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

Statistical Analysis Plan

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Abbreviations

ADP	Adenosine Diphosphate
AE	Adverse Event
aHR	Adjusted Hazard Ratio
ASPECTS	Alberta Stroke Program Early CT Score
BMI	Body Mass Index
CIs	Confidence Intervals
CRF	Case Report Form
EC-IC	Extracranial-Intracranial
EQ-5D	EuroQol-Five-Dimensions
ER	Endovascular Recanalization
ERNA-IAO	Endovascular Recanalization for Non-Acute Intracranial Artery Occlusion
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
HR	Hazard Ratio
LDL	Low Density Lipoprotein
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
pc-ASPECTS	Posterior Circulation Alberta Stroke Program Early CT Score
PSM	Propensity Score Matching
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
sNA-IAO	Symptomatic Non-Acute Intracranial Artery Occlusion
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack

1. Introduction

This statistical analysis plan (SAP) documents the planned statistical analyses for this prospective cohort study and is based on the protocol, together with any subsequent amendments. This SAP is intended for the use of project team members and should be read in conjunction with the aforementioned protocol.

2. Study Objective

To investigate whether endovascular recanalisation plus medical treatment is superior to medical treatment alone for symptomatic non-acute intracranial artery occlusion (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 from 30 days to 1 year after enrollment).

3. Statistical Hypotheses

The primary hypothesis is:

Patients in the endovascular recanalisation group are expected to demonstrate a lower incidence of primary outcome (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).

4. Study Design

The Endovascular Recanalization for Non-Acute Intracranial Artery Occlusion (ERNA-IAO) study is a multicenter, prospective, cohort study, this cohort prospectively enrolls consecutive patients with radiologically confirmed sNA-IAO at 6 comprehensive stroke centers in China from January 1, 2020 to October 31, 2023. All study centers were required to have performed at least 120 endovascular procedures annually, including at least 40 cases of endovascular interventions involving intracranial arteries. The interventional neuroradiologists at these centers had each performed over 100 endovascular procedures. All participants or their legal representatives provide written informed consent prior to enrollment. 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 endovascular recanalization 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 group. 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 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline.

Endovascular recanalization (ER):

Patients will receive ER (details in procedure part in Supplement 1) plus medical treatment (same as the control group). All procedures are performed under general anesthesia by an experienced interventional neuroradiologist.

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.

Risk factor management:

Risk factor management is based on 2014 American Heart Association/American Stroke Association guidelines[1] for the clinical management of cerebrovascular disorders. (details of risk factor control targets in Supplement 1)

Follow-up:

All participants will be followed up by the neurologists at 30±7 days, 90±7 days, 1 year ±30 days. All imaging studies will undergo blinded review by experienced neuroradiological experts (over 10 years in advanced neuroimaging evaluation experience). All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment regime.

5. Outcomes

5.1. 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.

5.2. Secondary Outcomes

The secondary outcomes are as follows:

(1) Mortality within 1 year;

(2) Ischemic stroke outside the territory of the qualifying artery within 1 year;

(3) Disabling stroke within 1 year;

(4) Transient ischemic attack (TIA) in the territory of the qualifying artery within 1 year;

(5) Unplanned revascularization (extracranial-intracranial [EC-IC] bypass surgery or ER) of the qualifying artery within 1 year;

(6) Myocardial infarction within 1 year;

(7) Composite vascular events within 1 year, including any stroke, myocardial infarction, and unplanned revascularization;

(8) Quality of life assessment (EuroQol-Five-Dimensions [EQ-5D] scale questionnaire) at 1 year;

(9) Modified Rankin Scale (mRS) score at 1 year;

(10) Periprocedural outcomes, including the successful recanalization rate, periprocedural complications, residual stenosis, National Institute of Health Stroke Scale (NIHSS) score at 24-72 hours, death within 7 days, etc;

(11) Restenosis or reocclusion (symptomatic or asymptomatic).

5.3 Safety Outcomes

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. 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. In this study, SAEs primarily refer to disabling strokes, symptomatic intracranial hemorrhages or death within 1 year after enrollment.
(Details of relevant definitions of outcome measures in Supplement 1)

6. Treatment Comparisons

The treatment comparison of interest in this study is to assess the effect of ER combined with medical treatment versus medical treatment alone in decreasing the risk of the primary outcome (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) in patients with sNA-IAO.

7. Statistical Analysis Method and Plan

7.1 General Considerations for Data Analyses

All analyses will be performed with using SAS Version 9.4. All analysis output will use the following treatment group naming conventions and treatment order:
ER group: patients will receive ER (details in procedure part) plus medical treatment (same as the control group);
Medical group: patients will receive the medical treatment alone.
All statistics is two sided with a $P < 0.05$ considered significant.

Examination of Subgroups

The rates of the primary outcome will be presented for each level of the covariates listed below. We will assess the extent to which the treatment effect varies across levels of each subgroup using interaction tests.

Multiple Comparisons and Multiplicity

A single primary efficacy variable has been defined for this study, with all other efficacy variables identified as secondary or other. Similarly, only one treatment comparison is of interest in the study and therefore there are no requirements to adjust for multiple comparisons or multiple endpoints within this study.

7.2 Data Handling Conventions

Premature withdrawal and missing data

If any subject withdraws prematurely from the study (prior to the final visit), they are required to complete the withdrawal visit in the case report form (CRF). The reasons for withdrawal will be presented in a summary table. For the purposes of summaries and analysis of clinic visit data, this visit will be assigned to the next scheduled clinic visit for that subject, regardless of whether the date falls within the next visit window.
Efforts will be undertaken at study sites to reduce the amount of missing data. For the primary efficacy outcome, multiple imputations in a model including strong prognostic variables will be used. Also, sensitivity analyses will be undertaken to explore the effect of missing data on the endpoint and test the robustness of the estimate.
Ultimately, only patients who entirely completed the 1-year follow-up are included in the final analysis.

Event rates

The number of people and person-time of events should be recorded in detail and showing the event rate of each treatment group in summary statement.

The event rate for each treatment group will be calculated as: the sum of number of event for all the patients/the sum of number of treatment periods for all the patients.

Time to event analysis

Differences between treatments in the risk of any stroke (ischemic or haemorrhagic) event or composite vascular events during follow-up will be assessed using standard Kaplan-Meier time-to-event approaches. The time to the first event will be used in the model when there are multiple events of the same type. Patients will be considered censored at the time of study termination or death if there are no events occurred during the study.

7.3 Study Population

The number of all participants included in the screening will be calculated. Listing will be presented for participants of deviations from the inclusion/exclusion criteria, the reasons for screening failures will also be documented. Based on all enrolled participants, the number and percentage of participants who completed the study and withdrew early, the number and percentage of participants who withdrew early for various reasons, as well as the number of participants who lost to 1-year follow-up, will be calculated and summarized. Finally, participant distribution flow chart will be presented.

7.4 Demographic and Baseline Characteristics

The following demographic information baseline characteristics, such as age, sex, medical history, smoking history, alcohol history, treatment history, qualifying ischemic event characteristics, Alberta Stroke Program Early CT Score (ASPECTS) for anterior circulation stroke as well as posterior circulation ASPECTS (pc-ASPECTS), baseline mRS score and NIHSS score, will be listed and summarized for subjects in each treatment group.

The continuous data followed normal distribution will be presented as mean and standard deviation, and the continuous data followed skewness distribution will be presented as median and interquartile range; categorical data will be presented as n (%). T-test or Wilcoxon-Mann-Whitney test will be used for comparison between two continuous data, and Chi-squared tests, Fisher exact test will be used for comparison between two categorical data.

7.5 Primary Efficacy Outcome

The difference in primary outcome between groups was assessed using Kaplan-Meier analysis and compared via log-rank test. Hazard ratio (HR) between the two groups and its 95% CI will be calculated using a Cox proportional hazards regression model. Furthermore, a multivariate Cox proportional hazards model will be used to perform multivariable adjustment for the primary outcome, yielding the adjusted hazard ratio (aHR) and its 95% CI.

7.6 Subgroup Analysis

Summary tables will be produced for the predefined subgroups, and the interactions between treatment and these subgroups will be analyzed using a Cox proportional hazards model. Individual models will be utilized for each interaction to assess the statistical significance. The results will also be depicted graphically in a forest plot. The modification of treatment effects on the primary outcome will be investigated within 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.

7.7 Secondary Outcomes

Time-to-event secondary outcomes will be evaluated using Kaplan-Meier survival analysis and Cox regression model. HR between the two groups and its 95% CI will be calculated using a Cox proportional hazards regression model. Non-time-endpoints of the secondary outcomes will be evaluated using logistic 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.

7.5 Safety Analyses

Summary tables and data displays will be provided for adverse events as well as serious adverse events (as detailed in the study protocol). Procedure-related complications in the endovascular recanalization group will be analyzed. The Chi-square test or Fisher's exact test will be used to compare the incidence of adverse events and serious adverse events between the treatment groups.

7.6 Propensity Score Matching Analysis

Propensity score matching $(PSM)^2$ 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.

7.7 Concomitant Medication and Risk Factor Management

Describe the list of concomitant medications, including antiplatelet drugs (aspirin, clopidogrel, ticagrelor, cilostazol), anticoagulants, lipid-lowering agents (such as statins), and so on. Additionally, outline the management of risk factors, which includes blood pressure, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, and hemoglobin A1c (HbA1c). Lifestyle factors to be considered include BMI, smoking status, alcohol consumption, and regular moderate physical exercise. Chi-squared tests or Fisher's exact test will be employed to compare the numbers between treatment groups.

8. Reference

1. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi: 10.1161/STR.0000000000000024
2. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55. doi: 10.1002/sim.3532