without ipsilateral extracranial ICA occlusion) confirmed on Computerized tomography angiography (CTA) or Magnetic resonance imaging angiography (MRA);
4. Baseline NIHSS score <6 before randomization (including cases with NIHSS ≥6 at onset but improves before randomization);
5. ASPECTS score ≥6 based on Non-contrast CT (NCCT) before randomization, and computerized tomography perfusion (CTP) or magnetic resonance imaging perfusion (MRP) imaging presented infarct core volume (relative cerebral blood flow (rCBF) <30%/DWI-ADC < 620) ≤50ml, and mismatch volume (Tmax>6 seconds volume - rCBF <30% /DWI-ADC < 620) ≥50mL;
6. The patient or their legal representatives voluntarily signed the informed.

3.2.2 Exclusion Criteria

Clinical Exclusion Criteria

1. Premorbid modified Rankin Scale (mRS) score ≥ 1;
2. Known allergy to iodine, heparin, anaesthesia, or other definite contraindication to receiving endovascular treatment (EVT) procedure;
3. Patient has severe or fatal co-morbidities that could interfere with outcome assessments and follow-up (such as malignant tumor, severe heart failure, or renal failure, or life expectancy less than 6 months);
4. Poorly controlled hypertension (systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg);
5. Baseline blood glucose <50mg/dL (2.78 mmol/L) or >400mg/dL (22.20 mmol/L);
6. Known bleeding tendencies, including but not limited to platelet count <100×109/L; received heparin treatment within 48 hours with an activated partial thromboplastin time (APTT) ≥35s; recent oral anticoagulant therapy with international normalized ratio (INR) >3;

   Note: Patients without a history of coagulation abnormalities or without suspicion of coagulation abnormalities do not need to wait for laboratory test results before enrollment;

7. Seizures at stroke onset or during the course, hard to accurately judge the baseline NIHSS score;
8. Female who is known to be pregnant, lactation, or tested positive for pregnancy at time of admission;
9. Currently participating in another investigational drug study or medical device treatments that may interfere with the results of this study;
10. Other conditions deemed unsuitable for participation, in the opinion of the investigator, or that may pose significant risks to the patient if participating the study.

Imaging Exclusion Criteria

1. Evidence of intracranial haemorrhage on CT/MRI, including cerebral parenchymal haemorrhage, intraventricular haemorrhage, subarachnoid haemorrhage, and subdural/extradural haemorrhage;
2. Significant midline displacement, hernia of brain, or ventricular mass effect with midline displacement confirmed on CT/MRI;
3. Anticipated impossibility to complete endovascular treatment, such as vascular tortuosity, severe vascular wall calcification, etc.;
4. Aortic dissection;
5. Multiple intracranial large vessel occlusions confirmed by CTA or MRA, unable to clearly identify the symptomatic vessel, such as bilateral MCA occlusions or occlusions involving both the MCA and basilar artery;
6. Suspected or confirmed occluded artery is non-acute occlusion.

3.3 Research group

Eligible subjects who have provided informed consent and meet inclusion/exclusion criteria, the research centers will use a central randomization system to allocate subjects in a 1:1 ratio to:

- Endovascular Treatment group (Intervention group): Patients assigned to the endovascular treatment group will receive EVT immediately, combining with best medical treatment according to the local guidelines. Interventionists choose the optimal EVT strategy and device based on the patient's condition and local guidelines. This may include, but not limited to, stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, balloon angioplasty, stent implantation or combined therapy.

- Best Medical Management group (Control group): Patients will receive the best medical treatment according to local guidelines, including antiplatelet agents, anticoagulants, thrombolysis, etc., but not any EVT. In the control arm, rescue EVT is allowed within 24 hours from stroke onset based on local guidelines, if patients with disease progression leading to an increase in NIHSS≥4 and excluding the cause of non-stroke factors The rescue EVT included, but not limited to, stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, balloon angioplasty, stent implantation and combined therapy.

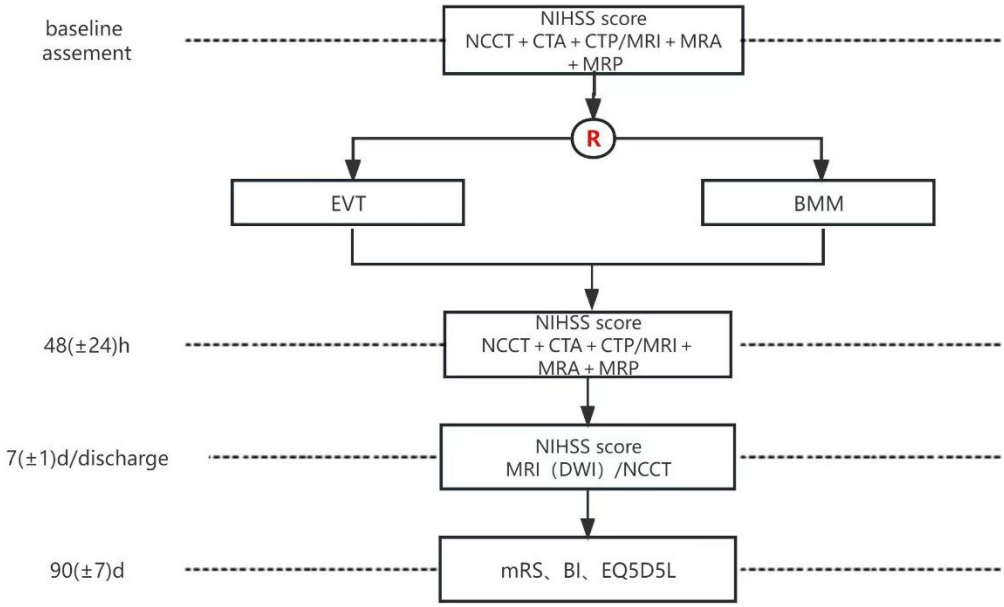


Figure2. Brief Plot of the flow

3.4 Ethical review

3.4.1Review by the Institutional Ethics Committee

This study will be conducted in compliance with the principles outlined in the World Medical Association's Declaration of Helsinki. Before the start of the trial, the investigator must submit the clinical study protocol to the Ethics Committee, and the protocol should be implemented only after the approval of the Ethics Committee. The qualification determination and review date of the voting members should be clearly recorded on the relevant documents of the Ethics Committee. During the clinical trial, any modifications to the study protocol should be reported to the Ethics Committee and approved before implemented. Any serious adverse event occurring during the trial that may affect patient safety or the continuation of the clinical trial, especially any change in safety, should be reported to the Ethics Committee in accordance with the site management regulations of the research center.

3.4.2 Consent

The informed consent form for patients will be created in accordance with relevant clinical research regulations and will be provide to the ethics committee as an independent document. Only the approved version will be used in this clinical trial. When obtaining and recording informed consent, investigators must comply with local regulatory requirements and adhere to the requirements of clinical research regulations and the Helsinki Declaration. Before conducting activities related to the clinical trial, the investigator must be in a quiet and undisturbed place, verbally describe to the subjects or their legal representative's information

about the study. These include details about the clinical trial institution, trial name, trial objectives, trial methods, trial content, trial procedures, rights and obligations of subjects, potential benefits and risks, treatment for risks, and information about alternative diagnostic and therapeutic methods along with their respective potential benefits and risks. Written information about the clinical trial must be provided to the subjects in a form that they can read and understand, and a written informed consent form must be voluntarily signed and dated by the subjects or their legal representatives. The written informed consent must be signed and dated by the personnel responsible for implementing the informed consent procedure.

Withdrawal consent

Simultaneously, investigators must inform patients who participating in this clinical trial that they have the right to refuse participation and can withdraw from the clinical trial at any stage without discrimination or retaliation. Refusal or withdrawal will not affect the subjects' medical treatment and rights.

Consent in special circumstances

If a patient is unable to comprehend or complete the informed consent process owing to their physical condition or any other reasons, their legal guardian or representative may fulfill the informed consent process on their behalf. When a patient's guardian or legal representative completes the informed consent process, they must receive adequate information about the study to allow them to comprehend enough about clinical trial so that they may voluntarily sign their name and date on the informed consent form. When the patient's condition improves to the state of being able to sign the informed consent form, the patient should complete the informed consent process and sign the form. Both the patient and their legal representative have the right to decline participation or withdraw from the clinical trial at any stage.

3.4.3 Confidentiality and Privacy

Every precaution will be taken to respect the privacy of patients in the conduct of the study. Only de-identified data will be used for statistical analyses and in the publication of results to maintain the confidentiality of participants. While monitoring data quality and adherence to the study protocol, the monitor will refer to medical records at the participating hospital. This information will be included in the patient information sheet and written informed consent. All individual and site information will be de-identified in reporting data and results to protect the confidentiality of participants.

3.5 Site Selection

Site eligibility criteria:

1. With an emergency department and a neurological ward for treating stroke patients;
2. With a 24 hours*7 days on call stroke emergent team;
3. Ability to perform intravenous thrombolysis and endovascular therapy for acute ischemic stroke;
4. Perfusion software is available during the study period;
5. At least 50 EVT cases per year;

Responsibilities of the site PI are:

6. Receive training on the protocol, and to ‘champion’ the study at the hospital;
7. Agree to comply with GCP/ICH-GCP requirements;

8. Submit and obtain EC approval and ensure compliance to EC requirements;
9. Ensure all sub-investigators, nursing staff and coordinators, undertake the necessary pre-study training programs regarding the protocol and positioning of the patients;
10. Regularly review the progress of the study at the center and provide targeted training to hospital investigators and other research personnel;
11. Conducting random inspections of the study at the center to ensure adherence to the protocol;
12. Assist in problem-solving during the conduct of the study;
13. Oversee the data collection;
14. Supervise and review safety data.

3.6 Treatment

After emergency admission, patients will receive basic diagnostic and treatment in accordance with local clinical guidelines, including assessment of vital signs and neurological deficits in the hyperacute phase, airway protection and respiratory support, monitoring of circulation and blood pressure, laboratory and imaging examinations, assessment of acute etiology, intravenous thrombolysis, anticoagulation, antiplatelet therapy, etc. After screening and obtaining informed consent, randomized subjects assigned to the intervention group should receive endovascular treatment on basis of best medical treatment, while subjects in the control group should maintain best medical treatment alone.

3.6.1 Medical Treatment

All the subjects in this study will receive the best medical treatment according to current diagnostic and therapeutic standards. Patients who meet the criteria for intravenous thrombolysis should receive intravenous thrombolysis treatment according to local guidelines. The names, doses, and times of use of thrombolytic drugs for all patients must be documented in detail. Additionally, investigators may prescribe anticoagulants and antiplatelet agents based on the patient's condition and current clinical guidelines.

3.6.2 Endovascular Treatment

During endovascular treatment, the operator will decide the anesthesia method based on the patient's medical condition, including local anesthesia, sedation, intubation sedation, or general anesthesia. The arterial approach may be determined by the operator based on preoperative imaging, including femoral artery access, radial artery access, or brachial artery access. After successful arterial puncture, the operator will administer venous or arterial heparin according to the center's practice. The EVT plan can be selected after judging the nature of the lesion site according to the target angiography and preoperative imaging data, including but is not limited to stent-retriever thrombectomy, aspiration thrombectomy, balloon angioplasty, stent implantation and combined therapy.

The NeuroHawk stent-retriever from MicoPort NeuroTech is prioritized to be applied to reduce potential bias caused by different retrieval devices. If unsuccessful, alternative retrieval devices should be used, or additional measures such as balloon angioplasty or stent implantation may be performed as a rescue treatment. Additionally, antiplatelet glycoprotein IIb/IIIa receptor antagonists may be administered for atherosclerosis stenosis occlusion according to local clinical guidelines.

In the control arm, rescue EVT is allowed within 24 hours from stroke onset based on current guidelines, if patients with disease progression leading to an increase in NIHSS≥4 and excluding the cause of non-stroke factors.

3.7 Study Outcomes

- **Primary efficacy outcome:**

The rate of excellent outcome at 90±7 (mRS score 0-1) days

Note:mRS score is an ordinal stratification scale, ranging from 0 to 6, and the higher the score, the higher the severity of disability. The "death" score was 6. The investigator who is not informed of the subject group will evaluates the score and the output the evaluation record.

- **Secondary efficacy outcome:**

1. NIHSS score change at 7±1 days or discharge;

2. Distribution of mRS scores at 90±7 days (mRS shift);

3. Proportion of subjects with good neurological function prognosis (mRS 0-2) at 90±7 days;

4. EQ-5D-5L score at 90±7 days;

5. Proportion of subjects with Barthel Index score of 95 or 100 at 90±7 days;

- **Primary Safety outcome:**

1. Proportion of subjects with symptomatic intracranial hemorrhage within 48 hours (according to the Heidelberg criteria);

2. Proportion of subjects with early neurological deterioration (END) within 7 days (defined as an increase in NIHSS≥4 or an increase of ≥2 in any individual item within 7 days);

3. Overall mortality rate at 90±7 days.

- **Secondary Safety outcome:**

1. Proportion of subjects with any type of intracranial hemorrhage post-randomization (according to the Heidelberg criteria);

2. Rate of secondary endovascular treatment;

Note: The safety endpoints are calculated for the control group;

3. Complications related to endovascular treatment;

3.8 Bias Control Measures

3.8.1 Randomization

This study adopts a randomized grouping method to allocate subjects to the intervention group and control group. Central static block group randomization was used and the stratification factors were:1) Research center; 2) Occlusion site (intracranial ICA; MCA M1; MCA M2). Subjects entering the screening stage may be excluded from the randomization stage for various reasons. Once a screened subject is excluded during the randomization stage, further completion of the scheduled follow-up will no longer be required.

3.8.2 Endpoint Evaluation Methods

1. Blinded assessors at the research center who are unaware of subject groupings will evaluate the postoperative 90-day EQ-5D-5L scale score, and postoperative 90-day Barthel Index and will output assessment records.

2. This study establishes a core laboratory to collect baseline, intraoperative and postoperative imaging records. An independent reader, unaware of subject groupings, will assess subjects' vascular occlusion and perfusion status, intraoperative vascular reperfusion status, and postoperative hemorrhage events.

3. This study establishes a clinical endpoint committee. Independent readers will assess postoperative 90-day mRS scores which are unaware of subject groupings.

4. This study establishes a clinical events committee. Independent readers will assess whether serious adverse events related to EVT occurred during the procedure and determine whether intracranial hemorrhage is symptomatic intracranial hemorrhage which are unaware of subject groupings.

3.9 Economic evaluation

Economic evaluation is crucial in determining whether individuals with mild strokes should undergo EVT and in formulating related policies. For individuals with mild strokes caused by LVO, opting for endovascular treatment may result in higher treatment costs during hospitalization. However, these patients may experience better long-term prognosis, enhanced quality of life, and improved work capacity. Additionally, the proportion of hospitalizations due to recurrent vessel occlusion may be lower. Considering these factors, the overall medical and life burden in the long term might be lower. Therefore, conducting a comprehensive assessment of the health economic effects of endovascular treatment and medical treatment is meaningful for this study.The study will collect data on subjects' treatment costs during hospitalization, costs of emergency treatment or hospitalization for cerebrovascular disease during the follow-up period, and the recovery of work capacity. A comparative evaluation of the health economic effects of the two treatment modalities will be conducted.

3.10 Data Collection and Follow-up

3.10.1 Summary of Study Execution and Visit Plan

The total follow-up period is 90±7days with a total of 4 visit points. The randomization day, randomization 48±24 hours, and randomization 7±1 days, are completed at the research center. Visit points at randomization 90±7 days can be conducted as in-person or telephone follow-up. Follow-up participants should be the patients or their cohabiting caregivers, and the follow-up personnel should be researchers from the research center who are unaware of the subject's group allocation. Specific procedures are outlined in Table 1.

Table 1 Visit Plan

Measure	randomization day	randomization 48±24 hours	randomization 7±1 days	randomization 90±7 days
informed consent form	×			
demographic data/medical and surgical history	×			
laboratory examination	×			
ECG	×			
NCCT +CTA+ CTP or MRI+ MRA+ MRP/MRI or NCCT	×[1]	×[2]	×[3]	
NIHSS	×	×	×[4]	
mRS	×[5]			×

ASPECT	×			
inclusion / exclusion criteria	×			
randomization	×			
Surgical records[6]	×			
TOAST			×	
EQ-5D-5L scale score				×
Basel Stroke Index score				×
AE/SAE[7]		×	×	×
Concomitant medications[8]	×	×	×	×

1、For all enrolled cases, NCCT + CTA + CTP or MRI + MRA + MRP examinations are preferred before randomization to evaluate the presence of hemorrhage, ASPECT score, site of vascular occlusion, core infarct volume, and ischemic penumbra.

2、For all enrolled cases, it is recommended to review multimodal imaging 48 hours after randomization. The imaging evaluation should be the same as that done before randomization to assess intracranial hemorrhage, ASPECTS score, infarction volume, and vascular recanalization. If multimodal imaging is not performed, at least CT or MRI scan should be completed.

3、Subjects should review MRI (DWI) or NCCT at 7 days after randomization or before discharge.

4、If the subjects are discharged before 7 days after surgery, the NIHSS was performed before discharge.

5、Premorbid mRS scores will need to be recorded for all subjects.

6、All operators undergoing interventional procedures (including subjects in the drug therapy group) need to record the intraoperative DSA vessel occlusion location, eTICI before vascular therapy, endovascular devices (such as thrombectomy, the number of thrombectomy), eTICI after endovascular treatment, time of puncture to recanalization, etc

7、This clinical trial records all endovascular treatment-related complications, intracranial hemorrhage related adverse events, and serious adverse events.

8、This trial only records key concurrent drugs, including thrombolytic drugs (including intravenous thrombolysis and arterial thrombolysis), antiplatelet drugs (including intravenous drugs, arterial drugs, oral drugs), anticoagulants, antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs, drugs to reduce intracranial pressure, etc.

3.10.2 Study Execution and Visit Plan Details

Visit 1 (Randomization Day)

Before the start of the trial, subjects or their family members should receive both written and verbal explanations of the trial.

- Sign the informed consent form
- Demographic data
- Medical and surgical history
- Vital signs physical examination
- Evaluating the presence of bleeding, ASPECTS score, vessel occlusion, core infarct volume, and ischemic penumbra volume (based on NCCT+CTA +CTP/MRI+MRA+MRP)
- Electrocardiogram
- Baseline NIHSS score and Pre-mRS
- Laboratory tests
- Review inclusion and exclusion criteria
- Randomization: All subjects screened and meeting inclusion and exclusion criteria must undergo randomization.
- Surgical records: All operators performing intervention procedures (including subjects in the best medical treatment group undergoing rescue treatment) should record intraoperative DSA vessel occlusion location, vessel treatment pre-eTICI, intravascular treatment devices (such as retrieval devices, with the number of retrievals recorded), post-intravascular treatment eTICI, and time from puncture to vessel reperfusion.
- Concomitant medications: only key concomitant medications will be recorded, including thrombolytic drugs (including intravenous and arterial thrombolysis), antiplatelet drugs (including intravenous, arterial, and oral medications), anticoagulants, antihypertensive drugs, antidiabetic drugs, lipid-lowering drugs, and intracranial pressure-lowering drugs.
- Record AE (intracranial hemorrhage-related adverse events and intravascular treatment-related complications), SAE

Visit 2 (48±24 hours after randomization)

- NIHSS score
- For all enrolled cases, it is recommended to perform a follow-up multimodal imaging at 48±24 hours after randomization. The imaging evaluation should be the same as that done before randomization to assess intracranial hemorrhage, ASPECTS score, infarct volume, and vessel reperfusion. If multimodal imaging is not performed, at least NCCT or MRI should be completed
- Concomitant medications: only key concomitant medications will be recorded, including thrombolytic drugs (including intravenous and arterial thrombolysis), antiplatelet drugs (including intravenous, arterial, and oral medications), anticoagulants, antihypertensive drugs, antidiabetic drugs, lipid-lowering drugs, and intracranial pressure-lowering drugs.
- Record AE (intracranial hemorrhage-related adverse events and intravascular treatment-related complications), SAE

Visit 3 (7±1 days/discharge after randomization)

- NIHSS score
- Subjects should undergo MRI (DWI) or NCCT at 7±1 days after randomization or before discharge.
- TOAST classification

- Concomitant medications: only key concomitant medications will be recorded, including thrombolytic drugs (including intravenous and arterial thrombolysis), antiplatelet drugs (including intravenous, arterial, and oral medications), anticoagulants, antihypertensive drugs, antidiabetic drugs, lipid-lowering drugs, and intracranial pressure-lowering drugs.
- Record AE (intracranial hemorrhage-related adverse events and intravascular treatment-related complications), SAE

Visit 4 (90±7days after randomization)

- mRS score, EQ-5D-5L scale score, Basel Stroke Index score
- Concomitant medications: only key concomitant medications will be recorded, including thrombolytic drugs (including intravenous and arterial thrombolysis), antiplatelet drugs (including intravenous, arterial, and oral medications), anticoagulants, antihypertensive drugs, antidiabetic drugs, lipid-lowering drugs, and intracranial pressure-lowering drugs.
- Record AE (intracranial hemorrhage-related adverse events and intravascular treatment-related complications), SAE

Unscheduled Visit

- If subjects receive rescue endovascular treatment, at least one unscheduled visit must be conducted to record endovascular treatment details.
- If subjects experience neurological deterioration at any stage, unscheduled Visit could be conducted, and NIHSS evaluation should be conducted. Moreover, a non-contrast CT or MRI scan should be performed.

3.10.3 Withdrawal of allocated management and Procedures

- In cases where enrolled subjects experience conditions that make it inappropriate to continue the study during the research process (such as the occurrence of serious adverse events, unsuitability for subsequent treatment), the investigator decides to withdraw the case from the study.
- According to the informed consent form, subjects have the right to withdraw from the study at any time.
- Other situations that may lead to the withdrawal of subjects from the clinical study.

Note: After withdrawal, it is necessary to ensure that the subjects receive appropriate treatment. If subject withdraws voluntarily, investigator should attempt to contact the subject through various means such as scheduling follow-up appointments or phone calls and inquire about the reasons. For those who withdraw due to adverse events, if the relationship between the adverse event and the treatment is not clear after follow-up, it must be recorded in the eCRF form. All enrolled subjects, withdraw whether or not, should retain all source data and source files. Clinical study completion summaries and reasons for subject withdrawal should be recorded in the case report form for all withdrawn cases.

3.11 Protocol Deviation

In the event of protocol deviation during the execution of the study, if it is deemed that the deviation will not pose safety issues to subjects and will not impact the treatment of the disease, the deviation should be truthfully reported. The study should then proceed with follow-up according to the prescribed research procedures.

4. Safety

4.1 Data and Safety Monitoring Board (DSMB)

The whole study will be supervised by an independent Data Safety Monitoring Board (DSMB) to ensure the safety of the whole intervention. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for participant efficacy and safety outcomes, and make recommendations to SC concerning the continuation, modification, or termination of the trial. A charter will govern the DSMB, outlining its responsibilities, procedures, and confidentiality. DSMB members will review unblinded data from the study at regular intervals during follow-up and monitor the differences in outcomes between the two groups. The first meeting will be held before the start of the study recruitment. Meetings will be held once every six months once the study recruiting begins. One formal interim analysis will be planned to review data relating to treatment efficacy and safety of trial conduct.

4.2 AEs

Any adverse medical event that occurs from the start of patient randomization to the last follow-up period, regardless of whether there is a causal relationship with the trial, is considered an adverse event. In clinical studies, any unexpected event that occurs in a subject is considered an adverse event.

4.3 SAEs

SAE is any untoward medical occurrence that:

1. results in death

2. is life-threatening in the opinion of the attending clinician (i.e., the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe)

3. requires inpatient hospitalization or prolongation of existing hospitalization

4. results in persistent or significant disability or incapacity

5. results in congenital anomaly or birth defect

6. is an important medical event in the opinion of the attending clinician

4.4 Management of AE and SAE

Once an adverse event occurs in the study, the investigators must immediately organize the rescue to ensure the safety of the subjects. When a serious adverse event occurs, appropriate treatment measures should be taken to ensure the safety of the subjects, and the applicant should be promptly reported in writing and reported in accordance with the relevant management regulations of the research center.

4.5 Observation and record of AE and SAE

The study records intracranial haemorrhage-related adverse events, complications related to endovascular treatment, and all serious adverse events. Adverse events are recorded from randomization until 90 days after enrollment or the end of the last follow-up. If the subject experiences adverse events that need to be recorded, they will be followed up until the adverse events disappear, return to baseline level, or show significant improvement/stability without the need for further follow-up.

5. Quality Assurance

During the clinical trial process, the clinical research associate will conduct regular on-site visits to the research sites to ensure that all contents of the research protocol are strictly followed, and the original data will be checked to ensure in accordance with the eCRF.Personnel participating in the clinical trial should receive uniform training. The investigators should record the contents truthfully and carefully to ensure that the contents are true and reliable.
The document must not be altered. If there is a clerical error, only a horizontal line should be drawn on the item filled in incorrectly, and the correct content should be filled in. The correct content should be signed next to it and indicate the date. All observations and findings in the clinical trial should be verified to ensure the reliability of the data and to ensure that all the conclusions in the clinical trial are derived from the original data.

5.1 Monitoring of Participating Centres/Sites

During the study, the Steering Committee will regularly contact the study site, including:

1. visiting the research center to provide information and support to researchers for research

2. confirming that the facilities meet the requirements

3. confirming that all investigators' stakeholders followed the protocol and that data records on the eCRF were timely and accurate

4. conducting the raw data verification(data on the eCRF were compared to the subjects' hospital records and other records related to the study), including a review of the informed consent of the subjects. It is necessary to directly refer to all original records of each patient (such as hospitalization records).

If the investigators or other staff of the site need information and recommendations regarding study implementation, contacting the Steering Committee during the follow-up interval.

5.2 Auditing and Inspection by Government Regulatory Authorities

In addition, the study may also be audited by a third party and inspected by inspectors appointed by government regulatory authorities. CRFs, source documents, and other study files must be accessible at all study sites at the time of auditing and inspection during the course of the study, and after the completion of the study.

6. Data Management

The design of CRF ensures the data specified in the study protocol meets statistical analysis requirements and establishes filling guidelines for the corresponding CRF.
This study uses an electronic data collection (EDC) system to collect data. Logical verification is established based on CRF and database design instructions. It is put to use online after passing the user acceptance test (UAT).

The test data, the time of entry/import into the database, the entry person, the data audit track, and the documents formed by the data management process all need to be kept completely. The data formed by the data management process usually include, but are not limited to, clinical trial data, external data, database metadata information, laboratory test reference value range, logical test and derivative data change control list, data challenge table program code, etc. The documents formed by the data management process usually include, but are not limited to, a data management plan, blank CRF, CRF filling guideline, PDF format file for completing CRF, annotation CRF, database design description, database entry description, data verification plan,

data quality control verification report, etc. The test data, management documents, media, and archiving methods shall be specified in the data management plan.
For the management of external data such as core laboratories, data transmission protocols are used, including data categories, data providers, data formats, transmission methods, transmission frequencies, etc., as well as quality control of external data.

Data collection and management of this study refer to the relevant requirements of NMPA Technical Guidelines for Electronic Data Collection of Clinical Trial and Technical Guidelines for Clinical Trial Data Management.

7. Statistical Considerations

7.1 Sample Size Calculation

This study is a parallel randomized controlled trial with endovascular treatment in the experimental group and best medical treatment in the control group. The primary outcome measure is the proportion of patients with an excellent outcome (defined as mRS 0-1) at 90 days.

the estimated proportion of subjects with mRS 0-1 in the experimental group is 67.5%, while the control group is 51.0%. The false positive rate (I class error, α) is a two-side 0.05 and the power (1-β) is 0.8. The ratio of sample size between the two groups is 1:1. The interim analysis is planned during the 90-day follow-up of 50% of the subjects. The O'Brien-Fleming consumption function is used to ensure that the overall false positive rate (I class error) did not exceed two-side 0.05, Hence, the sample size for each group is estimated to be 135 using PASS 2023, approximately two-side 0.003 of α will be spent at the interim analysis and approximately two-side 0.048 of α will remain at the final analysis. Upon considering the 10% of loss to follow-up, it assumes that the sample size for each group will include a total of 150 subjects. For the final analysis, a cohort of 300 subjects will be enlisted in total.

7.2 Analysis of Datasets

Statistical Analysis will based on Intention to Treat (ITT) set.

7.3 Statistical Analysis

7.3.1 General Statistical Analysis Methods

Descriptive statistics for measurement data will include mean, standard deviation, median, minimum, maximum, lower quartile (Q1), and upper quartile (Q3). Enumeration data describe the number and percentiles of each class.

The statistical tests of this study are the comparison between the two groups. The inter-group ratio of measurement data that follows a normal distribution will be analyzed using an independent sample t-test. Conversely, the Wilcoxon rank sum test will be employed to analyze the comparison of measurement data that deviates from a normal distribution. Categorical data comparisons between the two groups will use the Pearson chi-square test or Fisher's exact test. The Wilcoxon rank-sum test or Cochran-Mantel-Haenszel (CMH) test will be used to compare ranked data between groups. All statistical tests will be two-sided unless otherwise specified, and $P < 0.05$ (both sides) will be considered to be statistically significant.

7.3.2 Efficacy Analysis

Primary Endpoint:

At a significance level of α=0.048(two-side) and β=0.2, the excellent neurological functional prognosis rates at 90±7 days after randomization will be compared between the experimental and control groups. The two groups were compared utilizing the CMH chi-square test, taking into account the critical prognostic factors. The Mantel-Haenszel method was employed to

evaluate the rate difference between the two groups with a 95% confidence interval. The prognostic factors were adjusted accordingly.

Secondary Endpoint:

The Proportion of subjects with a good neurological functional prognosis (mRS 0-2) at 90±7 days after randomization will be statistically described according to enumeration data, with comparisons between the two groups. Distribution and comparison of mRS scores at 90±7 days after randomization, with the presentation of the mRS transition diagram. In addition, to evaluate the distribution of mRS scores, ordered logistic regression is used to calculate the common odds ratio. If needed, variables that affect prognosis can be adjusted.

Changes in NIHSS score within 7±1 days or at discharge, and EQ-5D-5L scale scores at 90±7 days after randomization will be described for measurement data and compared between the two groups.

The proportion of subjects with a Basel Index (Barthel Index) score of 95 or 100 at 90 ± 7 days after randomization were statistically described according to the count data and compared in two groups.

7.3.3 Safety Analysis

Proportions of subjects with symptomatic intracranial hemorrhage within 48 hours after randomization (according to the Heidelberg criteria), early neurological deterioration within 7 days, all-cause mortality within 90±7 days, any intracranial hemorrhage after randomization (the location is defined according to the Heidelberg definition), rescue endovascular treatment rate (control group only), and endovascular treatment-related complications will be described for count data and compared between the two groups.

7.4 Interim Analysis Plan

With a planned sample size of 300 subjects, a formal interim analysis will be conducted after 50% (150 subjects) of the subjects have completed the 90-day follow-up. The interim analysis will perform a superiority test. Multiple testing adjustments will use the O'Brien-Fleming method, with a spending α of approximately two-side 0.003 at the interim analysis and approximately two-side 0.048 at the final analysis.

The interim analysis will be conducted independently by the Data and Safety Monitoring Board (DSMB), consisting of third-party medical and statistical experts.

8. Publication and Data Sharing

The publication of the main reports from the study will be done in the name of the MILD-MT Investigators. Full editorial control will reside with a Writing Committee approved by the SC. The Writing Committee will consist of committee members, statisticians, and investigators. They will write the main reports of the study and publish them in authoritative journals on stroke and cerebrovascular diseases, domestically and internationally, in the name of "MILD-MT investigators."The results will be presented at relevant domestic and international conferences on stroke and cerebrovascular diseases.

The authors of publications must adhere to the authorship criteria of the International Committee of Medical Journal Editors (ICMJE):

1. Authors must have made substantial contributions to the conception and design of the trial, data acquisition, data analysis, and interpretation of results.

2. Authors must draft the publication or contribute substantially during the review process (data analysis, interpretation, or other significant content) to make important revisions to the manuscript, with the agreement of other authors.

3. Authors must approve the final version of the manuscript before submitting it for publication. According to ICMJE regulations, any contributors who do not meet these criteria need to be listed in the acknowledgments section of the publication.

However, as this is a multi-site academic study, investigators agree not to publish or publicly present any results of the study without the prior written consent of the SC. Investigators further agree to provide the SC, at least 30 days prior to submission for publication or presentation, a review of copies of abstracts or manuscripts (including, without limitation, text and PowerPoint presentation slides and any other texts of transmissions or media presentations) that report any results of the study. The SC also has the right to review and comment on the data analysis and presentation about the accuracy of the information, the protection of the rights of individuals, and to ensure that the presentation is balanced and in compliance with appropriate regulations (such as the protection of the subject's privacy). If the parties disagree concerning the appropriateness of the data analysis and presentation and/or confidentiality, the investigator(s) will agree to meet with members of the SC for the purpose of making good faith efforts to discuss and resolve any disagreements.

9. Organization

9.1 General Consultant

The General Consultant will be responsible for the overall direction and design of the study, ensuring the correctness of the study plan's orientation. The general consultant will be composed of international academic leaders.

9.2 Steering Committee (SC)

The SC will be responsible for the interpretation, supervision, and reporting of the study (published in international medical conferences and peer-reviewed journals), which also includes the development of the study protocol and its amendments. The SC will provide recommendations to the study sites based on information provided by the Data Safety Monitoring Board (DSMB) regarding whether the study needs to be terminated or adjusted. The SC will consist of designated international academic leaders and non-voting members of the sponsor, operating according to independent bylaws.

9.3 Data Safety Monitoring Board (DSMB)

To enhance the safety of the intervention, an independent Data Safety Monitoring Board (DSMB) will supervise the trial. The DSMB will dynamically assess the risks and benefits of both therapies by monitoring effectiveness and safety data, providing recommendations to the SC on whether the study should be terminated or adjusted. The DSMB operates independently with independent personnel according to separate bylaws.

9.4 Core Laboratory

Core laboratory will be established to minimize research bias caused by investigators, subjects, etc., and to make the results of the imaging subgroup studies more objective and effective. The core laboratory will consist of three personnel with qualifications in neuroradiology or equivalent, responsible for reading and interpreting imaging data related to this clinical study. Imaging analysis, including the vascular occlusion and perfusion status of subjects, intraoperative vascular recanalization, and postoperative hemorrhage.

9.5 Outcome Assessment Committee (OAC)

In order to minimize the deviation of investigators and subjects in the primary endpoint and make the study results more objective and effective, a Clinical Endpoint Committee (OAC) was set up. The OAC will consist of at least three doctors with experience in neurology or neurosurgery unrelated to this study.

9.6 Clinical Events Committee (CEC)

To minimize research bias caused by investigators, subjects, etc., and make the results of the study's primary endpoints more objective and effective, a Clinical Events Committee (CEC) will be established. The CEC will consist of at least three with neurointerventional or neurosurgical experience unrelated to this study, including at least one member with neurointerventional experience. Responsibilities include reviewing severe adverse events and specifically monitoring adverse events, ensuring consistent diagnostic criteria for respective events.

10. Founding

The study is funded by the Beijing Health Promotion Association(BHPA2021N002) and MicroPort NeuroTech Company(Shanghai).

11. References

[1] GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0

[2] Wang YJ, Li ZX, Gu HQ, et al. China Stroke Report 2020 (Chinese version) (3). Chinese Journal of Stroke. 2022;17(7):8.

[3] Hu Y, Zhang X, Zhang A, et al. Global burden and attributable risk factors of acute lymphoblastic leukemia in 204 countries and territories in 1990-2019: Estimation based on Global Burden of Disease Study 2019. Hematol Oncol. 2022;40(1):92-104. doi:10.1002/hon.2936

[4] Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke [published correction appears in N Engl J Med. 2015 Jan 22;372(4):394]. N Engl J Med. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587

[5] Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009-1018. doi:10.1056/NEJMoa1414792

[6] Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-1030. doi:10.1056/NEJMoa1414905

[7] Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296-2306. doi:10.1056/NEJMoa1503780

[8] Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061

[9] Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442.

[10] Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973 .

[11] Bourcier R, Goyal M, Liebeskind DS, et al. Association of Time From Stroke Onset to Groin Puncture With Quality of Reperfusion After Mechanical Thrombectomy: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials [published correction appears in JAMA Neurol. 2019 May 28;:]. JAMA Neurol. 2019;76(4):405-411. doi:10.1001/jamaneurol.2018.4510 .

[12] Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2018 Mar;49(3):e138] [published correction appears in Stroke. 2018 Apr 18;]. Stroke. 2018;49(3):e46-e110. doi:10.1161/STR.0000000000000158.

[13] Chinese Stroke Association, Society of Neurointervention of Chinese Stroke Association, Interventional Group of the Stroke Prevention and Control Committee of the Chinese Preventive Medicine Association. Chinese guidelines for endovascular treatment of acute ischemic stroke 2023. Chinese Journal of Stroke. 2023;18(6):684-711.

doi:10.3969/j.issn.1673-5765.2023.06.010.

[14] Reeves M, Khoury J, Alwell K, et al. Distribution of National Institutes of Health stroke scale in the Cincinnati/Northern Kentucky Stroke Study. Stroke. 2013;44(11):3211-3213. doi:10.1161/STROKEAHA.113.002881

[15] Maas MB, Furie KL, Lev MH, et al. National Institutes of Health Stroke Scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. Stroke. 2009;40(9):2988-2993. doi:10.1161/STROKEAHA.109.555664.

[16] Chinese Society of Neurology, Chinese Medical Association; Cerebrovascular Disease Group, Chinese Society of Neurology, Chinese Medical Association. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chinese Journal of Neurology. 2018;51(9):666-682. doi:10.3760/cma.j.issn.1006-7876.2018.09.004.

[17] Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021;6(1):I-LXII. doi:10.1177/2396987321989865

[18] Mokin M, Masud MW, Dumont TM, et al. Outcomes in patients with acute ischemic stroke from proximal intracranial vessel occlusion and NIHSS score below 8. J Neurointerv Surg. 2014;6(6):413-417. doi:10.1136/neurintsurg-2013-010720.

[19] Heldner MR, Chaloulos-Iakovidis P, Panos L, et al. Outcome of patients with large vessel occlusion in the anterior circulation and low NIHSS score. J Neurol. 2020;267(6):1651-1662. doi:10.1007/s00415-020-09744-0

[20] Hu Y, Huang S, Li G, et al. Clinical effect of successful reperfusion in patients presenting with NIHSS < 6 and large vessel occlusion. J Stroke Cerebrovasc Dis. 2022;31(10):106684. doi:10.1016/j.jstrokecerebrovasdis.2022.106684

[21] Kaesmacher J, Chaloulos-Iakovidis P, Panos L, et al. Clinical effect of successful reperfusion in patients presenting with NIHSS < 8: data from the BEYOND-SWIFT registry. J Neurol. 2019;266(3):598-608. doi:10.1007/s00415-018-09172-

[22] Arquizan C, Lapergue B, Gory B, et al. Evaluation of acute mechanical revascularization in minor stroke (NIHSS score ⩽ 5) and large vessel occlusion: The MOSTE multicenter, randomized, clinical trial protocol [published online ahead of print, 2023 Jul 16]. Int J Stroke. 2023;17474930231186039. doi:10.1177/17474930231186039

[23] McCarthy DJ, Tonetti DA, Stone J, et al. More expansive horizons: a review of endovascular therapy for patients with low NIHSS scores. J Neurointerv Surg. 2021;13(2):146-151. doi:10.1136/neurintsurg-2020-016583

[24] Haussen DC, Lima FO, Bouslama M, et al. Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: an analysis from STOPStroke and GESTOR cohorts. J Neurointerv Surg. 2018;10(4):325-329. doi:10.1136/neurintsurg-2017-013243

[25] Nagel S, Bouslama M, Krause LU, et al. Mechanical Thrombectomy in Patients With Milder Strokes and Large Vessel Occlusions. Stroke. 2018;49(10):2391-2397. doi:10.1161/STROKEAHA.118.021106

[26] Shang XJ, Shi ZH, He CF, et al. Efficacy and safety of endovascular thrombectomy in mild ischemic

stroke: results from a retrospective study and meta-analysis of previous trials. BMC Neurol. 2019;19(1):150. Published 2019 Jul 5. doi:10.1186/s12883-019-1372-9

[27] Sarraj A, Hassan A, Savitz SI, et al. Endovascular Thrombectomy for Mild Strokes: How Low Should We Go?. Stroke. 2018;49(10):2398-2405. doi:10.1161/STROKEAHA.118.022114

[28] Krementz NA, Landman A, Gardener HE, et al. Endovascular Therapy in Mild Ischemic Strokes Presenting Under 6 hours: An International Survey. J Stroke Cerebrovasc Dis. 2020;29(11):105234. doi:10.1016/j.jstrokecerebrovasdis.2020.105234

[29] Seners P, Perrin C, Lapergue B, et al. Bridging Therapy or IV Thrombolysis in Minor Stroke with Large Vessel Occlusion. Ann Neurol. 2020;88(1):160-169. doi:10.1002/ana.25756

[30] Broccolini A, Brunetti V, Colò F, et al. Early neurological deterioration in patients with minor stroke due to isolated M2 occlusion undergoing medical management: a retrospective multicenter study [published online ahead of print, 2023 Mar 28]. J Neurointerv Surg. 2023;jnis-2023-020118. doi:10.1136/jnis-2023-020118

[31] Gwak DS, Kwon JA, Shim DH, Kim YW, Hwang YH. Perfusion and Diffusion Variables Predict Early Neurological Deterioration in Minor Stroke and Large Vessel Occlusion. J Stroke. 2021;23(1):61-68. doi:10.5853/jos.2020.01466

[32] Wang P, Chen W, Chen C, et al. Association of Perfusion Lesion Variables With Functional Outcome in Patients With Mild Stroke and Large Vessel Occlusion Managed Medically. Neurology. 2023;100(6):e627-e638. doi:10.1212/WNL.0000000000201498

[33] Werdiger F, Parsons MW, Visser M, et al. Machine learning segmentation of core and penumbra from acute stroke CT perfusion data. Front Neurol. 2023;14:1098562. Published 2023 Feb 23. doi:10.3389/fneur.2023.1098562

[34] Liu F, Shen H, Chen C, et al. Mechanical Thrombectomy for Acute Stroke Due to Large-Vessel Occlusion Presenting With Mild Symptoms. Front Neurol. 2021;12:739267. Published 2021 Oct 28. doi:10.3389/fneur.2021.739267

[35] Sarraj A, Albers GW, Blasco J, et al. Thrombectomy versus Medical Management in Mild Strokes due to Large Vessel Occlusion: Exploratory Analysis from the EXTEND-IA Trials and a Pooled International Cohort. Ann Neurol. 2022;92(3):364-378. doi:10.1002/ana.26418

[36] Seners P, Arquizan C, Fontaine L, et al. Perfusion Imaging and Clinical Outcome in Acute Minor Stroke With Large Vessel Occlusion. Stroke. 2022;53(11):3429-3438. doi:10.1161/STROKEAHA.122.039182

Appendix

Appendix.1 Modified Rankin Scale

Patient condition	Score
Completely asymptomatic	0
Despite the symptoms, but no obvious dysfunction, can complete all the daily work and life	1
Mildly disabled, unable to complete all pre-illness activities, but do not need to take care of their daily affairs	2
Moderate disability, requiring partial help, but being able to walk independently	3
Moderate to severe disability, unable to walk independently, and need help from others in their daily life	4
Severe disability, bedridden, second incontinence, and completely dependent on others in daily life	5
Death	6

Assessment method for the modified Rankin scale

The modified Rankin scale is used to measure the outcome of functional recovery after stroke. Boldface shows the formal definition at each level. Italics provides further guidance to reduce possible errors between different observers, but there is no requirement for the architecture of the interview. Note that only the symptoms occurring since the stroke are considered. A patient is considered able to walk independently without external assistance. If both levels seem to be equally applicable to the patient, and further questioning is unlikely to make the absolutely correct choice, the more serious level should be chosen.

0-No symptoms at all

Despite mild symptoms, patients have not noticed any new functional limitations and symptoms since stroke.

1-No significant disability despite symptoms; able to perform all frequent duties and activities

Patients have certain symptoms caused by stroke, whether physical or cognitive (such as affecting speech, reading, writing; or physical movement; or feeling; or vision; or swallowing; or emotion), but may continue in all work, social and leisure activities prior to stroke. The key question used to distinguish between levels 1 and 2 (see below) could be, " Is there something you used to do regularly, but you can't do it until after a stroke?"。 Activities with a frequency greater than once a month were considered 'frequent'.

2-Mild disability; unable to perform all previously possible activities but able to handle personal matters without assistance

Some activities that can be completed before stroke (such as driving, dancing, reading, or working) are no longer possible to treat patients after stroke, but they can still take care of themselves daily without the assistance of others. Patients can dress, walk, eat, go to the bathroom, prepare simple food, shop, and travel locally without needing their help. The patient lives without supervision. Patients at this level can stay alone for a week or longer without care.

3-Moderate disability; requiring some assistance, but not for walking

At this level, patients can walk independently (with the help of auxiliary walking machinery), go to the bathroom, eat, etc., but more complex tasks need to be completed with the help of others. For example, need someone to replace shopping, cooking or cleaning, and visit patients more than once a week to ensure the above activities are completed. Assistance is needed in not just physical care, but also advice: for example, patients at this level will need supervision or encouragement to handle their finances.

4-Severe disability; inability to walk without assistance and inability to care for their own physical needs

Patients need others to help manage their daily lives, whether by walking, dressing, going to the bathroom or eating. Patients need to be attended to at least once a day, usually twice or more, or have to live close to the caregiver. To distinguish between levels 4 and 5 (see below), consider whether the patient is able to live routinely alone for an appropriate time during the day.

5-Severe disability; bedridden, incontinence, requiring continuous care and care

Although trained nurses are not required, someone needs to care several times throughout the day and night.

6-The subject has died

Appendix 2 Expanded treatment in cerebral ischemia (eTICI) score

eTICI classify	Short description	Long description
0	**nonperfusion**	There was no antegrade blood flow outside the occlusion point
1	**The reperfusion was limited**	There was anteograde reperfusion after initial occlusion but limited distal branch perfusion, almost no distal reperfusion or slower distal reperfusion
2a	**reperfusion < 50%**	Anterograde reperfusion was less than half of the occluded target artery in the previous ischemic region (e. g., MCA and one of the major branches of its region)
2b	**reperfusion And 50% but <90%**	Anterograde reperfusion of more than half of the previously occluded target artery region (e. g., the MCA and the two main branches of its region)
2c	**reperfusion ≥90%**	The ischemic area of the previously occluded target artery almost completely reached antegrade reperfusion, except for slower flow or distal occlusion of a few distal cortical vessels
3	**reperfusion 100%**	Previous occlusion of the ischemic area of the target artery completely achieved anterograde reperfusion with no visible occlusion of all distal branches

MCA: middle cerebral artery; eTICI: Volume of expanded treatment for cerebral ischemia

Appendix.3 National Institute of Health Stroke Scale

Assessment	Response	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	
1b. LOC Questions: 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. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be	0 = Normal. 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where	

Assessment	Response	Score
scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	

Assessment	Response	Score
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:	-
	5a. Left Arm	
	5b. Right Arm	
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement. 9 = Amputation, joint fusion explain:	-
	6a. Left Leg	
	6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent . 1 = Present in one limb . 2 = Present in two limbs If present, is ataxia in?	
	Right arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
	Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain : _____	-
	Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-

Assessment	Response	Score
	Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	0 = No aphasia, normal. 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be	0 = Normal.	

Assessment	Response	Score
obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain: _____	
11. Extinction and Inattention **(formerly Neglect):** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	
TOTAL		

Appendix.4 EuroQoL Group 5-Dimension Self-report Questionnaire

Subject	Score
Mobility	1= I have no problems in walking about 2= I have slight problems in walking about 3= I have moderate problems in walking about 4= I have severe problems in walking about 5= I am unable to walk about
Self-care	1= I have no problems washing or dressing myself 2= I have slight problems washing or dressing myself 3= I have moderate problems washing or dressingmyself 4= I have severe problems washing or dressing myself 5= I am unable to wash or dress myself
Usual activities (e.g. work, study, housework, family, or leisure activities)	1= I have no problems doing my usual activities 2= I have slight problems doing my usual activities 3= I have moderate problems doing my usual activities 4= I have severe problems doing my usual activities 5= I am unable to do my usual activities
Pain/ discomfort	1= I have no pain or discomfort 2= I have slight pain or discomfort 3= I have moderate pain or discomfort 4= I have severe pain or discomfort 5=I have extreme pain or discomfort
Anxiety/ depression	1= I am not anxious or depressed 2= I am slightly anxious or depressed 3= I am moderately anxious or depressed 4= I am severely anxious or depressed 5= I am extremely anxious or depressed

The questionnaire was completed by:

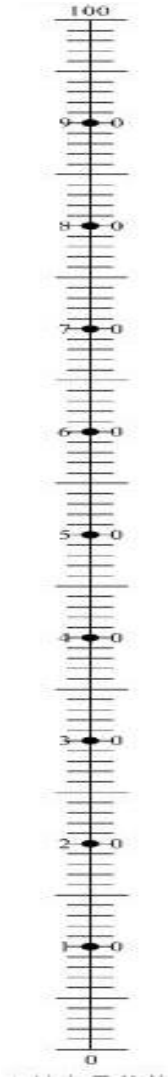
☐1Subject ☐2Subjects with the help of a third party ☐3Agent

To help you reflect your health, we drew a scale (kind of a thermometer) on which:

100 means the best health you can imagine.

0 means the worst health you can imagine.

Please write the number you marked on the scale in the box below:



Appendix.5 Barthel Index

Assessment	Score	Content
1、FEEDING	**10**	In a reasonable time (about 10 seconds to eat a bite), you can eat the food in front of you with chopsticks. If accessories are needed, they should wear and take them off on their own.
	5	Need some help.（ Cut bread, spread butter, pick up food, serve rice, etc. ）
	0	Dependent。
2.TRANSFERS	**15**	Independent。
	10	Need a small amount of help (1 person) or language guidance
	5	Need the help of two or one strong and skillful person.
	0	Totally dependent on others.
3、GROOMING	**5**	Someone can wash his face, hands, brush his teeth and comb his hair independently.
	0	Needs to help with personal care
4、TOILET USE	**10**	Someone can go in and out of the toilet without getting dirty, and can put on good clothes. Those who use bedpans can clean the bedpans themselves.
	5	Need help to keep balance, tidy up clothes or use sanitary pads. Those who use bedpans can pick up and put bedpans on their own, but they have to rely on others to clean them.
	0	Need other's help。
5、BATHING	**5**	independent (or in shower)
	0	dependent 。
6、MOBILITY (ON LEVEL SURFACES 45 m)	**15**	Can walk independently for over 50 meters with or without the use of accessories
	10	Need a little support or oral guidance to walk more than 50 meters.
	5	Although it is unable to walk, someone can operate the wheelchair independently (including turning, entering the door, and approaching the table and the edge of the bed) and can push the wheelchair more than 50 meters.
	0	Need other’s help.
	10	Independent (handrails and crutches are allowed)

7、Stairs	**5**	Need a little help or oral guidance.
	0	Unable to go up and down stairs
8、DRESSING	**10**	Someone can wear clothes, shoes and accessories by himself / herself .
	5	With the help of others, someone can complete more than half of the actions by himself / herself.
	0	Need other's help
9、BOWELS	**10**	Controllable
	5	Occasional incontinence (less than once a week).
	0	Incontinence or coma.
10、BLADDER	**10**	Controllable
	5	Occasional incontinence (less than once a week) or urgent urination (unable to wait for the bedpan or unable to get to the toilet immediately) or need help.
	0	Incontinence, coma or need for catheterization.
TOTAL		

Appendix 6. Classification of Heidelberg bleeding

According to the Heidelberg criteria of the 12th Symposium on Thrombosis treatment of Ischemic Stroke held in Germany in 2015

The criteria defines symptomatic intracranial hemorrhage as (with the following):

1. symptomatic intracranial hemorrhage (including Heidelberg criteria 1a, 1b, 1c, 2, 3a, 3b, 3c, 3D) found by imaging examination (head CT or MRI) ;

2. Severe clinical symptoms: 4 points higher in the NIHSS score relative to the final score, or 2 points higher in any one of the NIHSS scale, or leading to endotracheal intubation, flap decompression, ventricular drainage or other major medical / surgical intervention;

3, no other cause other than intracranial hemorrhage can explain the deterioration of clinical symptoms.

Heidelberg classification	
Grading / typing	**Grading / typing**
Infarct brain tissue hemorrhage with no significant occupancy effect **(Level 1)**	☐
Scattered small bleeding sites, with no occupancy effect ***(Grade 1a / Type H-1)***	☐
The eding spots fused into plaques with no occupancy effect ***(Grade 1b / Type H2)***	☐
Hemhematoma within infarct tissue <30% infarct volume without large occupancy effect, cerebral hemorrhage within or beyond the infarct tissue ***(Grade 1c / PH Type 1)***	☐

Infarct brain tissue hemorrhage, hematoma volume 30% infarct volume, and has an obvious occupancy effect **(Grade 2 / Type PH2)**	☐
Brain hemorrhage outside of the infarcted tissue **(Level 3)**	☐
Hemhematoma in the distal site of infarction ***(Level 3a)***	☐
ventricular hemorrhage ***(Level 3b)***	☐
subarachnoid hemorrhage ***(Grade 3c)***	☐
subdural hemorrhage ***(3d level)***	☐

Appendix 7. Alberta Stroke Project early CT score (ASPECTS)

Alberta Stroke Project early CT score (Alberta Stroke Program Early CT Score, ASPECTS) is a ten-point systematic quantitative scoring method to evaluate ischemic changes in NCCT in patients with acute ischemic stroke in the MCA supply area. The MCA blood feeding area was divided according to the figure below, and one point was subtracted from the total score of 10 for each area involved by the ischemic changes.10 represents normal brain imaging and 0 represents extensive involvement of the MCA by ischemic infarction.(Yoo AJ, Lancet Neurology)。

A: anterior circulation ; P: posterior circulation.

10 partitions: Ten subdivisions: C = caudate nucleus; L = lentiform nucleus; IC= internal capsule; I = insular cortex; M1 = MCA anterior cortex, equivalent to insular tectum; M2 = MCA internal parapsular cortex, equivalent to anterior temporal lobe; M3 = MCA posterior cortex, equivalent to posterior temporal lobe; MCA anterior cortex on M4=M1; M5 = MCA lateral cortex on M2; MCA posterior cortex on M6=M3