Endovascular Recanalization vs Medical Treatment for Non-Acute Intracranial Artery Occlusion (ERNA-IAO): A Multicenter, Prospective, Cohort Study

Study Protocol

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Protocol V1.0

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Protocol Signature Page

STUDY TITLE:	Endovascular Recanalization vs Medical Treatment for Non-Acute Intracranial Artery Occlusion (ERNA-IAO): A Multicenter, Prospective, Cohort Study
VERSION NUMBER:	V 1.0
VERSION DATE:	20 November 2019

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices, applicable international regulations, local regulations, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the designed time flow.

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

I will fulfill the requirements of my Ethics Committee (EC), and/or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by my reviewing oversight committee(s).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in this protocol to my reviewing oversight committee, where required. I agree to permit regulatory authority access to all records relating to the clinical investigation, whether paper-based or electronic data capture.

The below signature confirms I have read and understood this clinical investigational protocol and its associated amendments or attachments.

PRINTED OR TYPED NAME	SIGNATURE	DATE
Principal Investigator		

PRINTED OR TYPED NAME	SIGNATURE	DATE
Study Statistician		

Table of Contents

List of Abbreviations

ADP	Adenosine Diphosphate
AE	Adverse Event
aHR	Adjusted Hazard Ratio
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ASTIN/SIR	American Society of Therapeutic and Interventional Neuroradiology /Society of Interventional Radiology
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar Artery
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CICAS	The Chinese Intracranial Atherosclerosis (study)
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion Imaging
DWI	Diffusion Weighted Imaging
DSA	Digital Subtraction Angiography
EC	Ethics Committee
EC-IC	Extracranial-Intracranial
OEAC	Outcome Event Arbitration Committee
EVT	Endovascular Treatment
ER	Endovascular Recanalisation
ERNA-IAO	The Endovascular Recanalization for Non-Acute Intracranial Artery Occlusion (study)
EQ-5D	EuroQOL-Five-Dimensions
FIB	Fibrinogen
GCS	Glasgow Coma Scale
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
HI1	Hemorrhagic Infarction 1
HI2	Hemorrhagic Infarction 2
HR	Hazard Ratio

IAO	Intracranial Artery Occlusion
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
IQR	Interquartile Range
LDL	Low Density Lipoprotein
INR	International Normalized Ratio
IVH	Intraventricular Hemorrhage
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis In Cerebral Infarction Score
NA-IAO	Non-Acute Intracranial Artery Occlusion
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
pc-ASPECTS	Posterior Circulation Alberta Stroke Program Early CT Score
PH1	Parenchymal Hemorrhage 1
PH2	Parenchymal Hemorrhage 2
PMI	Pons-Midbrain Index
PSM	Propensity Score Matching
PT	Prothrombin Time
PWI	Perfusion Weighted Imaging
RAPID	Rapid Processing of Perfusion and Diffusion
RIH	Ischemic Field
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SD	Standard Deviation
sICH	Symptomatic Intracranial Hemorrhage
sNA-IAO	Symptomatic Non-Acute Intracranial Artery Occlusion
TIA	Transient Ischemic Attack
TT	Thrombin Time
VA	Vertebral Artery

Protocol Synopsis

Title	Endovascular Recanalization vs Medical Treatment for Non-Acute Intracranial Artery Occlusion (ERNA-IAO): A Multicenter, Prospective,Cohort Study
Sponsor	Beijing Tiantan Hospital, Capital Medical University
Study period	Enrollment from January 1,2020 to October 31, 2023 (and 1 year follow-up)
Study Centers	Interventional Neuroradiology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University; Department of Neurology, Beijing Liangxiang Hospital; Department of Neurointerventional Radiology, Beijing Fengtai You'anmen Hospital; Department of Neurology, Ordos Central Hospital; Department of Neurology, Jingjiang People's Hospital Affiliated to Yangzhou University; Department of Neurology, Taizhou first people's Hospital.
Study Objectives	The primary objective of this study is to investigate whether endovascular recanalisation (ER) plus medical treatment is superior to medical treatment alone for symptomatic non-acute intracranial artery occlusion (sNA-IAO) in the primary outcome.
Study Design	multicenter, prospective, cohort study
Study Population	Patients with sNA-IAO, with the time from the latest ischemic event (ischemic stroke or transient ischemic attack) in the territory of the qualifying artery to enrollment being beyond 24 hours and within 90 days, as confirmed by computed tomography angiography (CTA) or digital subtraction angiography (DSA).
Inclusion Criteria	• (1) Age ranging between 18 and 80 years. • (2) sNA-IAO defined as： ① Time from latest ischemic event (ischemic stroke or TIA) in territory of the qualifying artery to enrollment is beyond 24 hours and within 90 days. ② Occlusion of intracranial internal carotid artery, M1 segment of middle cerebral artery, intracranial vertebral artery (with contralateral vertebral artery hypoplasia or occlusion) or basilar artery confirmed by computed CTA or DSA. • (3) Computed tomographic (CT) or magnetic resonance imaging (MRI) demonstrating ASPECTS ≥6 (for anterior circulation), or pc-ASPECTS ≥6 and

	pons-midbrain index (PMI) <3 (for posterior circulation). • (4) Modified Rankin Scale (mRS) score 0-2 at the time of enrollment. • (5) Technical feasibility of endovascular recanalization for the qualifying artery evaluated by two experienced interventional neuroradiologists. • (6) More than one risk factor for atherosclerosis. • (7) Signed informed consent form.
Exclusion Criteria	• (1) Severe stenosis or occlusion of other arteries, or tandem stenosis proximal to the qualifying artery. • (2) Intracranial hemorrhagic diseases such as definite Intracranial tumors, any intracranial vascular malformations, hemorrhagic transformation of infarction, spontaneous intracranial hemorrhage (cerebral parenchymal, subarachnoid, subdural, or epidural) within 30 days. • (3) Non atherosclerotic intracranial arterial disease: arterial dissection, moyamoya disease or moyamoya syndrome demonstrated by imaging examination, or a definite medical history of autoimmune vasculitis. • (4) Evidence of cardioembolic embolism such as atrial fibrillation, prosthetic valve(s), infective endocarditis, mitral stenosis, atrial myxoma, intracardiac clot or vegetation, left ventricular aneurysms and so on. • (5) Known unstable angina or myocardial infarction within the last 6 months. • (6) Intolerance or allergic reaction to any treatment-related medication, including aspirin, clopidogrel, heparin, and local or general anesthetics. • (7) History of life-threatening allergy to contrast dye. • (8) Severe liver impairment (AST or ALT > 3 times normal, cirrhosis), serum creatinine > 3.0 mg/dl. • (9) Past history of EC-IC bypass surgery or EVT. • (10) Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment. • (11) Late-stage malignant tumors, cachexia, or other serious diseases and an expected life expectancy of less than 1 year. • (12) Pregnant, perinatal stage or lactating women.
Treatments and Study Groups	The technical feasibility of ER for all sNA-IAO patients in this study will be collaboratively evaluated by two experienced interventional neuroradiologists. The decision to select either medical treatment alone or additional ER is made by the patients themselves or their legal representatives. Patients are subsequently divided into two groups based on selection of treatment approach: the medical group and the ER group.

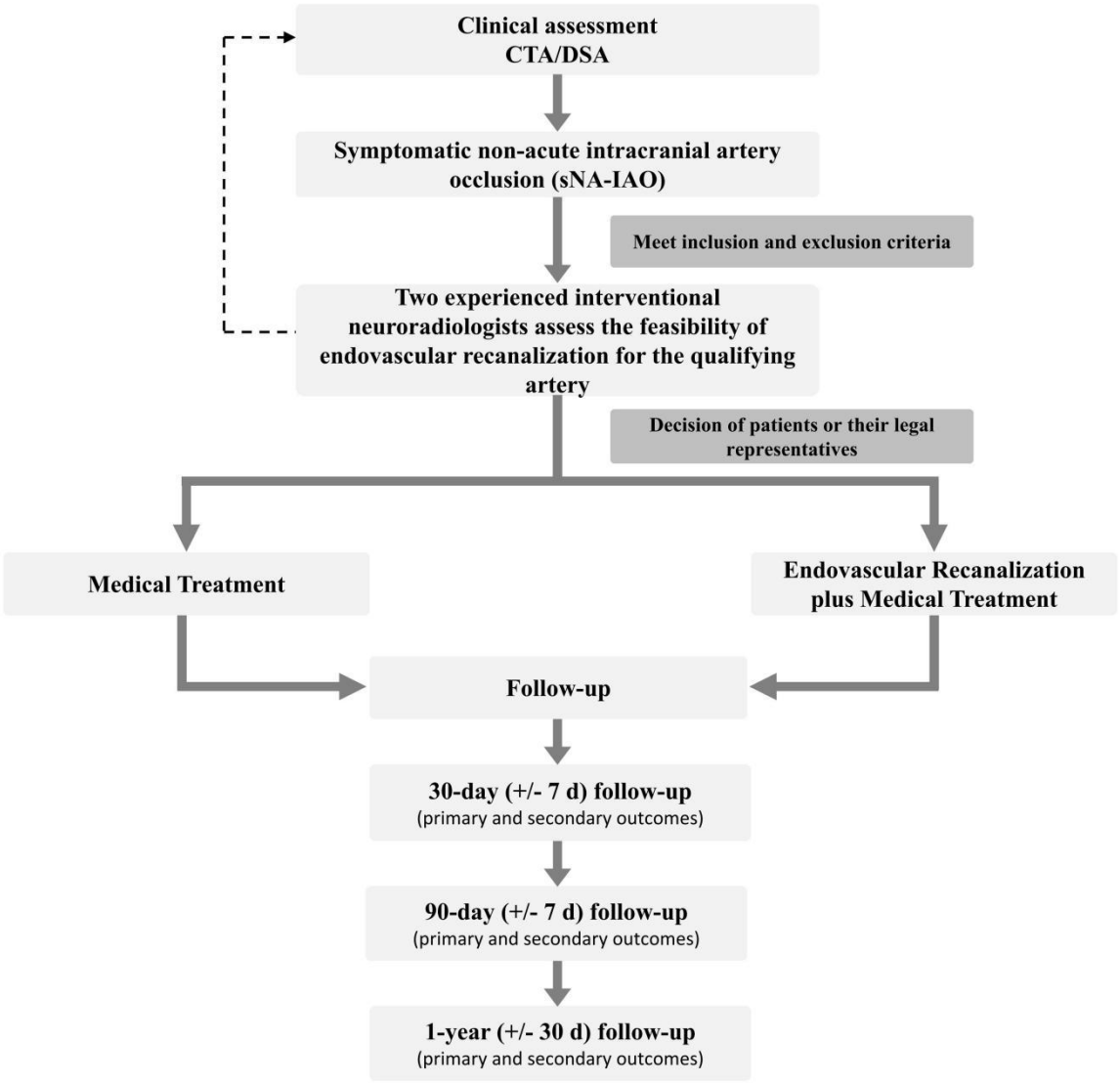
Follow-up schedule	Baseline, 30±7 days, 90±7 days, 1 year±30 days
Primary Outcome	The primary outcome is a composite outcome as follows: • Any stroke or death within 30 days after enrollment • Ischemic stroke in the territory of the qualifying artery form 30 days to 1 year after enrollment.
Secondary Endpoints	Secondary outcomes as follows: • Mortality within 1 year; • Ischemic stroke outside the territory of the qualifying artery within 1 year; • Disabling stroke within 1 year; • TIA in the territory of the qualifying artery within 1 year; • Unplanned revascularization (EC-IC bypass surgery or ER) of the qualifying artery within 1 year; • Myocardial infarction within 1 year; • Composite vascular events within 1 year, including any stroke, myocardial infarction, and unplanned revascularization; • Quality of life assessment (EuroQol-5-Dimensions scale questionnaire) at 1 year; • mRS score at 1 year; • Periprocedural outcomes; • Restenosis or reocclusion (symptomatic or asymptomatic).
Statistical Methods	• Categorical variables will be compared between treatment groups using χ^2 or Fisher's exact test. Continuous variables or ordinal variables will be compared between treatment groups using t-test or Wilcoxon-Mann-Whitney test. • The primary and time-to-event secondary outcomes will be compared between the groups using log-rank test. • Kaplan-Meier curves wil be used to show the incidence of outcomes over time. • The hazard ratio (HR) and adjusted hazard ratio (aHR) between groups, along with their 95% CIs, will be determined using univariate and multivariate Cox proportional hazards regression models. • Propensity score matching (PSM) will be performed to reduce the possible influence of selection bias and confounders on the outcomes. • A 2-sided P value less than 0.05 is considered to demonstrate a statistically significant difference. • All analyses will be performed with using SAS Version 9.4.

Schedule of assessments

Table 1: Summary of Study Treatment and Study Assessments

Study Requirements	Screening and Baseline	Endovascular recanalisation			Discharge	Follow-up Visits		
		Pre-procedure	Intra-procedure	Post-procedure		30-Day (±7 days)	90-Day (±7 days)	1-Year (±30 days)
Inclusion/Exclusion	X	X						
Informed Consent	X							
Clinical Assessment, Vital Signs, and Physical Exam	X	X			X	X	X	X
Laboratory tests	X					X	X	X
NIHSS (blinded to treatment)	X				X	X		
mRS (blinded to treatment)	X				X	X	X	X
EQ-5D (blinded to treatment)						X	X	X
mTICI assessment		X	X	X				
CT/MRI	X			X			X	X
CTP/PWI	X						X	X
CTA/DSA	X						X	X
Protocol Deviations		X	X	X	X	X	X	X
Medication review and patient compliance survey	X	X	X	X	X	X	X	X
Primary and secondary outcomes			X	X	X	X	X	X

Figure 1. Study design and treatment grouping flowchart



1. Background

Intracranial large artery atherosclerotic stenosis or occlusion constitutes one of the major etiologies of ischemic stroke worldwide.[1,2] Previous studies have showed that ischemic stroke among Asian populations, African Americans, and Hispanic populations are primarily attributable to intracranial large artery stenosis and occlusion.[3,4] The Chinese Intracranial Atherosclerosis (CICAS) Study revealed that in the Chinese population, 33%-50% of ischemic strokes and over 50% of transient ischemic attacks (TIAs) were caused by intracranial artery stenosis or occlusion.[5] Furthermore, patients with intracranial artery occlusion (IAO) exhibit higher mortality rates, stroke incidence, and recurrence rates.[5] Beyond this, a series of studies have consistently demonstrated that the most common location for IAO is in the anterior circulation, with middle cerebral artery occlusion being the most prevalent, while in the posterior circulation, basilar artery occlusion is frequently observed.[6,7]

Endovascular treatment (EVT) has been proven to be an effective treatment option within the established time window for acute ischemic stroke attributable to IAO.[8,9,10,11,12] Additionally, the relevant clinical trials have collectively established the extension of the therapeutic window for EVT in acute IAO to 24 hours.[13,14] However, a significant number of patients with acute ischemic stroke attributable to IAO frequently fail to achieve endovascular recanalisation (ER) during the acute phase due to delays in reaching a qualified stroke center in time after symptom onset.[15] Consequently, these patients were compelled to transition into the non-acute phase. Currently, there is no definite definition for non-acute intracranial artery occlusion. To distinguish the therapeutic time window for acute occlusion, previous studies has defined occlusion with a duration exceeding 24 hours as non-acute occlusion.[16,17] In patients with symptomatic non-acute intracranial artery occlusion (sNA-IAO), severe hemodynamic compromise resulting from chronic cerebral hypoperfusion has emerged as a significant contributor to both initial occurrence and recurrence of ischemic stroke, demonstrating strong correlation with adverse functional outcomes.[1,18] Nevertheless, the optimal therapeutic approach for sNA-IAO beyond 24 hours after symptom onset continues to pose a significant clinical challenge.

Clinical experience suggests that for sNA-IAO patients presenting with significant clinical manifestations or experiencing symptom progression/recurrence despite receiving optimal medical management, ER or extracranial-intracranial (EC-IC) bypass surgery may be considered as therapeutic options. With respect to EC-IC bypass surgery, previous studies have failed to demonstrate superior efficacy compared to medical treatment in patients with symptomatic atherosclerotic large artery occlusion accompanied by severe hemodynamic compromise.[19,20,21] Regrettably, large-scale prospective controlled studies specifically investigating the potential superiority of endovascular recanalization for patients with sNA-IAO remain scarce. Notably, a collection of case series reports and small retrospective analyses have demonstrated that ER for carefully selected sNA-IAO patients beyond the 24-hour window seems feasible and may represent a promising therapeutic option.[16,17,22,23,24,25,26,27,28,29,30] Nonetheless, this studies were single arm, small sample size, retrospective studies. While ER may represent a potential therapeutic alternative for sNA-IAO patients refractory to medical treatment, there is a paucity of controlled studies establishing its definitive superiority over medical management. Furthermore, compared to EVT in acute IAO, recanalization procedures in non-acute cases are associated with elevated procedure-related risks and increased susceptibility to symptomatic intracranial hemorrhage, raising substantial safety concerns.

Consequently, We conducted a multicenter, prospective, cohort study to investigate whether ER combined with medical treatment is superior to medical treatment alone for sNA-IAO.

2. Study Objective

The primary objective of this study is to investigate whether ER plus medical treatment is superior to medical treatment alone for sNA-IAO in the primary outcome (any stroke or death within 30 days after enrollment or ischemic stroke in the territory of the qualifying artery beyond 30 days through 1 year after enrollment).

3. Methods

3.1 Study Design

The Endovascular Recanalization for Non-Acute Intracranial Artery Occlusion (ERNA-IAO) study is a multicenter, prospective, cohort study, this cohort prospectively will enroll consecutive patients with radiologically confirmed sNA-IAO at 6 comprehensive stroke centers in China from January 1,2020 to October 31, 2023. All participants or their legal representatives provide written informed consent before enrollment. The primary objective of this study is to evaluate whether ER plus medical treatment is superior to medical treatment alone for patients with sNA-IAO presenting beyond 24 hours after symptom onset. All study centers complied with the Expert Consensus on Standardized Diagnosis and Treatment in China, ensuring consistent data acquisition across sites. The study protocol was approved by the Institutional Ethics Committee of Beijing Tiantan Hospital (approval number: KY2020-114-02), and each subcenter, and will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

3.2 Participants Selection and Enrollment

Patients eligible for initial study screening are those who present with occlusion in the intracranial internal carotid artery (ICA), M1 segment of middle cerebral artery (MCA), intracranial vertebral artery (VA) or basilar artery (BA), presenting beyond 24 hours of symptom onset. All such patients who meet all eligibility criteria as follows and with informed consent will be enrolled in the study.

3.2.1 Inclusion criteria

Patient eligibility for study enrollment is determined based on the following inclusion criteria:

(1) Age ranging between 18 and 80 years.

(2) sNA-IAO defined as：

- ① Time from latest ischemic event (ischemic stroke or TIA) in territory of the qualifying artery to enrollment is beyond 24 hours and within 90 days.
- ② Occlusion of intracranial ICA, M1 segment of MCA, intracranial VA (with contralateral VA hypoplasia or occlusion) or BA confirmed by computed tomographic angiography (CTA) or digital subtraction angiography (DSA).

(3) Computed tomographic (CT) or magnetic resonance imaging (MRI) demonstrating Alberta Stroke Program Early CT Score (ASPECTS) ≥6 (for anterior circulation) or Posterior Circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) ≥6 and pons-midbrain index (PMI) <3 (for posterior circulation).

(4) Modified Rankin Scale (mRS) score 0-2 at the time of enrollment.

(5) Technical feasibility of endovascular recanalization for the qualifying artery evaluated by two experienced interventional neuroradiologists.

(6) More than one risk factor for atherosclerosis.

(7) Signatured informed consent form.

3.2.2 Exclusion criteria

Patients are deemed ineligible for study participation if they meet any of the following exclusion criteria:

(1) Severe stenosis or occlusion of other arteries, or tandem stenosis proximal to the qualifying artery.

(2) Intracranial hemorrhagic diseases such as definite Intracranial tumors, any intracranial vascular malformations, hemorrhagic transformation of infarction, spontaneous intracranial hemorrhage (cerebral parenchymal, subarachnoid, subdural, or epidural) within 30 days.

(3) Non atherosclerotic intracranial artery disease: arterial dissection, moyamoya disease or moyamoya syndrome demonstrated by imaging examination, or a definite medical history of autoimmune vasculitis.

(4) Evidence of cardioembolic embolism such as atrial fibrillation, prosthetic valve(s), infective endocarditis, mitral stenosis, atrial myxoma, intracardiac clot or vegetation, left ventricular aneurysms, etc.

(5) Known unstable angina or myocardial infarction within the last 6 months.

(6) Intolerance or allergic reaction to any treatment-related medication, including aspirin, clopidogrel, heparin, and local or general anesthetics.

(7) History of life-threatening allergy to contrast dye.

(8) Severe liver impairment (AST or ALT > 3 times normal, cirrhosis), serum creatinine > 3.0 mg/dl.

(9) Past history of EC-IC bypass surgery or EVT.

(10) Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment.

(11) Late-stage malignant tumors, cachexia, or other serious diseases and an expected life expectancy of less than 1 year.

(12) Pregnant, perinatal stage or lactating women.

3.3 Participating Center Eligibility

To minimize selection bias, all participating centers are mandated to systematically enroll consecutive eligible patients according to predefined protocol criteria. To be fully eligible for participation in this study, participating centers selection are required to meet the following minimum criteria:(1) all study centers are required to have performed at least 120 endovascular procedures annually, including at least 40 cases of intracranial artery endovascular procedures; (2) the interventional neuroradiologists at these centers had each performed over 100 endovascular procedures..

3.4 Ethical Issues

All the patients gave written informed consent to participate. The study protocol was approved by the Institutional Ethics Committee of Beijing Tiantan Hospital (approval number: KY2020-114-02), and the respective institutional review boards of all participating centers. Participation in the study did not alter the standard clinical care protocols for enrolled patients.

3.5 Baseline Imaging Evaluation

All participants will have baseline imaging (MRI or CT to rule out ICH and exclude major infarction, and CTA/DSA to confirm an occlusion in the MCA, BA, intracranial ICA or VA), performed as part of institutional standard of care procedures for stroke management. All imaging data of this baseline imaging (including raw data) must be provided to the imaging core laboratory for assessment of collateral

compensation, location of the occlusion and determination of ASPECTS (pc-ASPECTS for posterior circulation), etc.

3.6 Treatments and Study Groups

The technical feasibility of endovascular recanalization for all sNA-IAO patients in this study will be collaboratively evaluated by two experienced interventional neuroradiologists. The decision to select either medical treatment alone or additional ER is made by the patients themselves or their legal representatives. Patients are subsequently divided into two groups according to the treatment they received: the medical group and the endovascular recanalization (ER) group. Patients in ER group will receive endovascular recanalisation procedure (details in procedure part below) plus medical treatment (same as the control group).

3.6.1 Endovascular recanalisation (ER)

For patients presenting with ICA or MCA M1 segment occlusion, ipsilateral cerebral hemodynamic compromise is rigorously evaluated through computed tomography perfusion (CTP) or magnetic resonance perfusion imaging prior to enrollment according to a previous study.[31] Moreover, the non-contrast and perfusion scans are additionally transferred to the Rapid Processing of Perfusion and Diffusion (RAPID) system, providing analysis of perfusion source images with respect to the DEFUSE 3 criteria[13].

All patients who are scheduled to undergo ER should receive dual antiplatelet therapy (aspirin 100 mg per day and clopidogrel 75 mg per day) for at least three days before the procedure.

All procedures are performed under general anesthesia by an experienced interventional neuroradiologist. After placement of sheath introducers, heparin is given intravenously to maintain the coagulation time between 200 and 300 s. The 6- or 8- French guiding catheter is located distal to the occluded artery as much as possible. Under the route map, the micro guidewire in combination with a microcatheter and the microcatheter are used to carefully pass through the occluded segment. Angiography with the microcatheter should confirm that the guidewire is in the true lumen. The exchange micro guidewire is then sent into the micro catheter, and the microcatheter is exchanged out. The balloon catheter is advanced smoothly into the occluded segment along the exchange micro guidewire. After the occluded segment is dilated with the balloon, angiography with a guiding catheter is performed. Stents are deployed in cases of residual severe stenosis, vascular dissection and failure to maintain forward flow (according to the judgment of the neuroradiologist to select the stent). If one stent cannot completely cover the lesion, multiple stents can be implanted. Successful recanalization was defined as achieving a modified Thrombolysis in Cerebral Infarction (mTICI)[32] grade of 2b or higher, coupled with residual arterial stenosis less than 50% in immediate post-procedural DSA imaging..

After the procedure, if there are no evidence of hemorrhagic complications on the head CT scan, dual antiplatelet therapy is systematically continued. Aspirin 100 mg per day must be used for the entire duration of follow-up, and clopidogrel 75 mg per day (or ticagrelor 90mg twice a day) must be used for 90 days after procedure. After 90 days, the decision to whether to continue clopidogrel therapy will be based on the patient's clinical condition and the investigator's assessment.

3.6.2 Medical treatment

Medical treatment will be identical in both groups. Both groups are prescribed with an medical treatment (includes aspirin 100 mg per day for the entire follow-up and clopidogrel 75mg per day for the first 90 days after enrollment). In instances where clopidogrel pharmacogenetic resistance testing is performed, and the results demonstrate either a loss-of-function CYP2C19 allelic variant or an adenosine diphosphate (ADP)-induced platelet aggregation rate exceeding 40%, alternative antiplatelet agents such as ticagrelor or cilostazol may be strategically implemented as therapeutic substitutes. Atorvastatin will be administered at a dosage of 20 mg to 80 mg per day for one year following enrollment, with the continuation of treatment thereafter contingent upon the patient's condition.

3.7 Risk Factor Management

Risk factor management is based on 2014 American Heart Association/American Stroke Association guidelines[33] for the clinical management of cerebrovascular disorders. Medical management of risk factors consists of normalizing low-density lipoprotein (LDL-C) (target LDL-C: <2.59 mmol/L [100mg/dL]), hypertension (systolic pressure <140 mmHg and a diastolic pressure <90 mmHg; patients with diabetes should be controlled with a blood pressure of <130/80 mmHg), diabetes (hemoglobin A1c [HbA1c] <6.5%), and lifestyle modification(include encompassing smoking cessation, alcohol consumption reduction[up to 2 drinks per day for men and half for women], and targeted weight management interventions [BMI <25 kg/m^2], moderate physical exercise [at least 40 minutes per session, 3-4 times per week]).

At each research site, neurologists and study investigators will be principally entrusted with comprehensive management of patients' cerebrovascular risk factors. Should a patient fail to achieve the target goals for risk factor management, a face-to-face clinical consultation with the local neurologist will be required to adjust the patient's medical management.

3.8 Follow-up

All participants will be followed up by the neurologists at 30±7 days, 90±7 days, 1 year ±30 days. The preferred follow-up modality is to implement face-to-face clinical evaluations. At every scheduled follow-up visit, the participants' medication regimens, laboratory tests, risk factor management (as previously outlined), and potential adverse clinical events/outcomes are evaluated by an experienced neurologist and/or neurointerventionalist.When patients are unable to attend on-site clinical follow-ups, a remote telephonic follow-up will be utilized as an alternative method of patient assessment.During the 1-year follow-up period, all patients are required to undergo a neurovascular imaging examination including DSA, CTA or MRA.

For perioperative patients in ER group, a clinical examination including the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) will be carried out at 24-72 hours after the procedure. Meanwhile, patients will undergo CT to assess the cerebral hemorrhage at 24-72 hours, if possible, supplementary assessment of vessel recanalization status will be conducted through CTA or MRA. At the one-week post-intervention assessment, a clinical evaluation will be conducted,including patients' clinical status, NIHSS score, GCS score, and adverse events.

3.9 Outcomes

3.9.1 Primary outcome

The primary outcome is a composite of any stroke or death within 30 days after enrollment or ischemic stroke in the territory of the qualifying artery from 30 days to 1 year after enrollment.

Ischemic stroke is defined as a new focal neurological deficit of sudden onset persisting for at least 24 hours and confirm by cerebral infarction on CT or MRI. Ischemic stroke are further classified as being either in or out of the territory of the qualifying artery. We regard ischemic stroke either in or out of the territory of the qualifying artery within 30 days after enrollment as a primary outcome, but beyond 30 days through 1 year, only ischemic stroke in the territory of the qualifying artery is considered as a primary outcome. We define symptomatic intracranial hemorrhage (sICH) as parenchymal, intraventricular, or subarach noid hemorrhage identified on brain MRI or CT, which led to new emergence or worsening of neurological symptoms lasting more than 24 hours or a seizure. Death is categorized as vascular-related or non-vascular-related, and all-cause death is considered a primary outcome within 30 days.

Ischemic stroke and intracranial hemorrhage will be determined by core-lab assessment of imaging, and neurological assessment will be performed at the study site by independent neurologist certified in NIHSS, adjudication of outcomes will be done by an outcome adjudication committee.

3.9.2 Secondary outcomes

Secondary outcomes as follows:

- Mortality within 1 year;
- Ischemic stroke outside the territory of the qualifying artery within 1 year;
- Disabling stroke within 1 year;
- TIA in the territory of the qualifying artery within 1 year;
- Unplanned revascularization (EC-IC bypass surgery or ER) of the qualifying artery within 1 year;
- Myocardial infarction within 1 year;
- Composite vascular events within 1 year;
- Quality of life assessment (EuroQol -Five-Dimensions [EQ-5D] scale questionnaire) at 1 year;
- mRS score at 1 year;
- Periprocedural outcomes;
- Restenosis or reocclusion (symptomatic or asymptomatic).

Disabling stroke is defined by any of the following: (1) an mRS score of 3 or more, (2) an increase of at least 1 point in the mRS score from prestroke baseline, (3) a score on the composite NIHSS of 7 or more, or (4) an increase of at least 4 points in the NIHSS score from pre-stroke baseline.
TIA is defined as duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarction.
Composite vascular events within 1 year included any stroke, myocardial infarction, and unplanned revascularization within 1 year.
Periprocedural outcomes are: (1) successful recanalization rate, (2) periprocedural complications: in-stent thrombosis, distal embolization, symptomatic intracranial hemorrhage, parenchymal hematoma type 2 (defined by the Heidelberg classification[34]), arterial dissection, arterial perforation, (3) residual stenosis, (4) NIHSS score at 24-72 hours, (5) death within 7 days.
Restenosis is defined as >50% stenosis within or immediately adjacent (within 5 mm) of the treated segment and >20% absolute luminal loss, reocclusion is defined as total occlusion of the target artery segment.

3.10 Data Collection and Management

3.10.1 Baseline clinical data collection and evaluation

When the patient is enrollled, clinical and neurological assessments will be completed per institutional standard of care. linical data were comprehensively collected by independent neurologists. Data to be collected and then captured on Case Report Form (CRF) include:

- ✓ Medical history, concomitant medication, demographic data collection
- ✓ Ischemic stroke history record
- ✓ Relevant concomitant medications administered
- ✓ Vital signs: Blood pressure, heart rate, respiration, body temperature
- ✓ Laboratory tests: blood routine, urine routine, blood biochemistry, coagulation function examination
  - Blood biochemistry: Renal function: creatinine, urea (or urea nitrogen), glucose, uric acid, total bilirubin, direct bilirubin, indirect bilirubin, lactate dehydrogenase, creatine kinase isoenzyme; liver function: alkaline phosphatase, glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase; blood lipids: total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride;
  - Coagulation function: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), Fibrinogen (FIB), international normalized ratio (INR).
- ✓ Significant findings from clinical assessment and physical exam
- ✓ All significant neurological findings, pre-stroke mRS, mRS and NIHSS at enrollment assessed by qualified personnel at time of admission

3.10.2 Perioperative and 7-day postoperative follow-up data collection

These data include:

- ✓ Anesthesia Types: general anesthesia or local anesthesia
- ✓ Procedure times (groin puncture time, time of first microcatheter placement across the occlusion, time of initial flow restoration, time of guide catheter removal)
- ✓ Site-assessed mTICI score at post procedure
- ✓ Perioperative medication collection
- ✓ Perioperative complications
- ✓ Significant findings from clinical assessment and physical exam (e.g. all new, worsening or improved conditions)
- ✓ Patient compliance survey

3.10.3 30±7 days after enrollment data collection

- ✓ Relevant concomitant medications collection (including anti-platelet, lipid-lowering, and other medications)
- ✓ Blood pressure, blood routine, urine routine, blood biochemistry
- ✓ Fasting blood glucose, HbA1c (optional)
- ✓ Patient smoking cessation, weight, and exercise data are collected
- ✓ mRS
- ✓ The disease treatment-related cost information collection
- ✓ Outcome events observation
- ✓ Patient compliance survey

3.10.4 90±7 days after enrollment data collection

- ✓ Relevant concomitant medications collection (including anti-platelet, lipid-lowering, and other medications)
- ✓ Blood pressure, blood routine, urine routine, blood biochemistry
- ✓ Fasting blood glucose, HbA1c (optional)
- ✓ CT/MRI (optional)
- ✓ CTP/perfusion weighted imaging (PWI) (optional)
- ✓ CTA/DSA (optional)
- ✓ Patient smoking cessation, weight, and exercise data are collected
- ✓ mRS
- ✓ The disease treatment-related cost information collection
- ✓ Outcome events observation
- ✓ Patient compliance survey

3.10.5 1 year±30 days after enrollment data collection

- ✓ Relevant concomitant medications collection (including anti-platelet, lipid-lowering, and other medications)
- ✓ Blood pressure, blood routine, urine routine, blood biochemistry
- ✓ Fasting blood glucose, HbA1c (optional)
- ✓ CT/MRI (optional)
- ✓ CTP/PWI (optional)
- ✓ CTA/DSA (optional)
- ✓ Patient smoking cessation, weight, and exercise data are collected
- ✓ mRS, EQ-5D
- ✓ The disease treatment-related cost information collection
- ✓ Outcome events observation
- ✓ Patient compliance survey

3.11 Safety and Adverse Events

3.11.1 Adverse events (AE)

An adverse event (AE) is defined as any unfavorable and unintended sign, symptom, or disease that occurs to a study subject during the use of a medical treatment or intervention, regardless of whether it is deemed related to the treatment. A preexisting condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

3.11.2 Serious adverse events (SAE)

A serious adverse event (SAE) is defined as any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, causes a congenital anomaly or birth defect, or requires medical intervention to prevent one of the above-mentioned outcomes.

3.11.3 Anticipated Adverse Events

Anticipated AEs are events whose nature is consistent with the safety information contained in the device documentation, specifically in the Instructions for Use (IFU) of the medical device utilized for the

study-specific procedures. The term “anticipated” does not imply that these events are expected to occur as a consequence of the underlying disease.

The assessment of whether an event is anticipated or not will be carried out by the investigator and the second assessor.

The following list of adverse events and complications (derived from the Instructions for Use, IFUs) must be considered during the assessment of “anticipatedness”. Only the events listed below are regarded as anticipated：

- Hematoma and hemorrhage at puncture site
- Perforation or dissection of the vessel
- Vasoconstriction (Vasospasm)
- Change in mental status
- Persistent neurological deficits
- Neurologic deterioration including stroke progression and stroke in new vascular territory
- Brain edema
- Ischemia
- Infection
- Allergic reactions
- Air embolism
- Intracerebral/intracranial hemorrhage
- Vascular occlusion
- Pseudo aneurysm formation
- Aneurysm perforation
- Post procedure bleeding
- Distal embolization including to a previous uninvolved territory
- Adverse reaction/anaphylaxis to antiplatelet/anticoagulation agents
- Adverse reaction (anaphylaxis, kidney damage) to contrast media
- Device(s) deformation, collapse, fracture or malfunction
- Thrombosis (acute and subacute)
- Inability to completely remove thrombus
- Arteriovenous fistula
- Seizure
- Pain/headache

3.11.4 Documentation of Adverse Events

All SAEs will be recorded in the case report form (CRF) table. The details of the SAEs, including start time, end time, duration, treatment, outcome, and relationship to the intervention, will also be documented. The frequency of SAEs will be summarized according to the study assignments. All recorded AEs and SAEs will be reported to the investigator. In this study, SAEs primarily refer to disabling strokes, symptomatic intracranial hemorrhages or death within 1 year after enrollment.

3.12 Outcome Events and Adverse Events Assessment

Endpoint events determination will be conducted through a meticulous review process by an independent Outcome Event Arbitration Committee (OEAC), guaranteeing unbiased and systematic assessment.The OEAC is constituted by three independent clinical experts, strategically selected to ensure comprehensive and objective evaluation of critical research endpoints.First two independent experts will simultaneously conduct parallel, back-to-back arbitration assessments.In cases of assessment inconsistency,a third expert will be activated to render a conclusive judgment.

Meanwhile, members of the OEAC will systematically review and independently adjudicate all reported complications in strict accordance with the predefined adverse events in the clinical events committee manual of operations.When a potential endpoint may occur, the committee board will immediately convene a meeting to evaluate whether such an event can be categorized as the primary outcome.

3.13 Blinding

All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment regime.

3.14 Imaging Core Laboratory

A centralized imaging core laboratory will be utilized to provide uniform and objective assessment of radiological images.The imaging core laboratory evaluated the findings including the ASPECT (pc-ASPECTS for posterior circulation), baseline vessel imaging (CTA or DSA) for the location of the occlusion, baseline collateral circulation status evaluated by DSA (American Society of Therapeutic and Interventional Neuroradiology/Society of Interventional Radiology grade, ASTIN/SIR grade) , technical efficacy outcomes regarding recanalization and residual stenosis of the qualifying artery assessed via DSA, CTA or MRA at 24-72 hours for vessel recanalization status, and the CT at 24-72 hours for the occurrence of intracerebral hemorrhage, restenosis or reocclusion during follow-up subsequent evaluation via CTA or MRA and so on. All imaging studies will undergo blinded review by experienced neuroradiological experts (over 10 years in advanced neuroimaging evaluation experience). Two neuroradiologists perform independent, masked assessments of neuroimaging studies, ensuring complete blinding to treatment allocation, clinical data, and outcomes. In cases of interpretative disagreement, a third experienced neuroradiologist will be consulted to adjudicate and provide a definitive assessment.

3.15 Quality Control

Training of appropriate clinical site personnel will be the responsibility of the Sponsor or designee. To ensure uniform data collection and protocol compliance, personnel from the Sponsor or designee will review the techniques for the identification of eligible subjects, instructions on in-hospital data collection, methods for soliciting data from alternative sources, and schedules for follow-up with the study center.To ensure that the collected data is concordant with the protocol, each sub-center of this study will be regularly scrutinized.

3.16 Statistical Analyses

3.16.1 General statistical analyses

Categorical variables will be presented as numbers and percentages. Continuous variables or ordinal variables will be summarized as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables will be compared between treatment groups using χ^2 or Fisher's exact test. Continuous

variables or ordinal variables will be compared between treatment groups using t-test or Wilcoxon-Mann-Whitney test.

3.16.2 Primary and secondary outcomes

The difference in primary outcome between groups was assessed using Kaplan-Meier analysis and compared via log-rank test. The hazard ratio (HR) and adjusted hazard ratio (aHR) between groups, along with their 95% CIs, will be determined using univariate and multivariate Cox proportional hazards regression models. Time-to-event secondary outcomes will be evaluated using Kaplan-Meier survival analysis and Cox regression model. The 1-year mRS score will be analyzed using ordinal logistic regression to estimate the common odds ratio (OR). The 1-year EQ-5D scores will be compared between groups using general linear regression analysis.

3.16.3 Subgroup analyses

Subgroup analyses on the primary outcome will be performed in the following subgroups:

- ✓ Age, <65 years old vs. ≥ 65 years old;
- ✓ Sex, men vs. Women;
- ✓ Hypertension, yes vs. no;
- ✓ Diabetes, yes vs. no;
- ✓ Current smoking, yes vs. no;
- ✓ Body mass index (BMI), <25 Kg/m^2 vs. ≥25 Kg/m^2;
- ✓ Latest qualifying event, ischemic stroke vs. TIA;
- ✓ Time from latest ischemic event to enrollment, ≤2 weeks vs. >2 weeks, ≤6 weeks vs. >6 weeks;
- ✓ Occurrence of the qualifying event, first-onset vs. recurrent;
- ✓ Symptomatic qualifying artery, anterior circulation vs. posterior circulation;
- ✓ ASPECTS or pc-ASPECTS, 10 vs. 6-9.

3.16.4 Propensity score matching analysis

Propensity score matching (PSM)[35] will be performed to reduce the possible influence of selection bias and confounders on the outcomes. A PSM cohort will be established in a 1:1 ratio based on the nearest-neighbor matching algorithm with a caliper width of 0.2 of the propensity score with main variables associated with the primary outcome as covariates.Statistical analysis methods for baseline characteristics and outcome will remain consistent before and after PSM.

3.16.5 Statistical Significance and Software

All statistical tests are performed by 2-sided tests. A 2-sided P value less than 0.05 is considered to demonstrate a statistically significant difference. All analyses will be performed with SAS software version 9.4 (SAS Institute).

3.17 Publications

Based on the analysis pre-specified in this study protocol, the results of the study will be published in open-access peer-reviewed scientific journals and presented to academic and policy stakeholders. By signing the clinical trial protocol, the investigator agrees that the results of the clinical trial may be used for publication. The investigator also agrees that he is not permitted to publish any data related to the trial independent of the Sponsor.

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5. Appendix

Appendix 1. Modified Rankin Scale

The modified Rankin Scale (mRS)* is an ordinal scale ranging from 0 to 5, with higher scores indicating more severe disability. A score of 6 indicates death.

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Death	Death

*van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988 May;19(5):604-7. doi: 10.1161/01.str.19.5.604

Appendix 2. Modified TICI Scale (mTICI Scale)

The modified Thrombolysis in Cerebral Infarction (mTICI)* score is a grading system used to assess the degree of reperfusion in patients with acute ischemic stroke, which was modified from the original TICI (Thrombolysis in Cerebral Infarction)¶ scale.

Grades	Short description		Long description
0	No Perfusion		No Perfusion
1	Minimal Perfusion		Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2	Partial Perfusion	2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
		2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
3	Complete Perfusion		Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

*Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013 Sep;44(9):2650-63. doi: 10.1161/STROKEAHA.113.001972

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Appendix 3. National Institute of Health Stroke Scale (NIHSS)

The National Institute of Health Stroke Scale (NIHSS)* is an ordinal scale to evaluate the severity of stroke by assessing a patient's performance in the neurological exam. Scores range from 0 to 42, with higher scores indicating a more severe deficit.

Instructions	Scale definition
1a. Level of consciousness. The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; required 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 and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Phasic 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 examiners not "help" the patient with verbal or non-verbal clues.	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 hand 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 him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.

trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be 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 a 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, preexisting 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.	0= Normal. 1= Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2= Forced deviation; or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger 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 clearcut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed in this case. If there is extinction, the patient receives a 1, and the results are used to respond to item 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 response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 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).
5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	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. UN = Amputation or joint fusion: explain: _____ 5a = Left Arm. 5b = Right arm.
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls 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 leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0= No drift; leg holds 30-degree 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. UN = Amputation or 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, ensure testing is done in intact visual field. The	0= Absent. 1= Present in one limb. 2= Present in two limbs.

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, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	UN = Amputation or joint fusion: explain:_____
8. **Sensory:** Sensation or grimace to pinprick 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 sensory loss', 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 brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0= Normal; no sensory loss. 1= Mild-to-moderate sensory loss; patients 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 of being touched. 2= Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg.
9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, 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 a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for 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 conservation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content 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 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 patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0= Normal. 1= Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood by some difficulty. 2= Severe dysarthria: 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. UN = Intubated or other physical barrier.
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 extinction to more than one modality; does not recognize own hand or orients to only one side of space.

*Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-870. doi: 10.1161/01.str.20.7.864

Appendix 4. EuroQoL 5D-5L*

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

Self-care

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

Pain/discomfort

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/depression

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

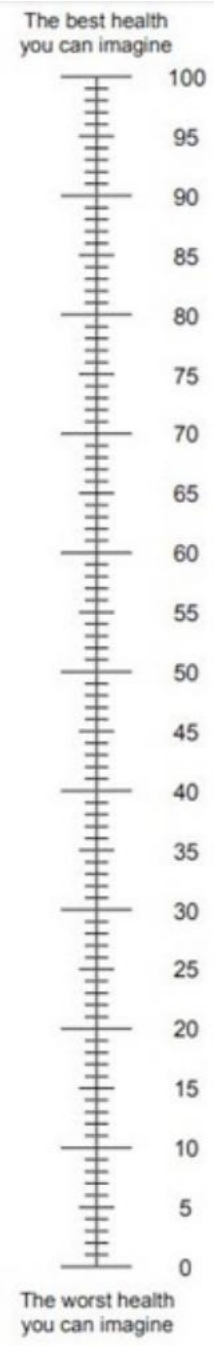
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TOADY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALEH TOADY = ☐



*Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 2011;20(10):1727-17.doi: 10.1007/s11136-011-9903-x

Appendix 5. Heidelberg bleeding classification*

Class Type Description of Intracranial Hemorrhages

1 Hemorrhagic transformation of infarcted brain tissue		
1a	HI1	Scattered small petechiae, no mass effect
1b	HI2	Confluent petechiae, no mass effect
1c	PH1	Hematoma within infarcted tissue, occupying < 30%, no substantive mass effect
2 Intracerebral hemorrhage within and beyond infarcted brain tissue		
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3 Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage		
3a		Parenchymal hematoma remote from infarcted brain tissue
3b		Intraventricular hemorrhage
3c		Subarachnoid hemorrhage
3d		Subdural hemorrhage

*von Kummer R, Broderick JP, Campbell BC, Demchuk A, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. *Stroke*. 2015 Oct;46(10):2981-6. doi: 10.1161/STROKEAHA.115. 010049

Appendix 6. Scoring System of Pons-Midbrain Index (PMI)*

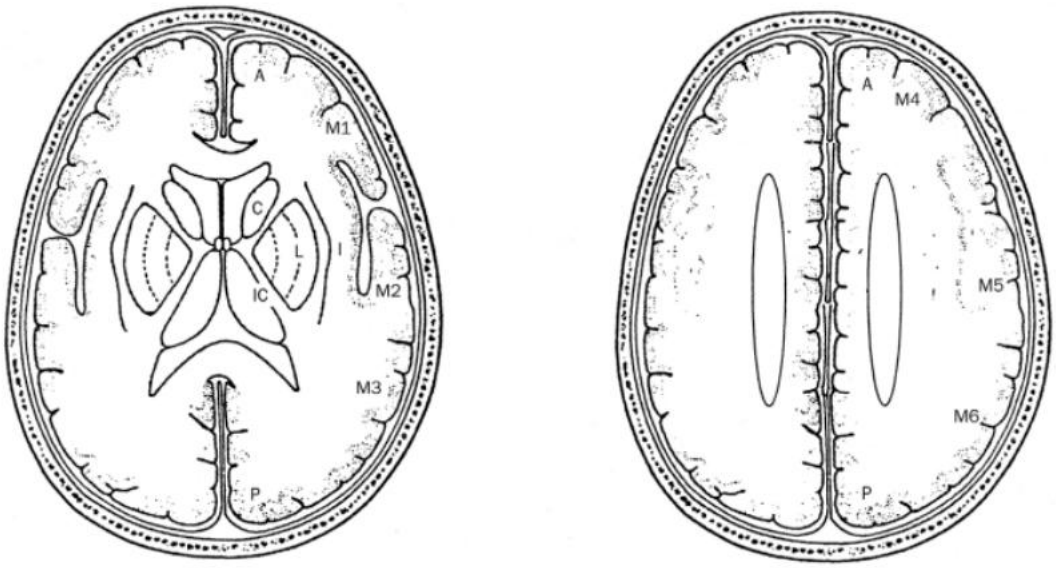
A PMI of 0 indicates absence of any ischemic changes in the pons and midbrain, and a score of 8 indicates greater than 50% hyperintensity bilaterally in these brainstem territories.

Lesion	Score (DWI as an example)
Left pons	0, no hyperintensity; 1, equal or less than 50% hyperintensity; or 2, greater than 50% hyperintensity
Right pons	0, no hyperintensity; 1, equal or less than 50% hyperintensity; or 2, greater than 50% hyperintensity
Left midbrain	0, no hyperintensity; 1, equal or less than 50% hyperintensity; or 2, greater than 50% hyperintensity
Right midbrain	0, no hyperintensity; 1, equal or less than 50% hyperintensity; or 2, greater than 50% hyperintensity

*Pallesen LP, Khomenko A, Dzialowski I, Barlinn J, et al. CT-angiography source images indicate less fatal outcome despite coma of patients in the Basilar Artery International Cooperation Study. *Int J Stroke*. 2017 Feb;12(2):145-151. doi: 10.1177/1747493016669886

Appendix 7.Alberta Stroke Program Early CT Score (ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS)* is a semiquantitative method of estimation of infarct size with non-contrast CT during the acute phase. The territory of the middle cerebral artery is allotted 10 points. 1 point is subtracted for an area of early ischaemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A normal CT scan has an ASPECTS value of 10 points. A score of 0 indicates diffuse ischaemia throughout the territory of the middle cerebral artery.



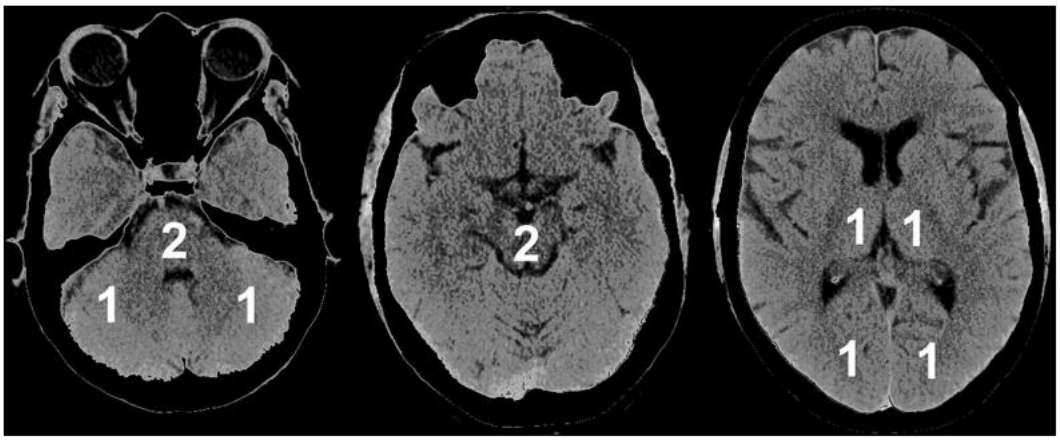
A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

Subcortical structures are allotted 3 points (C, L, and IC).

MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

*Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet*. 2000;355(9216):1670-1674. doi: 10.1016/s0140-6736(00)02237-6

Appendix 8. posterior circulation Alberta Stroke Program Early CT Score (pc-ASPECTS)*



pc-ASPECTS. From 10 points, 1 or 2 points each (as indicated) are subtracted for early ischemic changes (NCCT) or hypoattenuation (CTASI) in: left or right thalamus, cerebellum or PCA-territory, respectively (1 point); any part of midbrain or pons (2 points). Pc-ASPECTS=10 indicates a normal scan, pc-ASPECTS=0 indicates early ischemic changes (NCCT) or hypoattenuation (CTASI) in all above territories

*Puetz V, Khomenko A, Hill MD, et al; Basilar Artery International Cooperation Study (BASICS) Group. Extent of hypoattenuation on CT angiography source images in basilar artery occlusion: prognostic value in the Basilar Artery International Cooperation Study. *Stroke*. 2011 Dec;42(12):3454-9. doi: 10.1161/STROKEAHA.111.622175