Choice of anesthetic technique for endovascular treatment of posterior circulation acute ischemic stroke (CANVAS II)

This supplement contains the following items:

1. Original protocol/final protocol, summary of changes

2. Original/final statistical analysis plan, summary of changes

Trial Protocol summary of changes

Master Protocol v1.4, 2017/12/19

Original approved protocol

Master Protocol v1.5, 2020/11/1

final protocol

1) Table 'CANVAS II Investigators' and title page: addition of new researchers

2) Addition of new Funding 'Clinical Medicine Development of Special Funding Support (DFL20180502) and the Beijing Municipal Science & Technology Commission (Z19110700660000)'

3) Amendment of mail address of Chief Investigator and Clinical Trials Unit due to hospital relocation

4) Section 4.1.1 : amendment of 'January 2018 to December 2020' to 'January 2018 to December 2021'

5) Section 4.1.1 : addition of 'Baiyun Hospital, Guizhou Medical University' research subcenter

6) Section 3.3/4.4.2/4.8.2: deletion of 'NIHSS at 24h' secondary outcome measures, amendment of 'NIHSS at 7d/discharge' to 'NIHSS at discharge'

7) Section 4.3.2: deletion of 'invasive arterial pressure monitoring on radiologist arterial access line, arterial partial pressure of carbon dioxide (PaCO2)'

8) Section 4.8 : deletion of 'Visit 3(24h after EVT)' and 'Visit 4 (Day 7±2 Days)'

Section 4.8.9 schedule of data collection：deletion of time point ‘24h and Day7±2’

9) Section 4.13: Addition of “SPSS 26.0” in data analysis.

Statistical Analysis Plan summary of changes

v1.1, 2017/12/19

Original approved protocol

v1.2, 2020/11/1

final protocol

1) Title page of SAP: Addition of new researcher who involved in statistical analysis plan writing
2) Addition of new Funding 'Clinical Medicine Development of Special Funding Support (DFL20180502) and the Beijing Municipal Science & Technology Commission (Z19110700660000)'
3) Section 1 Introduction/ 4 Study Design:Addition "Baiyun Hospital" as second research center."
4) Section 2.2.2: Deletion of 'NIHSS at 24h' secondary outcome measures, amendment of 'NIHSS at 7d(or at discharge)'' to "at discharge"
5) Section 4: Amendment of 'January 2018 to December 2020' to 'January 2018 to December 2021'
6) Section 9 and section 12:Addition of "SPSS 26.0" in data analysis.
7) Section 12.1: Deletion of subgroups of " age, sex, baseline NIHSS score, time from onset of stroke to EVT, site of arterial occlusion, and mTICI score."
8) Section 12.3: Addition of logistic regression model and modified Poisson regression.

Choice of ANesthesia for Endo-VAScular treatment of acute ischemic stroke in the posterior circulation (CANVAS II)

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Research reference numbers

Protocol version number and date

V1.4; 2017-12-19

Registration number

NCT03317535

Sponsor name and reference

Beijing Tiantan Hospital, Capital Medical University

Funder name and reference

Clinical Medicine Development of Special Funding Support (ZYLX201708)

Chief Investigator

Ruquan Han, MD, PhD

Sponsor representative

Ruquan Han, MD, PhD

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

....//...../.....

Name (please print):

Position:

Chief Investigator:

Signature: ..... Date: ...../...../.....

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Sponsor	Beijing Tiantan Hospital, Capital Medical University
Funder	The Beijing Municipal Hospital Administration Clinical Medicine Development of Special Funding Support

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Summary

Data category	Information
Primary registry and trial identifying number	NCT03317535
Date of registration in primary registry	October 23, 2017
Source(s) of monetary or material support	Clinical Medicine Development of Special Funding Support
Primary Sponsor	Beijing Tiantan Hospital, Capital Medical University
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Public title	Choice of Anesthesia for Endovascular Treatment of Acute Ischemic Stroke in Posterior Circulation (CANVAS-II)
Scientific title	Choice of anesthesia for endovascular treatment of acute ischemic stroke in the posterior circulation (CANVAS II): An exploratory randomized controlled trial

Data category	Information
Countries of recruitment	China
Health condition(s) or problem(s) studied	Acute ischemic stroke in the posterior circulation
Intervention(s)	Interventions: GA vs CS
Key inclusion and exclusion criteria	Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Inclusion criteria: 1) Vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CT angiography (CTA)/magnetic resonance angiography (MRA) 2) Age ≥18 years 3) Stroke onset to treatment time ≤24 hours and modified Rankin score ≤2 4) Sign informed consent Exclusion criteria: 1) Patients with unclear radiological image to identify infarction and vessel occlusion 2) Patients with intracranial hemorrhage (ICH)

Data category	Information
	3) Patients with anterior circulation occlusion 4) Glasgow coma score (GCS)≤8 5) NIHSS score <6 or >30 6) Post circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) <6, 7) Pons-midbrain index ≥3 8) Patients with severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission 9) Patients intubated before EVT 10) Patients with unconsciousness and known allergy to anesthetics or analgesics 11) Patients whose legal relative refuses to participate
Study type	Interventional Allocation: Randomized Intervention Model: Parallel Assignment Blind: end-point assessor Primary purpose: Optimize disease treatment
Date of first enrolment	March 1, 2018
Target sample size	88
Primary outcomes	The primary endpoint is the neurological disability at 90 days after

Data category	Information
	EVT measured by mRS, which ranges from 0 (no symptoms) to 6 (death), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS ≤2. The score will be evaluated by outcomes assessor who are blinded to allocation.
Key secondary outcomes	1) Change in NIHSS, from baseline to 24 hours, 7 days (or at discharge), 30 days and 3 months after randomization. 2) The score of mTICI will be evaluated before and after endovascular treatment. 3) All- cause mortality up to 3 months after randomization. 4) The incidence of complications up to 3 months after randomization. 5) Time-related outcomes, such as, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care unit after randomization. 6) The rate of conversion from CS to GA. 7) Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time. 8) All adverse events associated with this study will be recorded.

Contents

Abbreviations

AIS	Acute ischemic stroke
EVT	endovascular therapy
GA	general anesthesia
LA	local anesthesia
CS	conscious sedation
MCA	monitoring sedation anesthesia
NIHSS	National Institute of Health Stroke Scale
mTICI	modified Thrombolysis in Cerebral Infarction Scale
mRS	modified Rankin score
ICH	intracranial hemorrhage
ECG	electrocardiogram
HR	heart rate
BP	non- invasive blood pressure
SpO2	pulse oxygen saturation
ETCO2	end- tidal carbon dioxide
FiO2	inspired oxygen fraction
BIS	bispectral index
UV	urine volume
AEs	adverse event

SAEs	Serious adverse events
PI	Principal Investigator

1. Background and rational

Acute ischemic stroke (AIS) is the second leading cause of death and disability worldwide, and the leading in China. In China, the average annual death toll from stroke has reached two million with an annual growth rate of 8.7%[1]. AIS at posterior circulation account for 17%–60% of acute stroke with difficulty in treatment, which result in a poor outcome and mortality rate of 80%–95%[2-4]. It brings great challenges to clinical treatment.

Early recanalization is one of the most crucial factors of favorable outcome for posterior circulation AIS patients at 90 days. The traditional treatment method for recanalization is intravenous thrombolysis, but the treatment time is only 3-4.5 hours. Due to the recanalization rate of large blood vessels is low, the effect of traditional thrombolysis is limited. With the rapid development of interventional materials and techniques, in order to obtain a higher vascular recanalization rate, the method of mechanical thrombectomy was on stage. From late 2014 to mid-2015, the results of several AIS endovascular treatment clinical trials worldwide were published and confirmed that endovascular treatment technology is beneficial for acute ischemic stroke[5-9]. Therefore, the European Stroke Association and the American Neurosurgery Intervention Association have successively issued an expert consensus to upgrade the evidence-based medical evidence of acute intravascular thrombectomy to level I recommendations and level A evidence[10]. China has also released the 2015 guidelines for intravascular treatment of acute ischemic stroke. Endovascular therapy has shown great application prospects in clinical treatment.

However, endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment with around 30% good clinical outcome improvement and 35% mortality decrease at 90 days[11-13], there is a substantial proportion of patients with poor clinical outcomes even after timely successful reperfusion. Many factors may contribute to the mismatched association of high reperfusion rate and poor clinical outcome, including patient- specific factors (age, collaterals status, initial stroke severity, infarct volume and site, and distal artery emboli), procedural- specific factors (time from onset to recanalization, degree of recanalization) and anesthesia management[14]. In some research of acute anterior circulation vascular occlusion, general anesthesia seems to be a crucial factor associated with poor prognosis of patients after recanalization[15, 16].

The most used anesthesia methods for endovascular treatment include general anesthesia (GA) with mechanical ventilation and local anesthesia (LA) with conscious sedation（CS）. The optimal anesthesia choice and management for AIS patients during EVT is still unclear. Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration, body immobility to avoid vessel perforation and better digital subtraction angiography imaging. On the other hand, hypotension, nosocomial infection, delayed procedure initiation, loss of neurological evaluation and hyperventilation may contribute to poor outcomes. CS management permits neurological function assessment, shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with GA. However, the risk of aspiration and substantial movement during endovascular procedural are the main two disadvantages associated with CS.

There have been many relevant studies on this issue, including many prospective clinical randomized trials. Since 2014, four randomized controlled studies on the choice of anesthesia method and the prognosis of neurological function in patients with AIS on the clinicaltrials.org website had registered including ANSTROKE (NCT01872884), CANVAS (NCT02677415), GOLIATH (NCT02317237) and SIESTA (NCT02126085). Unfortunately, most of these studies, whether retrospective or prospective, only focus on anterior circulation stroke, and there are very few studies on vertebrobasilar occlusive stroke.

Since the vertebrobasilar artery system is often responsible for the blood supply of important parts such as the medulla oblongata and the brain stem, in where important functional centers such as respiration and circulation are located. And many nuclei of cranial nerves are also distributed on the medulla oblongata brain stem, so when these parts are involved, the patient is likely to experience respiratory depression, circulatory depression, loss of protective reflexes, and so on. Therefore, many neurointerventionists and anesthesiologists prefer general anesthesia with mechanical ventilation to manage these patients. From the perspective of clinical safety, it seems that general anesthesia is more suitable for patients with posterior circulation occlusion. However, there is still a lack of reliable evidence to support general anesthesia. It is important to actively achieve early reperfusion due to the rapidly change in the condition of patients with posterior circulation large vessel occlusion. Monitoring anesthesia can save a lot of time in preparation for anesthesia. If the patient is given a certain degree of sedation, a certain braking effect can also be achieved, which facilitates the operation of the surgeon during the operation,

reduces unnecessary waste of time, and reduces some complications caused by the postoperative tracheal tube retention. As for safety, it can be managed by closely monitoring the patient's vital signs. A few studies observed the feasibility of monitored anesthesia care for elective endovascular procedures either in anterior or posterior circulations and demonstrated high technical success with low rates of periprocedural complications and mortality[15, 17]. In addition, many retrospective studies on the anterior circulation have shown that patients with acute stroke who receive endovascular therapy with general anesthesia or deeper sedation may experience a worse prognosis[14-16]. However, whether the same is true for stroke patients with vertebrobasilar system occlusion also need further research to explore.

Recently, Jadhav AP et al conducted a retrospective, paired, case-control study showing the feasibility of monitoring sedation anesthesia (MAC) in endovascular treatment of patients with vertebrobasilar occlusive stroke[17]. This study reviewed all 215 patients with vertebrobasilar artery occlusive stroke who received endovascular therapy from two research centers. Finally, a total of 122 patients were included in the analysis after matching (61 in MAC group vs 61 in GA group). It was found that compared with GA group, the patients receiving MAC treatment had similar successful reperfusion rate, good clinical outcome, bleeding complications and death toll. However, retrospective design and limited sample size may introduce undetected biases. Furthermore, there is no published randomized controlled trial that explored whether GA or CS are associated with different neurological outcomes at 90 days in patients undergoing EVT for posterior circulation AIS.

Our study will break through the limitations of retrospective studies and conduct an exploratory prospective clinical randomized study of anesthesia methods for vertebrobasilar occlusive stroke. There is few randomized controlled clinical to investigate the impact of anesthetic type on outcome in patients with acute ischemic stroke in posterior cerebral circulation. It is unknown whether the choice of anesthesia is impacted on the outcomes for these patients or not. The investigators will perform a randomized controlled pilot clinical trial of general anesthesia versus conscious sedation to explore and find out a potential fact whether anesthetic type alters perioperative neurological function in patients with acute ischemic stroke in posterior cerebral circulation.

2. Hypothesis

Based on previous studies, we propose that CS is feasible for intravascular treatment of patients with vertebrobasilar artery occlusion stroke. Compared with GA, there is no difference in neurological outcomes at 90 days.

3. Aims and objectives

3.1 Aim

The study aims to explore the feasibility of CS in intravascular treatment of vertebrobasilar artery occlusion stroke by clinical randomized controlled study and detect the difference of neurological function in patients with posterior circulation AIS under GA and CS, and

hence to provide high-quality evidence for anesthesia selection in patients with posterior circulation occlusion undergoing endovascular therapy.

3.2 Primary objective

To compare the proportion of posterior circulation stroke patients with good prognosis at 90 days between the two groups receiving GA and CS, and hence to observe the effect of anesthetic type on outcomes after EVT.

3.3 Secondary objectives

To compare, between the groups:

3.3.1 Change in NIHSS, from baseline to 24 hours, 7 days (or at discharge), 30 days and 3 months after randomization.

3.3.2 The score of mTICI will be evaluated before and after recanalization.

3.3.3 All- cause mortality up to 3 months after randomization.

3.3.4. The incidence of complications up to 3 months after randomization.

3.3.5. The length of stay in the hospital and in intensive care unit after randomization.

3.3.6. The rate of conversion from CS to GA.

3.3.7. Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.

3.3.8. Perioperative blood pressure management.

3.3.9. All adverse events associated with this study will be recorded.

4. Methods

4.1 Setting

4.1.1 Trial sites and Estimated trial duration

Posterior circulation AIS patients will be enrolled from Beijing Tiantan Hospital, Capital Medical University from January 2018 to December 2020.

4.1.2 Design

CANVAS II is a randomized, parallel- group, exploratory trial with blinded endpoint evaluation to determine whether GA or CS produces different neurological outcomes in posterior circulation AIS patients undergoing EVT. Due to the anesthesiologists, neuroradiologist as well as attending doctors in neurological intensive care unit need to participate in the safe administration of GA or CS and related medical care, the double-blind design is not suitable.

4.2 Population

Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial.

4.2.1 Inclusion criteria:

1) Vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed. by CT angiography (CTA)/magnetic resonance angiography (MRA).

2) Age ≥18 years.

3) Stroke onset to treatment time ≤24 hours and modified Rankin score ≤2.

4) Sign informed consent.

4.2.2 Exclusion criteria:

1) Patients with unclear radiological image to identify infarction and vessel occlusion.

2) Patients with intracranial hemorrhage (ICH).

3) Patients with anterior circulation occlusion.

4) Glasgow coma score (GCS)≤8.

5) NIHSS score <6 or >30.

6) Post circulation Alberta Stroke Program Early CT Score (pc- ASPECTS) <6.

7) Pons-midbrain index ≥3.

8) Patients with severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission.

9) Patients intubated before EVT.

10) Patients with unconsciousness and known allergy to anesthetics or analgesics.

11) Patients whose legal relative refuses to participate.

4.3 Intervention

4.3.1 Arms and Interventions

After the patients are formally enrolled, they will receive two anesthesia methods at random. GA and CS in this trial are defined according to the practice guidelines for sedation and

analgesia by non- anesthesiologists due to the continuum ranging of level of sedation from minimal sedation to GA. Both GA and CS will be monitored and applied by anesthesiologists.

Standard operating procedures are applied to both groups to ensure no principal differences generated and uniform protocol implemented. Patients in both groups will receive local anesthesia (LA) at puncture site, with 3–5 mL of 1% lidocaine hydrochloride prior to arterial puncture.

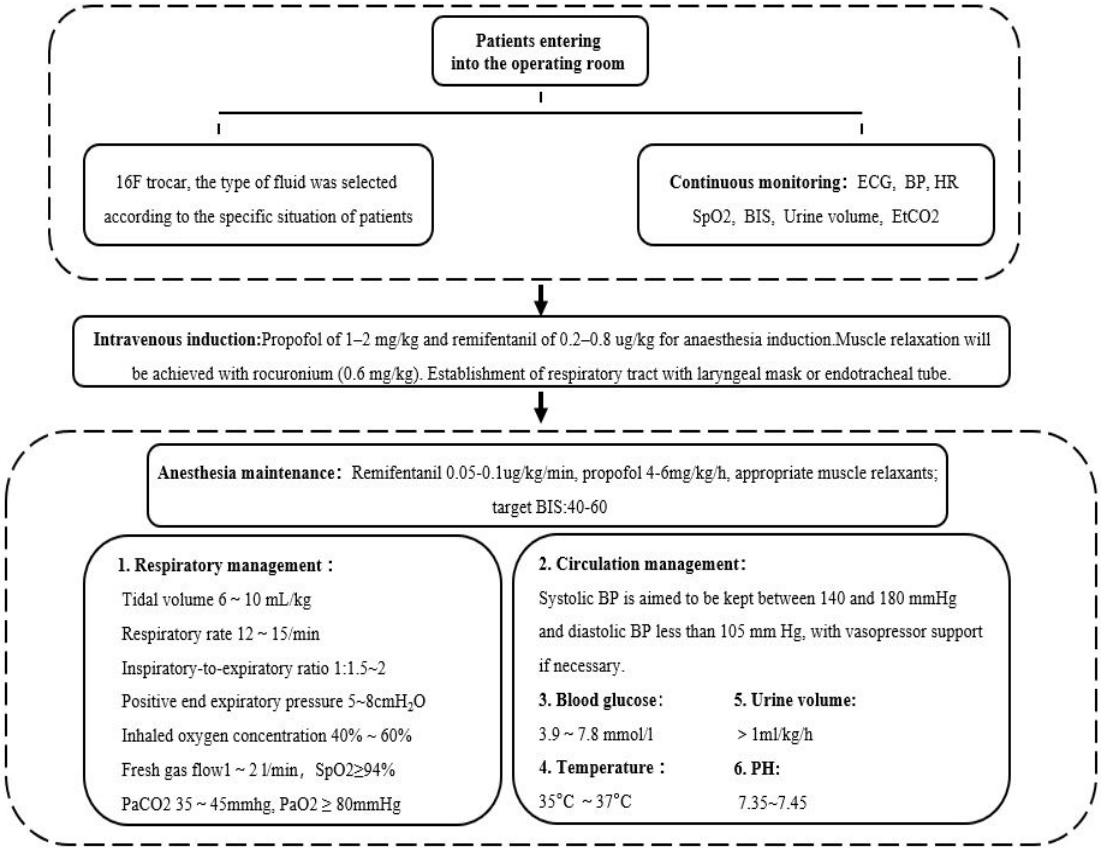
Local anesthesia/conscious sedation	Procedure: Local anesthesia/conscious sedation Patients will be injected with propofol and remifentanil with BIS value maintained above 70. Procedure: Spontaneous breath Patients will be kept spontaneous breath
General anesthesia	Procedure: General anesthesia Patients will be injected with propofol, remifentanil and muscular relaxant with BIS value is maintained between 40 and 60. Procedure: Controlled ventilation Patient will be kept with controlled ventilation

4.3.2 Monitoring indicators

All randomized patients will receive standard monitoring, including ECG, non- invasive blood pressure (BP), heart rate, pulse oxygen saturation (SpO2), invasive arterial pressure monitoring on radiologist arterial access line, arterial partial pressure of carbon dioxide (PaCO2), end- tidal carbon dioxide (ETCO2), inspired oxygen fraction (FiO2) and blood glucose. All patients will receive bispectral index (BIS) monitoring to assess the depth of sedation or anesthesia with BIS probe placed on the forehead. Physiologic parameters will be recorded using purposely designed data collection table. BP and blood glucose will be controlled according to current guidelines for stroke therapy[18].Specifically, systolic BP is aimed to be kept between 140- and 180-mm Hg and diastolic BP less than 105 mm Hg, with vasopressor support if necessary[19]. Plasma glucose will be maintained at level of 140–180 mg/dL while SpO2 is aimed to be over 94%, with FiO2 at a range from 40% to 60%[19]. It is anticipated that patients in the CS group may deteriorate during EVT and may, therefore, require endotracheal intubation or laryngeal mask insertion for airway protection. All anesthesia-related treatment will be performed by anesthesiologists of ischemia stroke team.

4.3.3 General anesthesia

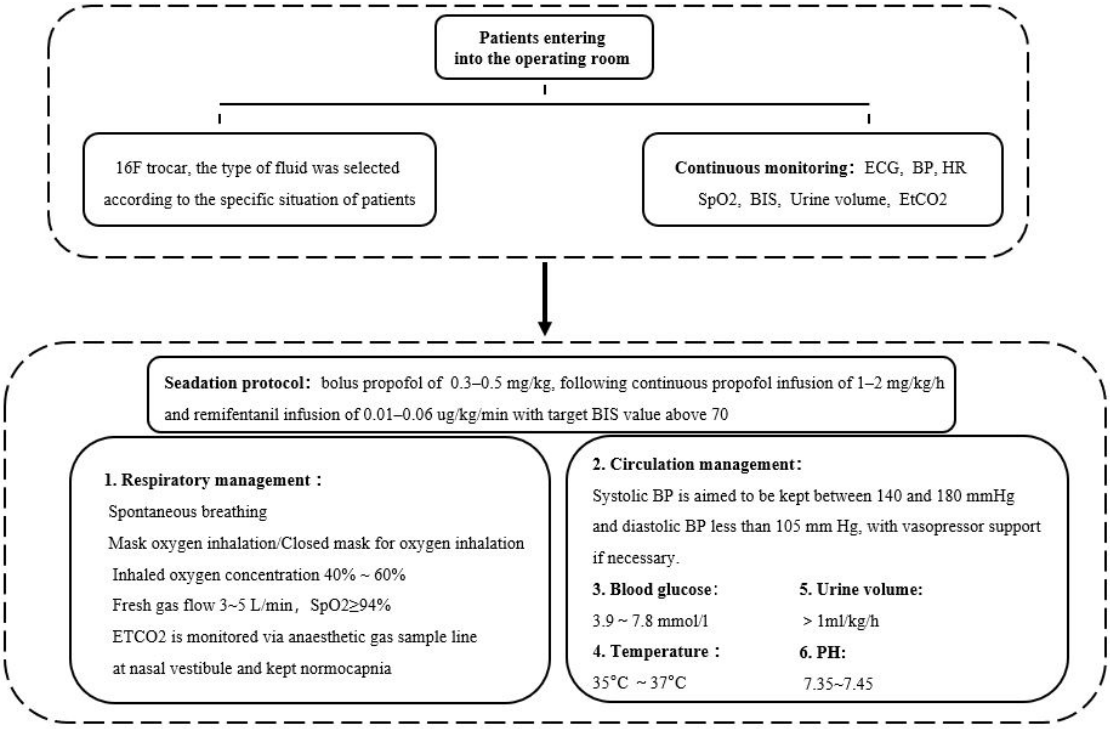
The study protocol specifies clinical criteria and procedures for the GA (see algorithm below).



Whether to remove endotracheal intubation immediately after operation is decided by the attending anesthesiologist and interventional physician according to the patient's situation.

4.3.4 Local anesthesia/conscious sedation

The study protocol specifies clinical criteria and procedures for the CS (see algorithm below).



Indications for conversion

To ensure the clinical safety of patients, patients in the conscious sedation will be converted to general anesthesia intubation if the following conditions occur:

1) Unconscious.
2) Glasgow Coma Scale decrease to or less than 8.
3) Increase of end- tidal carbon dioxide (ETCO2) ≥60 mm Hg and/or a decrease in pulse oxygen saturation (SpO2) <94% despite oxygen supplementation.
4) Vomiting/dysphoria/agitation that cannot be controlled with sedation and/or restraint.
5) Seizure attack.

6) Recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage.

The decision to convert from CS to GA will be made by the neuroradiologist in charge and the attending anesthesiologists. The number of patients and reasons for the conversion will be recorded in detail.

4.4 Outcome measures

4.4.1 Primary outcome

The primary endpoint is the neurological disability at 90 days after EVT measured by mRS, which ranges from 0 (no symptoms) to 6 (death), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS ≤2[10, 14, 20]. The score will be evaluated by outcomes assessor who are blinded to allocation.

4.4.2 Secondary outcome

The secondary endpoints include the followings:

1) Change in NIHSS, from baseline to 24 hours, 7 days (or at discharge), 30 days and 3 months after randomization.
2) The score of mTICI will be evaluated before and after endovascular treatment.
3) All- cause mortality up to 3 months after randomization.
4) The incidence of complications up to 3 months after randomization.
5) Time-related outcomes, such as, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care unit after randomization.
6) The rate of conversion from CS to GA.

7) Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.
8) All adverse events associated with this study will be recorded.

4.5 Recruitment and consent

4.5.1 Screening

Potentially eligible patients admitted/accepted for admission to the participating unit will be screened against the inclusion/exclusion criteria by the clinical team, supported by the Green Channel system. Both the attending interventional physician and anesthesiologist (the clinical team) must agree that the patient is suitable with either GA or CS management before recruiting. Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

Green channel system: In our hospital, we have built a multidisciplinary contact network through mobile app. When the potentially patient arrives at the emergency department, the interventional physician and anesthesiologist can quickly obtain the relevant information. Through communication with emergency physicians and the in-hospital electronic medical record system, clinical team can preliminarily determine whether the patient is suitable for surgical treatment or enrolled in this trial. When the potential patient arrives at the emergency room, the emergency doctor will conduct the initial assessment. After the diagnosis of acute stroke is confirmed, he/she will contact the interventional physician to determine whether intravascular treatment can be performed. Then, if the emergency EVT is necessary , the interventional physician will notify the anesthesiologist in advance for preoperative preparation. At least two designated anesthesiologists will arrive in the operating room or emergency room in advance to participate in the recruitment and

research intervention. One is the attending physician, mainly responsible for the implementation of clinical anesthesia, and the other is a resident physician, mainly responsible for research recruitment and baseline data collection.

4.5.2 Consent

Patients with acute stroke often have consciousness changes and cannot fully understand the complex explanations. Therefore, it is difficult to involve study participants in the consenting process. Consent will be sought for the patients from their legal representatives as this is where the responsibility for deciding on medical treatment resides. However, if the patients with clear consciousness can express themselves, we must consider the patient's willingness. There are the following situations:

1) If the patient can clearly express their willingness not to participate, we will not enroll the patient
2) If the patient can clearly express their willingness to participate, we will further ask the families'/ legal representatives' consent and enroll the patient after they agree

The clinical team will screen the patients according to the inclusion and exclusion criteria. The designated resident anesthesiologist will introduce the detailed information of this trial to the patients (if possible) or their families/ legal representatives, including the purpose, the content and the intervention measures of this trial, the randomization method, the potential risks and benefits of the patients after participating, participant confidentiality, use of personal data, data security, the future availability of the results of the study, etc.

After a detailed understanding, a Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is

given for access to medical records for data collection, to receive a follow-up questionnaire and for anonymized data to be shared with other researchers in the future. Families/ legal representatives will be given time to read the Consent Form and have an opportunity to ask any questions they may have about patients 'participation in CAVANS-II and to discuss with other family members or friends or the patient (If possible) before confirming their decision.

After the person seeking consent has checked that the CAVANS-II trials and Consent Form have been understood, they will invite the families/ legal representatives to sign the Consent Form and will then add their own name and countersign it.

It is obviously impossible for patients with acute stroke to read and sign the informed consent form. Therefore, after simply introducing the CANVAS-II (if appropriate), only ask for their oral consent.

Refusal or withdrawals of consent: If informed consent is refused or withdrawn, this decision will be respected and abided by, and no further contact made. All data occurring up to the point of this decision will be retained in the trial unless the families/ legal representatives requests otherwise.

4.6 Randomization and masking

Randomization will be conducted via a computer- generated table. Patients will be randomly allocated to receive either GA or CS in a 1 to 1 ratio with a block of four. A designated staff who will neither be involved in anesthesia management nor follow- up will perform generation as well as allocation randomization sequence. The staff will implement the allocation sequence through opaque, sealed, and stapled envelopes. Each envelope has a fixed number to ensure that it is opened in the correct order and be kept in a special

safe. Randomization occurs on the time of EVT when patients are admitted to the interventional neuroradiology suite, the decision for EVT has been made, the agreement from both the anesthesiologist and interventional physician has been reached, and written informed consent is obtained from patient's legal representatives. In order not to delay the treatment time of patients, The designated resident anesthesiologist should arrive at the emergency room or operating room as early as possible for informed consent. The stored allocation randomization envelopes will be opened by the attending anesthesiologist in the operation room.

The endpoint assessors (detials in 4.8.1) for postoperative visiting are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. The anesthesiologist, neuroradiologist as well as attending doctors in neurological intensive care unit will not be blinded as they need to participate in the safe administration of GA or CS and related medical care. The enrolled patients and his/her legal representatives will not be blinded, either.

4.7 Sample size calculation

The PASS V.15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint—favorable outcome (Mrs 0–2) at 3 months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only one indicated the association between anesthesia type and neurological outcome. In the case–control study of Jadhav et al, they reported the incidence of Mrs≤2 at 90 days was 38.3% in CS and 31.1% in GA[17]. On the other hand, we reviewed posterior circulation AIS cases in our institution (Beijing Tiantan Hospital) and found that a higher incidence of favorable neurological outcome at 90 days in CS compared with GA group

[64.7% (11/17) vs 34.9%(15/43)]. However, other factors including preoperative NIHSS score, preoperative intravenous thrombolysis treatment confound the results validity. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS. Taking this into account, we consider that the sample size to detect 30% difference in Mrs 0–2 would require 44 in each group to achieve power of 80% at a two- tailed significant level of 0.05, with a drop- out rate of 5%.

4.8 Follow-up information

4.8.1 Follow-up team

In this trial, follow-up work will be undertaken by the independent research team mainly composed of fixed graduate students, who are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. They must pass the examination before the implementation of the research to ensure that they accurately master the information collection skills, such as accurately scale evaluating, filing out CRF and etc. This team is only responsible for outcome data collection (details in 4.8.2). The resident anesthesiologist or attending anesthesiologist completes baseline and intraoperative data.

4.8.2 Data collection

1) Demographical data: gender, BMI, medical history (hypertension, atrial fibrillation, coronary artery disease [CAD], dyslipidemia, diabetes, transient ischemic attack [TIA], past stroke), smoking, drinking, etiology (cardiogenic thrombosis, atherosclerosis),

drug use (antiplatelet agent, anticoagulant agent, statin, hypoglycemic agent), American society of Anesthesiologists (ASA) physical status classification.

2) Stroke data: clinical status at admission (modified Rankin Scale, NIHSS score, Glasgow Coma Scale, systolic blood pressure, mean arterial pressure), lesion location (basilar artery, vertebral artery V4 segment or BA combined V4), IV-Tpa pretreatment.
3) Work-flow time-related data: from onset to emergency, from onset to door, from onset to puncture, from onset to reperfusion, door to puncture, door to reperfusion, puncture to reperfusion, operating time.
4) Data measured during EVT: Perioperative vital signs including supine blood pressure, heart rate, saturation, EtCO2 et al will also be listed and summarized in each treatment group. The rate of conversion from CS to GA, EVT related information (operation method, Mtici score, etc.) and adverse events (AEs).
5) Outcome data : NIHSS (24h, discharge, 30 days, 90 day), Mrs (discharge, 30 days, 90day), mortality (up to 90 days), Aes (during hospitalization), time-related outcomes (length of assisted ventilation, stay in hospital, stay in the neurological intensive) and any complications (up to 90 days).

4.8.3 Visit 1 , enrolment/randomization (Day 1)

Consenting patients are assessed to ensure they are eligible for the study (meet all inclusion criteria and none of the exclusion criteria), including by evaluation of CT and vessel imaging performed as standard of care. Patients who are not eligible must not be randomized in the study.

Patients should be enrolled, and consent informed as soon as possible and try to avoid delaying the start of the EVT. The randomization is completed after the patient enters the

operating room, and the designated attending anesthesiologist opens the allocation envelope stored in the safe. The preoperative baseline, intraoperative data and grouping information of patients were recorded by the anesthesiologist or his/her assistant.

The following will occur during Visit 1, which is an on-site visit:

1) Obtaining of signed informed consent before any study-related procedures
2) Confirmation of patient eligibility:

   -Randomization information （Code on the envelope）

   -Collection of data in CRF (visit date; date of informed consent; eligibility criteria; demographical data; stoke date; work-flow time related date; EVT period data; AEs/SAEs; any complications)
3) Reason for patients not eligible

4.8.4 Visit 2 (during EVT)

The following will occur during Visit 2, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; work-flow time-related data; perioperative vital signs [e.g., HR, SBP]; conversion from CS to GA; EVT related information [e.g., operation method, mTICI score]; AEs/SAEs; any complications; perioperative medication)

If an AE/SAE is occurred during EVT, an unscheduled visit to evaluate the patient may be needed (at the Investigator's discretion).

4.8.5 Visit 3 (24h after EVT)

The following will occur during Visit 3, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; medications information; AEs/SAEs, any complications)

If an AE/SAE is occurred during EVT, an unscheduled visit to evaluate the patient may be needed (at the Investigator's discretion).

4.8.6 Visit 4 (Day 7±2 days)

The following will occur during Visit 4, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; medications information; AEs/SAEs; any complications)

If the patient has been discharged during this period, the visit 5 will be taken as this record.

4.8.7 Visit 5 (discharge)

The following will occur during Visit 5, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; medications information; AEs/SAEs; any complications; time-related outcomes [length of assisted ventilation, stay in hospital, stay in the neurological intensive])

4.8.8 Visit 6 (Day 30±7 days)

The following will occur during Visit 6, which is a telephone contact:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; mRS; any complications)

4.8.9 Visit 7 (Day 90±14 days)

The following will occur during Visit 7, which is a telephone contact:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; mRS; any complications)

4.8.10 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits, e.g., to evaluate SAEs.

See details for definition of assessments/outcomes in Appendix B.

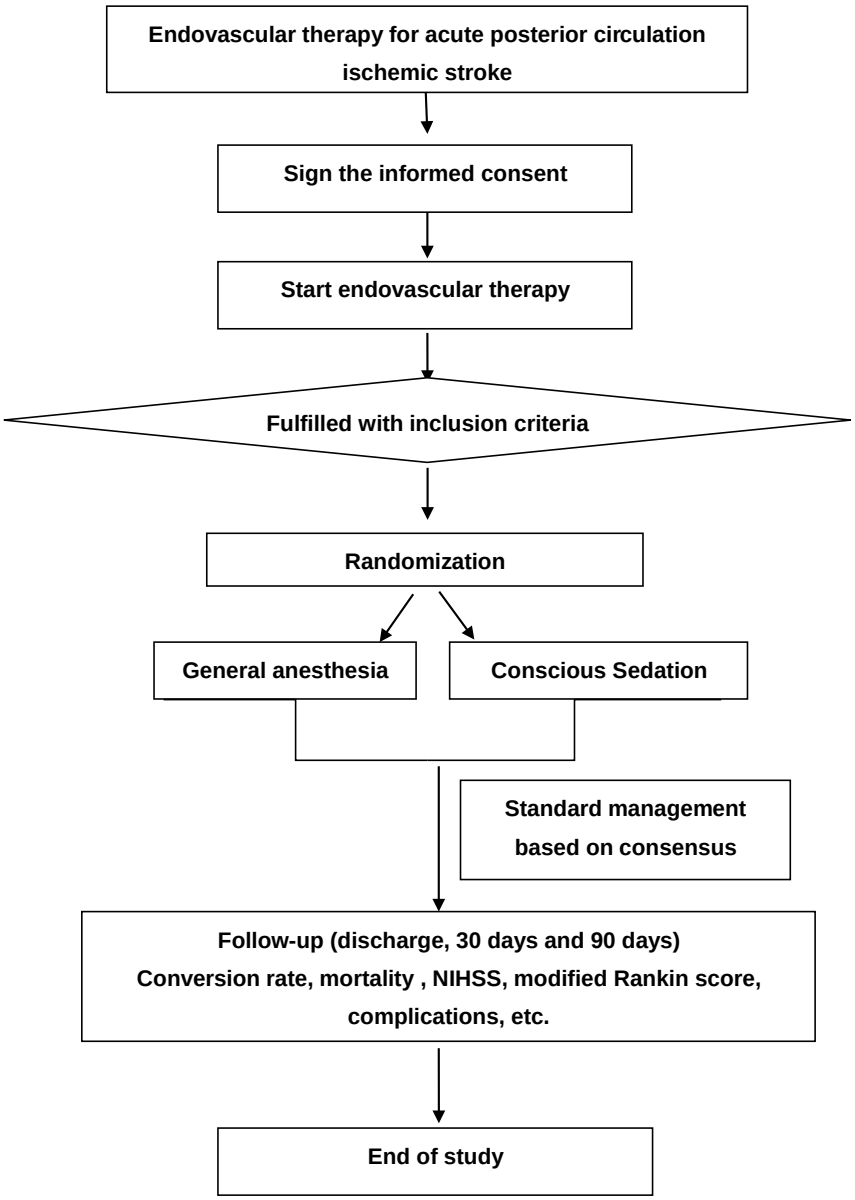
4.8.11 schedule of data collection

	STUDY PERIOD							
	Enrollment	Allocation	Post-allocation					
TIMEPOINT	At arrival	After evaluation	During treatment	24h after treatment	7±2 days after treatment	Discharge	30±7 days after treatment	90±14 days after treatment
ENROLMENT								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS								
GA			X					
LA/CS			X					
ASSESSMENTS								
Demographical data	X							
Stroke data	X							
Work-flow time	X	X	X					
Peri-op vital signs			X					
EVT information			X					
mTICI			X					
mRS	X						X	X
NIHSS	X			X	X	X	X	X
GCS	X			X	X	X	X	X
AEs/SAEs			X	X	X	X		
All-cause mortality								X
Any complications			X	X	X	X	X	X
length of stay						X		
NICU stay and						X		
Converting rate			X					

Tables marked in blue indicate completion by the independent follow-up team.

GA: general anesthesia; LA/CS: local anesthesia/conscious sedation; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; mTICI: modified Thrombolysis in Cerebral Infarction Scale

4.9 Participant timeline



4.10 Safety Monitoring and Reporting

4.10.1 Definition of AE

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to an intervention, whether considered causally related to the intervention. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, abnormal breathing), or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

4.10.2 Definition of SAE

An SAE is an AE occurring during any study phase, which fulfils one or more of the following criteria:

1) Results in death
2) Is immediately life-threatening
3) Requires in-patient hospitalization or prolongation of existing hospitalization
4) Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
5) Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further details, see Appendix C.

4.10.3 Recording and reporting of AEs

All adverse events associated with this study will be closely monitored until the adverse event is resolved, the situation is stable, or it can be confirmed that the adverse event is not related to this study. In the event of any adverse event, it should be reported to the study immediately, along with notification to the study principal, to determine the severity of the adverse event and the impairment it caused. All adverse events related to this study will be recorded and reported to the Ethics Committee within one week as part of the annual report. The study principal is responsible for all adverse event reporting.

The possibility of missing patients during follow-up requires standardized training in follow-up and establish a network of patient contacts.

The following variables will be collected for each AE fulfilling SAE criteria:

1) AE (verbatim)
2) The date when the AE started and stopped
3) Maximum intensity
4) Whether the AE is serious or not
5) Outcome
6) In addition, the following variables will be collected for SAEs:
7) Date AE met criteria for SAE
8) Date Investigator became aware of SAE
9) AE is serious due to
10) Date of hospitalization
11) Date of discharge
12) Probable cause of death
13) Date of death

14) Autopsy performed

15) Causality assessment in relation to study procedure(s)

16) Causality assessment in relation to other procedure(s)

17) Description of AE

For further details, see Appendix C.

4.11 Data confidentiality management

All raw data will be placed in a dedicated locker. In addition, all researchers should follow the rules of professional confidentiality and must keep all personally identifiable and medical information of patients confidential. The paper clinical report form will be destroyed two years after the completion of the study. The electronic data will be encrypted and preserved after hiding the patient's personal information, and access to the database will be restricted. All the work of data confidentiality management shall be carried out by designated data management team which is established by the principal investigator (PI) and independent statisticians. The PI will regularly inspect the content of the forms and database to ensure accurate and timely data entry, follow-up, and recruitment progress, as well as count withdrawal and loss-to-follow-up rates. At the end of this study, at least 20% of the clinical report forms will be randomly selected by the research department for integrity and authenticity review.

4.12 Monitoring and auditing

The study center and all data, including raw data, must be monitored by the responsible unit. Data Monitoring Committee (DMC) will randomly select no less than 20% of enrolled

patients from all case report forms in accordance with the monitoring plan and review the completeness and authenticity of the data against the registry's original documentation. All data corrections to the database will be electronically recorded in an audit trail. Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and good clinical practice (GCP)/regulatory compliance. A risk-based approach to monitoring will be applied. A mix of monitoring strategies will be implemented: on-site and remote monitoring (site-level monitoring activities performed at a location other than the research center). Monitoring strategies will be tailored to risks, permit timely oversight, and will be focused on Critical Processes and Critical Data.

4.13 Statistical Analysis

Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. The data will be analyzed on intention-to-treat and per protocol, however, the conclusion will be drawn according to the intention- to- treat analysis. The intention- to-treat analysis will depend on our definition in Statistical Analysis Plan (The Intent-to-treat population will comprise of all subjects randomized to receive at least one type of anesthesia and with 90-days mRS score) while the per- protocol population will consist of all subjects in the ITT population not identified as protocol violators. Differences in the primary endpoint will be compared between groups using Cochran- Mantel- Haenszel test. STATA V.14.0 for windows will be used for all statistical analyses. The statistical significance will be declared at type I error of 0.05. See Statistical analysis plan for details.

5. Ethics, approvals, and dissemination

5.1 Research ethics

Clinical studies will follow the World Medical Assembly Declaration of Helsinki and other relevant regulations. The 18th World Medical Declaration and the Code of Practice for the Administration of Clinical Trials of Medicinal Products will guide all applications of the amendments. The clinical study will be implemented only after approval of the trial protocol by the Ethics Committee prior to the start of the study. Progress reports of the clinical trial and a summary of clinical results after the clinical trial is completed should be submitted to the ethics committee annually.

5.2 Patient protection

Before each subject is enrolled in this study, it is the responsibility of the investigator to provide the subject or his or her representative with a complete and comprehensive description of the purpose, procedures and possible risks of the study and to sign a written informed consent, which should make the subject aware of their right to withdraw from the study at any time, and the informed consent should be retained as a clinical study document for review. The investigator should inform the subject about the study to the maximum extent possible in a language or terminology that the subject can understand. Subjects' personal privacy and data confidentiality will be protected during the study. Informed consent will be completed in a separate surgical interview room to avoid invasion/disclosure of patient privacy.

5.3 Informed Consent

Prior to participation in a clinical trial, the patient's legal representative should sign an informed consent form (name and date) with the investigator. If the legal representative is unable to read it, a witness is present throughout the informed process and signs it. The investigator should provide a copy of the signed informed consent form to the patient or the legal representative. The Principal Investigator(s) will:

1) Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
2) Ensure each patient is notified that they are free to discontinue from the study at any time
3) Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
4) Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
5) Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
6) Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

5.4 Protocol amendments

The principal investigator will be responsible for any decision to amend the protocol. If there is any modification (e.g., changes to eligibility criteria, outcomes, analyses), the principal investigator will communicate and gain approval from the Ethical Committee of Beijing

Tiantan Hospital, Capital Medical University prior to implementation and communicate with relevant parties.

5.5 Confidentiality

In accordance with GCP principles, the supervisory team (TSC/DMC) should verify the CRF against the original information. informed consent will include a statement that the patient is allowing authorized sponsors, ethics committees, and authorities direct access to relevant original information on the case report form (e.g., the patient's medical file, appointment records, original laboratory records, etc.). Researchers are expected to follow professional confidentiality rules and must keep all personally identifiable or medical information about the patient confidential.

5.6 Declaration of interests

CANVAS II Investigators report no conflicts of interest.

5.7 Dissemination policy

The findings of the study will be published in peer- reviewed journals and will be presented at national or international conferences.

5.8 Date sharing

The original research data can be shared only after contacting PI and obtaining the agreement of the research institution.

6. Trial closure

6.1 End of trial

The end of the trial will be defined as when the last participant has completed follow-up (Last participant, last follow-up). At this point, we will submit the 'Declaration of end of trial' to the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University.

6.2 Early discontinuation of the trial

This study has no interim analysis and no plan for early termination unless the data monitoring committee and the ethics committee stop it due to serious adverse events.

7. Trial management and oversight

7.1 Trial Management Group (TMG)

The TMG comprises the CANVAS II Trial Investigators – led by the Chief Investigator (PI). The day-to-day trial team will comprise the Chief Investigator, Clinical Trials Unit co-investigators (PX) alongside Trial Statisticians, Research Assistant. Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from another related research.

TMG members of this study are as follows:

PI: Ruquan Han (the chair), MD, PHD, Professor and Chairman of Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

PX: Fa Liang, MD, Department of Anesthesiology, the Beijing Tiantan hospital,

Capital Medical University

PX: Xiaochuan Huo, MD, Professor of Department of Interventional Neurology, the Beijing Tiantan hospital, Capital Medical University

Data Manager: Youxuan Wu, MD, Minyu Jian, MD, Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

Trial Statisticians: Anxin Wang, PHD, Department of Statistics, China National Clinical Research Centre for Neurological Diseases, Beijing

7.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established in line with the latest NIHR HTA guidelines. The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards. The TSC will be comprised by a majority of independent members (including the Chair) and include Patient and Public Involvement (PPI) representatives, in addition to the Chief Investigator. TSC members of this study are as follows:

Steering Committee:

Ruquan Han (the chair), MD, PHD, Professor and Chairman of Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

Matthew TV. Chan, MD, PHD, Professor of Department of Anesthesia and Intensive Care, the Chinese University of Hong Kong

Zhongrong Miao, MD, PHD, Professor and Chairman of Department of Interventional Neurology, the Beijing Tiantan hospital, Capital Medical University

Haiyang Liu, MD, Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University.

Anxin Wang, PHD, Department of Statistics, China National Clinical Research Centre for Neurological Diseases, Beijing.

7.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. The DMC will review all safety and efficacy data (endpoint data, SAEs), overall and by research center, on an ongoing basis. DMC members of this study are as follows:

Data Monitoring Committee:

Dongxin Wang MD, PhD, Professor and Chairman of Department of Anesthesiology and Critical Care Medicine, Peking University First Hospital, Beijing, China.

Nan Li MD, PhD, Professor, Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, China.

Liping Liu, MD, PHD, Professor and Chairman of Department of Neurointensive Care Unit, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

7.4 Patient and Public Involvement (PPI).

Not involved.

8. Sponsorship and funding

8.1 Sponsorship and indemnity

Beijing Tiantan Hospital, Capital Medical University

8.2 Funding

Clinical Medicine Development of Special Funding Support (ZYLX201708).

9. Reference

1. Vos T, Barber RM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386:743-800.

2. Lee YY, Yoon W, Kim SK, et al. Acute Basilar Artery Occlusion: Differences in Characteristics and Outcomes after Endovascular Therapy between Patients with and without Underlying Severe Atherosclerotic Stenosis. AJNR Am J Neuroradiol 2017; 38:1600-1604.

3. Kim YW, Hong JM, Park DG, et al. Effect of Intracranial Atherosclerotic Disease on Endovascular Treatment for Patients with Acute Vertebrobasilar Occlusion. AJNR Am J Neuroradiol 2016; 37:2072-2078.

4. Gao F, Lo WT, Sun X, Mo DP, Ma N, Miao ZR. Combined Use of Mechanical Thrombectomy with Angioplasty and Stenting for Acute Basilar Occlusions with Underlying Severe Intracranial Vertebrobasilar Stenosis: Preliminary Experience from a Single Chinese Center. AJNR Am J Neuroradiol 2015; 36:1947-52.

5. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372:11-20.

6. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372:1019-30.

7. 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; 372:2285-95.

8. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372:1009-18.

9. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372:2296-306.

10. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2015; 46:3020-35.

11. Gory B, Eldesouky I, Sivan-Hoffmann R, et al. Outcomes of stent retriever thrombectomy in basilar artery occlusion: an observational study and systematic review. J Neurol Neurosurg Psychiatry 2016; 87:520-5.

12. van Houwelingen RC, Luijckx GJ, Mazuri A, Bokkers RP, Eshghi OS, Uyttenboogaart M. Safety and Outcome of Intra-Arterial Treatment for Basilar

Artery Occlusion. Jama Neurol 2016; 73:1225-1230.

13. Singer OC, Berkefeld J, Nolte CH, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. Ann Neurol 2015; 77:415-24.

14. Brinjikji W, Murad MH, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2015; 36:525-9.

15. Abou-Chebl A, Yeatts SD, Yan B, et al. Impact of General Anesthesia on Safety and Outcomes in the Endovascular Arm of Interventional Management of Stroke (IMS) III Trial. Stroke 2015; 46:2142-8.

16. Wang A, Abramowicz AE. Role of anesthesia in endovascular stroke therapy. Curr Opin Anaesthesiol 2017; 30:563-569.

17. Jadhav AP, Bouslama M, Aghaebrahim A, et al. Monitored Anesthesia Care vs Intubation for Vertebrobasilar Stroke Endovascular Therapy. Jama Neurol 2017; 74:704-709.

18. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Republished: Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: Anesthetic management of endovascular treatment for acute ischemic stroke. Stroke 2014;45: e138-50.

19. Peng Y, Li Y, Jian M, et al. Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke: Protocol for a randomized controlled

(CANVAS) trial. Int J Stroke 2017; 12:991-997.

20. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006; 37:922-8.

10. Appendices

Appendix A. Definition of stroke

Acute ischemic stroke:

The definition for acute stroke is based on the standardized definitions (Hicks et al 2015).

An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered to be an ischemic stroke:

1) Rapid onset (or existence on awakening) of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)

2) Rapid worsening of an existing focal neurological deficit (e.g., the index stroke event) that is judged by the investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non-ischemic etiology. The progression of original angiogenic ischemic stroke (i.e., NIHSS increase ≥ 4 on the basis of primary ischemic stroke, excluding post infarction hemorrhage transformation or symptomatic intracranial hemorrhage), accompanied by new ischemic changes on head MRI or CT.

Etiological typing will be carried out according to TOAST criteria.

Acute ischemic stroke in the posterior circulation:

According to the above-described criteria, it is diagnosed as acute ischemic stroke, and it is preliminarily determined through imaging evidence (CT/CTA or MR/MRA) that the responsible vessels are the following vessels:

1) Basilar artery

2) Vertebral artery

3) Posterior cerebral artery

In CANVAS-II, imaging evidence are mainly based on CT and CTA, and the onset time described above is limited to less than 24 hours.

TOAST criteria

Large atherosclerotic	The patient's acute cerebral infarction was caused by moderate stenosis of intracranial large vessels, or brain CT and MRI showed that the diameter of the focus of acute cerebral infarction was greater than 1.5cm.
Cardiogenic	The focus of acute cerebral infarction is bilateral and cannot be explained by a single blood vessel. It is necessary to check whether there are cardiac diseases such as atrial fibrillation and atrial myxoma.
Arteriole occlusion	Normal CT or MRI examination of the head or the diameter of the infarct is less than 1.5cm.

Other etiological	Acute cerebral infarction caused by causes other than the above three causes
Unexplained	Two or more causes or no cause has been found so far.

CANVAS-II focused on patients with large atherosclerotic and cardiogenic subtypes, which are the main types suitable for EVT intervention.

wake-up stroke

It refers to patients with acute cerebral infarction who have no new stroke symptoms before sleeping but are found to have stroke symptoms by the patient himself or witnesses after awakening.

Appendix B Efficacy and Safety assessment

Efficacy assessment

1.mRS score

mRS score will be used as the main assessment to evaluate the prognosis of neurological function. mRS scores will be collected for all patients at Visit 1 by the interventional physician with an on-site visit, and at Visit 6, Visit 7 by the independent follow-up team with a telephone contact. mRS≤2 is defined as neurological independence. The following questionnaire will be used to determine the mRS score:

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
	Derived from: the Internet Stroke Center at www.strokecenter.org

2.NIHSS score

NIHSS scores at the time of randomization will be collected for all patients to verify patient eligibility. The scores will also be used to assist in the analysis of the disability endpoint. NIHSS score will be collected for all patients at Visit 1 by the interventional physician with an on-site visit and at Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 by the independent follow-up team with an on-site visit or a telephone contact. The following questionnaire will be used to determine the NIHSS score:

Interval: [ ] Baseline [ ] 24 hours post EVT [ ] 5-9 days [ ] 23-37 days [ ] 76-104 days

[ ] Other _____ (___ ___) Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, notwhat the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
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; requires repeated stimulation to attend, or isobtunded 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 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,	0 = Answers both questions correctly 1 =Answers one question correctly 2 = Answers neither question correctly	

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.		
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 him or her (pantomime), and the result scored (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 scored,	0 = Normal 1 = Partial gaze palsy; gaze is	

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.	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 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	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	

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 respond to item 11.		
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 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	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	

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.	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 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.	0 = Absent 1 = Present in one limb 2 = Present in two limbs 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	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	

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	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	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 materials difficult or impossible. For example, in conversation about	

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.	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 the patient is intubated or has other physical	0 = Normal 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty 2 = Severe dysarthria; patient's speech is so slurred as to be	

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.	unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthria UN = Intubated or another 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 anosognosia 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	

How to evaluate NIHSS score of comatose patients?

For patients with a score of less than 3 on item 1a, each item should be assessed according to the actual state. Item 1a is rated 3 only when the patient is completely unresponsive to any noxious stimuli (rubbing the sternum, pressing the orbit, etc.) and only has reflex activity.

If 1A = 3 points, other items shall be evaluated as:

1b. LOC Questions -2 **1c. LOC commands**-2 **2. Best Gaze** -1 (overcome by the head-eye reflex) or 2 (cannot overcome by the head-eye reflex) 3**. Visual**- assessment using visual threat **4. Facial Palsy**-3 **5. Motor Arm / 6. Motor Leg -** 4 for each limb **7. Limb Ataxia-** score can be given only when there is ataxia. If the patient's muscle strength decreases and cannot complete any examination of ataxia, 0 point will be given **8. Sensory**-2 **9. Best Language**-3 **10. Dysarthria**-2 **11. Extinction and Inattention (formerly Neglect)**-2

3.Glasgow Coma Score

Glasgow Coma scores at the time of randomization will be collected for all patients to verify patient eligibility. The scores will also be used to assist in the analysis of the disability endpoint. Glasgow Coma score will be collected for all patients at Visit 1 by the interventional physician with an on-site visit and at Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 by the independent follow-up team with an on-site visit or a telephone contact. The following questionnaire will be used to determine the Glasgow Coma score:

Interval: [ ] Baseline [ ] 24 hours post EVT [ ] 5-9 days [ ] 23-37 days [ ] 76-104 days

[ ] Other _____ (___ ___) Time: ___ ___: ___ ___ [ ]am [ ]pm

Person Administering Scale _____

Eyes opening Response	Spontaneous--open with blinking at baseline	4
	To verbal stimuli, command, speech	3
	To pain only (not applied to face)	2
	No response	1
	Cannot open eyes due to swollen eyes, fractures, etc.	C
Verbal response	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
	Unable due to intubation or pneumotomy	T
Motor response	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension response in response to pain (decerebrate posturing)	2
	No response	1
Total score		

4.mTICI score

mTICI score will be used to evaluate vascular reperfusion and assist in the evaluation of two anesthesia methods. mTICI score will be collected for all patients at Visit 2 by the interventional physician with an on-site visit. The following questionnaire will be used to determine the mTICI score:

Time: ___ ___: ___ ___ [ ]am [ ]pm _____ / _____ / _____ (Y /M / D)

Person Administering Scale _____

mTICI	Definitions
Grade o	No antegrade reperfusion at the occluded site and distal end of the responsible vessel
Grade I	antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade IIa	antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g., in one major division of the middle cerebral artery (MCA) and its territory)
Grade IIb	antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g., in two major divisions of the MCA and their territories)
Grade III	complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

5.Work-flow time:

Work-flow time will be recorded to compare the effect of the two anesthesia methods on the patient's time to achieve recanalization. It will be collected for all patients at Visit 2 by the resident anesthesiologist or the attending anesthesiologist with an on-site visit. The definitions of each time period are as follows:

From onset to emergency: It refers to the period from the symptom onset moment to the time when the patient arrives at emergency room after symptoms.

wake-up stroke: It refers to the period from the last asymptomatic moment to the time when the patient arrives at the emergency room after symptoms.

From onset to door: It refers to the period from the symptom onset moment to the time when the patient arrives at the operation room before EVT.

wake-up stroke: It refers to the period from the last asymptomatic moment to the time when the patient arrives at the operation room before EVT.

From onset to puncture: It refers to the period from the symptom onset moment to the time beginning of EVT for groin puncture.

Wake-up stroke: It refers to the period from the last asymptomatic moment to the time beginning of EVT for groin puncture.

Door to puncture: It refers to the period from the moment arriving at the operation room to the time beginning of EVT for groin puncture.

Door to reperfusion: It refers to the period from the moment arriving at the operation room to the time of first-time recanalization (maintenance time > 10min). For patients who need thrombectomy or stent placement due to re-occlusion after 10 minutes of reperfusion, the Door to reperfusion time is calculated according to the time achieving first recanalization. For patients who have not achieved recanalization (mTICI=0), the Door to reperfusion time is calculated according to the time starting femoral artery suturing.

Puncture to reperfusion: It refers to the period from the moment beginning of EVT for groin puncture to the time of first-time recanalization (maintenance time > 10min). For patients who need thrombectomy or stent placement due to re-occlusion after 10 minutes of reperfusion, the Puncture to reperfusion time is calculated according to the time achieving first recanalization. For patients who have not achieved recanalization (mTICI=0), the Puncture to reperfusion time is calculated according to the time starting femoral artery suturing.

Operating time: It refers to the time from the moment beginning groin puncture to the moment completing femoral artery suture.

6. Other safety outcomes:

Death

All deaths occurring post-randomization and up to 90 days (Visit 7) will be considered endpoints. Relevant data is mainly completed by the independent follow-up team with a telephone contact.

There are three causes of death: 1. Cardiovascular death 2. Non-cardiovascular death 3. Unknown cause

Cardiovascular death: Death from vascular causes includes death from stroke, sudden cardiac death, death from acute myocardial infarction, death from heart failure, pulmonary embolism, death from cardiac / cerebrovascular intervention or surgery (unrelated to acute MI), and death from other cardiovascular causes [such as arrhythmias unrelated to sudden cardiac death, rupture of aortic aneurysm, or peripheral arterial disease].

Any death with unknown / unclear cause within 90 days after stroke, myocardial infarction or cardio cerebrovascular operation / operation will be regarded as death caused by stroke, myocardial infarction or cardio cerebrovascular operation / operation, respectively.

Non-Cardiovascular death: include deaths due to bleeding (including gastrointestinal bleeding), pulmonary causes (respiratory failure, pneumonia), malignant tumors, trauma, suicide, infection / sepsis, or any other well-defined (such as liver failure or renal failure).

Time-related outcomes

Relevant data is mainly completed by the independent follow-up team by an on-site visiting at discharge (Visit 5).

Length of assisted ventilation: The length of time that the patient needs endotracheal intubation to assist breathing during hospitalization. Patients may need endotracheal intubation if they have the following conditions:

1) Endotracheal intubation was performed during EVT treatment. After treatment, retain

endotracheal intubation and continue treatment in the neurological intensive care unit.

- During EVT with CS, it is suspected that the disease is progressing, respiratory dysfunction (SpO2 cannot be maintained, or serious reflux aspiration) occurs, and the CS is converted to GA. It is expected that it will not recover in a short time after treatment, and retaining tracheal tube is required for a period of time.

- During EVT with GA, a large amount of gastric contents were aspirated through intubation, which confirmed that the patient had been complicated with serious aspiration before operation.

- During EVT with GA, the patient's respiratory status could not meet the extubation criterion (Spontaneous breathing, tidal volume ≥ 300ml, breath rate≥12 times/min, SpO2 maintained at ≥90% under oxygen concentration of 30-40%, EtCO2 maintain ≤ 45mmHg) and a long time of attempts (>1 hour) even had been tried.

- Requirements of the attending neurointerventional physician

2) In the neurointensive care unit, the patient developed respiratory failure and required endotracheal intubation assistance as the disease progressed. Patients may develop severe respiratory dysfunction in the following conditions.

- severe cerebral edema

- intracerebral hemorrhagic transformation

- Infarct enlargement/ new infarct

- severe pneumonia

- Obstruction of upper airway (e.g., gloss coma, laryngospasm) due to various causes (e.g., coma, excessive secretions)

Whether or when to remove endotracheal intubation is decided by the competent neurocritical care physician according to the patient's condition

Length of Staying in the neurological intensive care unit (NICU) or hospital:

Hospital stays: the time from EVT (date and time) to discharge.

NICU stay time: including the time of first and second entry into NICU.

The criteria for leaving NICU or discharge shall be determined by the competent neurocritical care physician.

Complication:

The following complications occurring post-randomization and up to 90 days (Visit 7) will be considered endpoints. Relevant data is mainly completed by the independent follow-up team with a telephone contact and review electronic medical record.

Post infarction hemorrhagic transformation

Hemorrhage may be a consequence of an ischemic stroke (the index event or a subsequent stroke), i.e., a hemorrhagic transformation. Hemorrhagic transformations may be either symptomatic or asymptomatic.

Symptomatic hemorrhagic transformation of an ischemic stroke must have imaging

evidence of extravascular blood within an area of known acute/subacute infarction that is judged to be nontraumatic and at least partially responsible for the patient's clinical neurological deterioration with neurological symptoms out of proportion to what would be expected for the size and location of the infarction.

Asymptomatic hemorrhagic transformation of an ischemic stroke must have imaging evidence of any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, with no detected worsening of neurological symptoms related to the hemorrhage.

myocardial infarction (MI)

Criteria for acute myocardial infarction: general definition of the Third Edition (Thygesen 2012).

If there is clinical evidence of myocardial necrosis consistent with acute myocardial ischemia, MI should be diagnosed. MI is diagnosed when any of the following criteria are met:

Cardiac biomarkers (preferably troponin [cTn]) are detected to be elevated or then decreased after elevated, with at least one value greater than the 99% upper limit of the reference value (URL), and at least one of the following:

1) Clinical symptoms of myocardial ischemia

2) New myocardial ischemia changes on the ECG, namely new ST-segment changes or left bundle branch block (LBBB) [according to whether there is ST-segment elevation on the ECG, it is divided into acute ST-segment elevation

myocardial infarction (STEMI) and non-acute ST-segment elevation myocardial infarction (NSTEMI)]

3) Pathological Q waves on the ECG

4) Imaging suggests new deactivated myocardium or new segmental wall motion abnormalities

5) Angiographic or autopsy-proven coronary thrombosis

Pulmonary embolism (PE)

Gold standard: radionuclide pulmonary ventilation/perfusion (V/Q) imaging scan is highly suspected, or confirmed by pulmonary angiography or spiral CT, or confirmed by autopsy.

Other aids in diagnosis:

Signs and symptoms of pulmonary embolism comprise sudden onset of dyspnea or deterioration of existing dyspnea, chest pain, syncope or dizziness due to hypotension or shock, hemoptysis, tachycardia, or tachypnoea.

Abnormalities on chest radiography, electrocardiography, or blood gas analysis are not specific for pulmonary embolism but might be useful in the differential diagnosis.

About 70% of patients with symptomatic pulmonary embolism have concomitant deep vein thrombosis, which is symptomatic in up to a quarter of cases. Conversely, silent pulmonary embolism is present in at least a third of patients with symptomatic deep vein thrombosis.

D-dimer abnormally increase (>500 μg/L).

Pneumonia

Hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) are the main type observed. According to the guidelines, the diagnosis of HAP and VAP requires all of the following:

- New lung infiltrates on chest imaging
- Respiratory decline
- Fever
- Productive cough

Absence of a new infiltrate significantly lowers the probability of VAP and can guide the clinician to alternative causes of inpatient respiratory decline, including pulmonary embolism. Once an infiltrate is observed and HAP or VAP is suspected as the cause of respiratory decline, several noninvasive tests are recommended to assist in diagnosis.

- Blood cultures
- Sputum cultures
- Polymerase chain reaction
- Procalcitonin testing

Deep venous thrombosis (DVT)

Clinical manifestations of deep vein thrombosis of the legs include swelling or pitting oedema, redness, tenderness, and presence of collateral superficial veins. The

compression ultrasonography confirms mid-echoic, or hypoechoic filling of the veins.

Indicators during treatment

The follow indicators during treatment (Visit 2) will be completed by the attending anesthesiologist with an on-site visit:

Hypotension: intraoperative systolic blood pressure lower than 120mmHg. When hypotension occurs, timely administration of vasoactive drugs to raise blood pressure

Dysphoria or motion: physical movement that interferes with the operator's operation, requiring a brief cessation of the operation or increased sedation

Conversion rate from CS to GA: detail in section 4.34

Intraoperative physiological parameters：

BP：monitoring noninvasive pressure, which is measured every 5 minutes.

HR: continuous monitoring through ECG monitoring and recording every 5 minutes.

SpO2: Continuous monitoring through oxygen monitoring and recording every 5 minutes.

EtCO2: monitored via anesthetic gas sample line at nasal vestibule in CS group and via endotracheal intubation at trachea in GA group.

Oxygen concentration: in CS group, recorded the oxygen flow value when the mask inhaled oxygen and the inhaled oxygen concentration was calculated by the formula:

Oxygen concentration (%) = 21 + Inhaled oxygen flow (L/min) × 4

in GA group, recorded the output oxygen concentration from the anesthesia machine.

Appendix C Additional safety information

Further guidance on the definition of a serious adverse event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the interventions would result in the patient's death (e.g., In CS group, sudden body movement caused vascular perforation and massive intracranial hemorrhage).'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., pneumonia resolved without respiratory failure).

Hospitalization

Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. (e.g., combined with chronic arterial stenosis, stenting was performed during follow-up).

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect intervention does not mean that it is an important medical

event; medical judgement must be used.

Possible serious adverse event and emergency plans during perioperative period

1) Respiratory dysfunction

Closely monitor the patient's respiratory function. Once the patient has respiratory dysfunction (EtCO2 exceeds 60mmHg or SpO2<92%), immediately stop the surgical operation and give the patient assisted ventilation. And converse from CS to GA, tracheal intubation, to ensure airway safety. At the same time, analyze the reasons and record in detail.

2) Severe hypotension

Closely monitor the patient's circulatory system and strictly control blood pressure according to the consensus of AIS intravascular anesthesia management. Once patients have severe hypotension (SBP < 120mmHg), they should be actively treated with vasoactive drugs. Analyze the reasons and deal with them.

3) respiratory and cardiac arrest:

Stop the operation immediately; Immediately perform external cardiac compression and electric defibrillation; Endotracheal intubation and mechanical ventilation; Intratracheal or intravenous administration of resuscitation drugs (epinephrine and vasoactive drugs, antiarrhythmic drugs and others); analyze the reasons and deal with them.

4) Acute myocardial infarction:

Prompt and definite diagnosis; suspend the operation or complete the operation as soon as possible; Sufficient oxygen supply; Apply inotropic drugs (dopamine, norepinephrine, etc.); Intensive intraoperative monitoring (MBA, CVP, T, urine output); Coronary expansion treatment, and reduce myocardial preload and myocardial oxygen consumption.

5) Acute pulmonary embolism:

Suspect diagnosis; Immediately carry out cardiopulmonary resuscitation when necessary; Endotracheal intubation to ensure adequate oxygen supply and analgesia; Control the treatment of heart failure and arrhythmia; Anti shock and anticoagulation therapy.

6) Arrhythmia

Clarify the type and cause of arrhythmia; Treat the cause immediately; Prevent the recurrence of arrhythmia while terminating the attack of arrhythmia and striving for radical cure; Pay attention to the side effects caused by treatment while actively treating.

7) Intracranial hemorrhage

Keep the airway unobstructed; Give respiratory support; Maintain hemodynamic stability; Give drug support when necessary; Patients with significant intracranial pressure increase were treated with hyperventilation, osmotic diuretics and hormone therapy to reduce brain edema.

8) Malignant hyperthermia

Stop all anesthetic drugs and operations immediately, hyperventilate with pure oxygen, and promote CO2 emission; Active cooling treatment; Correct acidosis; Rehydration and diuresis; Use a lot of hormones; Apply anti skeletal muscle contracture drugs.

9) Hypertensive crisis

When the blood pressure reaches 220/140-150mmhg, it can be regarded as a crisis. Rapid blood pressure reduction is the only effective method to prevent further damage to important organs such as heart, brain and kidney; Artificial hibernation to prevent hypertensive convulsion; Reduce intracranial pressure.

10) Bronchospasm

Clear incentives and eliminate stimulating factors; If the anesthesia is too shallow, the anesthesia should be deepened; Inhale oxygen, assist or control breathing; Symptomatic treatment, intravenous infusion of corticosteroids, aminophylline, etc.

11) Adverse drug reactions

Stop administration immediately and treat symptomatically; Patients with severe allergy may have bronchospasm, airway edema, hypotension, etc., and should be treated with antispasmodic, fluid infusion and pressor drugs. If there is airway obstruction, all methods should be used to ensure effective ventilation; Use diazepam to prevent convulsion. In case of convulsion, immediately use drugs to relieve convulsion and protect patients from accidental injury.

This plan should be adjusted according to the actual condition of the subjects.

Choice of ANesthesia for Endo-VAScular treatment of acute ischemic stroke in the posterior circulation (CANVAS II)

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Clinical Medicine Development of Special Funding Support (ZYLX201708; DFL20180502) and the Beijing Municipal Science & Technology Commission (Z19110700660000)

Chief Investigator

Ruquan Han, MD, PhD

Sponsor representative

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

....//...../.....

Name (please print):

Position:

Chief Investigator:

Signature: ..... Date: ...../...../.....

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Summary

Data category	Information
Primary registry and trial identifying number	NCT03317535
Date of registration in primary registry	October 23, 2017
Source(s) of monetary or material support	Clinical Medicine Development of Special Funding Support and the Beijing Municipal Science & Technology Commission
Primary Sponsor	Beijing Tiantan Hospital, Capital Medical University
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Public title	Choice of Anesthesia for Endovascular Treatment of Acute Ischemic Stroke in Posterior Circulation (CANVAS-II)
Scientific title	Choice of anesthesia for endovascular treatment of acute ischemic stroke in the posterior circulation (CANVAS II): An exploratory randomized controlled trial

Data category	Information
Countries of recruitment	China
Health condition(s) or problem(s) studied	Acute ischemic stroke in the posterior circulation
Intervention(s)	Interventions: GA vs CS
Key inclusion and exclusion criteria	Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Inclusion criteria 1) Vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CT angiography (CTA)/magnetic resonance angiography (MRA) 2) Age ≥18 years 3) Stroke onset to treatment time ≤24 hours and modified Rankin score ≤2 4) Sign informed consent Exclusion criteria 1) Patients with unclear radiological image to identify infarction and vessel occlusion 2) Patients with intracranial hemorrhage (ICH)

Data category	Information
	3) Patients with anterior circulation occlusion 4) Glasgow coma score (GCS)≤8 5) NIHSS score <6 or >30 6) Post circulation Alberta Stroke Program Early CT Score (pc- ASPECTS) <6, 7) Pons-midbrain index ≥3 8) Patients with severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission 9) Patients intubated before EVT 10) Patients with unconsciousness and known allergy to anesthetics or analgesics 11) Patients whose legal relative refuses to participate
Study type	Interventional Allocation: Randomized Intervention Model: Parallel Assignment Blind: end-point assessor Primary purpose: Optimize disease treatment
Date of first enrolment	March 1, 2018
Target sample size	88
Primary outcomes	The primary endpoint is the neurological disability at 90 days

Data category	Information
	after EVT measured by mRS, which ranges from 0 (no symptoms) to 6 (death), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS ≤2. The score will be evaluated by outcomes assessor who are blinded to allocation.
Key secondary outcomes	1) Change in NIHSS, from baseline to discharge, 30 days and 3 months after randomization. 2) The score of mTICI will be evaluated before and after endovascular treatment. 3) All- cause mortality up to 3 months after randomization. 4) The incidence of complications up to 3 months after randomization. 5) Time-related outcomes, such as, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care unit after randomization. 6) The rate of conversion from CS to GA. 7) Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.

Data category	Information
	8) All adverse events associated with this study will be recorded.

Contents

Abbreviations

AIS	Acute ischemic stroke
EVT	endovascular therapy
GA	general anesthesia
LA	local anesthesia
CS	conscious sedation
MCA	monitoring sedation anesthesia
NIHSS	National Institute of Health Stroke Scale
mTICI	modified Thrombolysis in Cerebral Infarction Scale
mRS	modified Rankin score
ICH	intracranial hemorrhage
ECG	electrocardiogram
HR	heart rate
BP	non- invasive blood pressure
SpO2	pulse oxygen saturation
ETCO2	end- tidal carbon dioxide
FiO2	inspired oxygen fraction
BIS	bispectral index
UV	urine volume
AEs	adverse event

SAEs	Serious adverse events
PI	Principal Investigator

1. Background and rational

Acute ischemic stroke (AIS) is the second leading cause of death and disability worldwide, and the leading in China. In China, the average annual death toll from stroke has reached two million with an annual growth rate of 8.7%[1]. AIS at posterior circulation account for 17%–60% of acute stroke with difficulty in treatment, which result in a poor outcome and mortality rate of 80%–95%[2-4]. It brings great challenges to clinical treatment.

Early recanalization is one of the most crucial factors of favorable outcome for posterior circulation AIS patients at 90 days. The traditional treatment method for recanalization is intravenous thrombolysis, but the treatment time is only 3-4.5 hours. Due to the recanalization rate of large blood vessels is low, the effect of traditional thrombolysis is limited. With the rapid development of interventional materials and techniques, in order to obtain a higher vascular recanalization rate, the method of mechanical thrombectomy was on stage. From late 2014 to mid-2015, the results of several AIS endovascular treatment clinical trials worldwide were published and confirmed that endovascular treatment technology is beneficial for acute ischemic stroke[5-9]. Therefore, the European Stroke Association and the American Neurosurgery Intervention Association have successively issued an expert consensus to upgrade the evidence-based medical evidence of acute intravascular thrombectomy to level I recommendations and level A evidence[10]. China has also released the 2015 guidelines for intravascular treatment of acute ischemic stroke. Endovascular therapy has shown great application prospects in clinical treatment.

However, endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment with around 30% good clinical outcome improvement and 35% mortality

decrease at 90 days[11-13], there is a substantial proportion of patients with poor clinical outcomes even after timely successful reperfusion. Many factors may contribute to the mismatched association of high reperfusion rate and poor clinical outcome, including patient- specific factors (age, collaterals status, initial stroke severity, infarct volume and site, and distal artery emboli), procedural- specific factors (time from onset to recanalization, degree of recanalization) and anesthesia management[14]. In some research of acute anterior circulation vascular occlusion, general anesthesia seems to be a crucial factor associated with poor prognosis of patients after recanalization[15, 16].

The most used anesthesia methods for endovascular treatment include general anesthesia (GA) with mechanical ventilation and local anesthesia (LA) with conscious sedation（CS）. The optimal anesthesia choice and management for AIS patients during EVT is still unclear. Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration, body immobility to avoid vessel perforation and better digital subtraction angiography imaging. On the other hand, hypotension, nosocomial infection, delayed procedure initiation, loss of neurological evaluation and hyperventilation may contribute to poor outcomes. CS management permits neurological function assessment, shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with GA. However, the risk of aspiration and substantial movement during endovascular procedural are the main two disadvantages associated with CS.

There have been many relevant studies on this issue, including many prospective clinical randomized trials. Since 2014, four randomized controlled studies on the choice of anesthesia method and the prognosis of neurological function in patients with AIS on the

clinicaltrials.org website had registered including ANSTROKE (NCT01872884), CANVAS (NCT02677415), GOLIATH (NCT02317237) and SIESTA (NCT02126085). Unfortunately, most of these studies, whether retrospective or prospective, only focus on anterior circulation stroke, and there are very few studies on vertebrobasilar occlusive stroke.

Since the vertebrobasilar artery system is often responsible for the blood supply of important parts such as the medulla oblongata and the brain stem, in where important functional centers such as respiration and circulation are located. And many nuclei of cranial nerves are also distributed on the medulla oblongata brain stem, so when these parts are involved, the patient is likely to experience respiratory depression, circulatory depression, loss of protective reflexes, and so on. Therefore, many neurointerventionists and anesthesiologists prefer general anesthesia with mechanical ventilation to manage these patients. From the perspective of clinical safety, it seems that general anesthesia is more suitable for patients with posterior circulation occlusion. However, there is still a lack of reliable evidence to support general anesthesia. It is important to actively achieve early reperfusion due to the rapidly change in the condition of patients with posterior circulation large vessel occlusion. Monitoring anesthesia can save a lot of time in preparation for anesthesia. If the patient is given a certain degree of sedation, a certain braking effect can also be achieved, which facilitates the operation of the surgeon during the operation, reduces unnecessary waste of time, and reduces some complications caused by the postoperative tracheal tube retention. As for safety, it can be managed by closely monitoring the patient's vital signs. A few studies observed the feasibility of monitored anesthesia care for elective endovascular procedures either in anterior or posterior

circulations and demonstrated high technical success with low rates of periprocedural complications and mortality[15, 17]. In addition, many retrospective studies on the anterior circulation have shown that patients with acute stroke who receive endovascular therapy with general anesthesia or deeper sedation may experience a worse prognosis[14-16]. However, whether the same is true for stroke patients with vertebrobasilar system occlusion also need further research to explore.

Recently, Jadhav AP et al conducted a retrospective, paired, case-control study showing the feasibility of monitoring sedation anesthesia (MAC) in endovascular treatment of patients with vertebrobasilar occlusive stroke[17]. This study reviewed all 215 patients with vertebrobasilar artery occlusive stroke who received endovascular therapy from two research centers. Finally, a total of 122 patients were included in the analysis after matching (61 in MAC group vs 61 in GA group). It was found that compared with GA group, the patients receiving MAC treatment had similar successful reperfusion rate, good clinical outcome, bleeding complications and death toll. However, retrospective design and limited sample size may introduce undetected biases. Furthermore, there is no published randomized controlled trial that explored whether GA or CS are associated with different neurological outcomes at 90 days in patients undergoing EVT for posterior circulation AIS. Our study will break through the limitations of retrospective studies and conduct an exploratory prospective clinical randomized study of anesthesia methods for vertebrobasilar occlusive stroke. There is few randomized controlled clinical to investigate the impact of anesthetic type on outcome in patients with acute ischemic stroke in posterior cerebral circulation. It is unknown whether the choice of anesthesia is impacted on the

outcomes for these patients or not. The investigators will perform a randomized controlled pilot clinical trial of general anesthesia versus conscious sedation to explore and find out a potential fact whether anesthetic type alters perioperative neurological function in patients with acute ischemic stroke in posterior cerebral circulation.

2. Hypothesis

Based on previous studies, we propose that CS is feasible for intravascular treatment of patients with vertebrobasilar artery occlusion stroke. Compared with GA, there is no difference in neurological outcomes at 90 days.

3. Aims and objectives

3.1 Aim

The study aims to explore the feasibility of CS in intravascular treatment of vertebrobasilar artery occlusion stroke by clinical randomized controlled study and detect the difference of neurological function in patients with posterior circulation AIS under GA and CS, and hence to provide high-quality evidence for anesthesia selection in patients with posterior circulation occlusion undergoing endovascular therapy.

3.2 Primary objective

To compare the proportion of posterior circulation stroke patients with good prognosis at 90 days between the two groups receiving GA and CS, and hence to observe the effect of anesthetic type on outcomes after EVT.

3.3 Secondary objectives

To compare, between the groups:

3.3.1 Change in NIHSS, from baseline to discharge, 30 days and 3 months after randomization.

3.3.2 The score of mTICI will be evaluated before and after recanalization.

3.3.3 All- cause mortality up to 3 months after randomization.

3.3.4. The incidence of complications up to 3 months after randomization.

3.3.5. The length of stay in the hospital and in intensive care unit after randomization.

3.3.6. The rate of conversion from CS to GA.

3.3.7. Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.

3.3.8. Perioperative blood pressure management.

3.3.9. All adverse events associated with this study will be recorded.

4. Methods

4.1 Setting

4.1.1 Trial sites and Estimated trial duration

Posterior circulation AIS patients will be enrolled from Beijing Tiantan Hospital, Capital Medical University and the Baiyun Hospital, Guizhou Medical University from January 2018 to December 2021.

4.1.2 Design

CANVAS II is a randomized, parallel-group, exploratory trial with blinded endpoint evaluation to determine whether GA or CS produces different neurological outcomes in posterior circulation AIS patients undergoing EVT. Due to the anesthesiologists, neuroradiologist as well as attending doctors in neurological intensive care unit need to participate in the safe administration of GA or CS and related medical care, the double-blind design is not suitable.

4.2 Population

Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial.

4.2.1 Inclusion criteria

1) Vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CT angiography (CTA)/magnetic resonance angiography (MRA)

2) Age ≥18 years

3) Stroke onset to treatment time ≤24 hours and modified Rankin score ≤2

4) Sign informed consent

4.2.2 Exclusion criteria

1) Patients with unclear radiological image to identify infarction and vessel occlusion

2) Patients with intracranial hemorrhage (ICH)

3) Patients with anterior circulation occlusion

4) Glasgow coma score (GCS)≤8

5) NIHSS score <6 or >30

6) Post circulation Alberta Stroke Program Early CT Score (pc- ASPECTS) <6,

7) Pons-midbrain index ≥3

8) Patients with severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission

9) Patients intubated before EVT

10) Patients with unconsciousness and known allergy to anesthetics or analgesics

11) Patients whose legal relative refuses to participate

4.3 Intervention

4.3.1 Arms and Interventions

After the patients are formally enrolled, they will receive two anesthesia methods at random. GA and CS in this trial are defined according to the practice guidelines for sedation and analgesia by non- anesthesiologists due to the continuum ranging of level of sedation from minimal sedation to GA. Both GA and CS will be monitored and applied by anesthesiologists.

Standard operating procedures are applied to both groups to ensure no principal differences generated and uniform protocol implemented. Patients in both groups will receive local anesthesia (LA) at puncture site, with 3–5 mL of 1% lidocaine hydrochloride prior to arterial puncture.

Local anesthesia/conscious sedation	Procedure: Local anesthesia/conscious sedation Patients will be injected with propofol and remifentanil with BIS value maintained above 70. Procedure: Spontaneous breath Patients will be kept spontaneous breath
General anesthesia	Procedure: General anesthesia Patients will be injected with propofol, remifentanil and muscular relaxant with BIS value is maintained between 40 and 60. Procedure: Controlled ventilation Patient will be kept with controlled ventilation

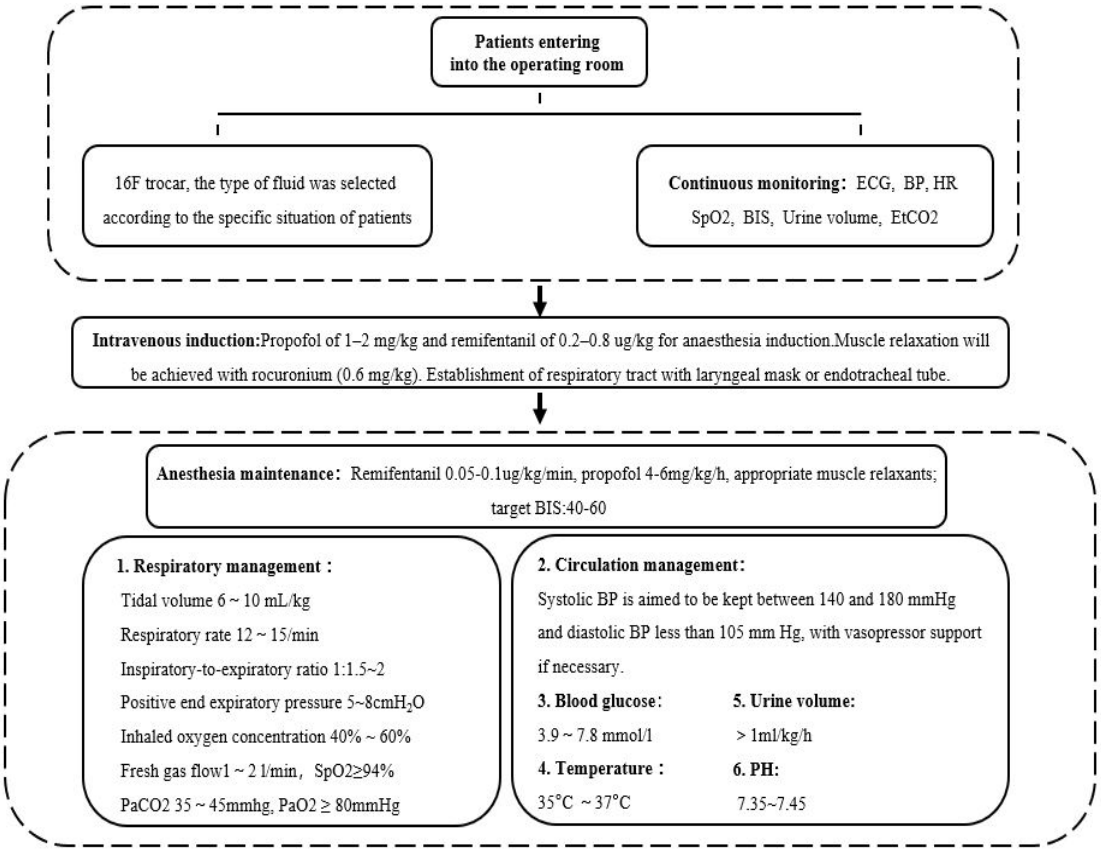
4.3.2 Monitoring indicators

All randomized patients will receive standard monitoring, including ECG, non- invasive blood pressure (BP), heart rate, pulse oxygen saturation (SpO2), end- tidal carbon dioxide (ETCO2), inspired oxygen fraction (FiO2) and blood glucose. All patients will receive bispectral index (BIS) monitoring to assess the depth of sedation or anesthesia with BIS probe placed on the forehead. Physiologic parameters will be recorded using purposely designed data collection table. BP and blood glucose will be controlled according to current guidelines for stroke therapy[18].Specifically, systolic BP is aimed to be kept between 140

and 180mm Hg and diastolic BP less than 105 mm Hg, with vasopressor support if necessary[19]. Plasma glucose will be maintained at level of 140–180 mg/dL while SpO2 is aimed to be over 94%, with FiO2 at a range from 40% to 60%[19]. It is anticipated that patients in the CS group may deteriorate during EVT and may, therefore, require endotracheal intubation or laryngeal mask insertion for airway protection. All anesthesia-related treatment will be performed by anesthesiologists of ischemia stroke team.

4.3.3 General anesthesia

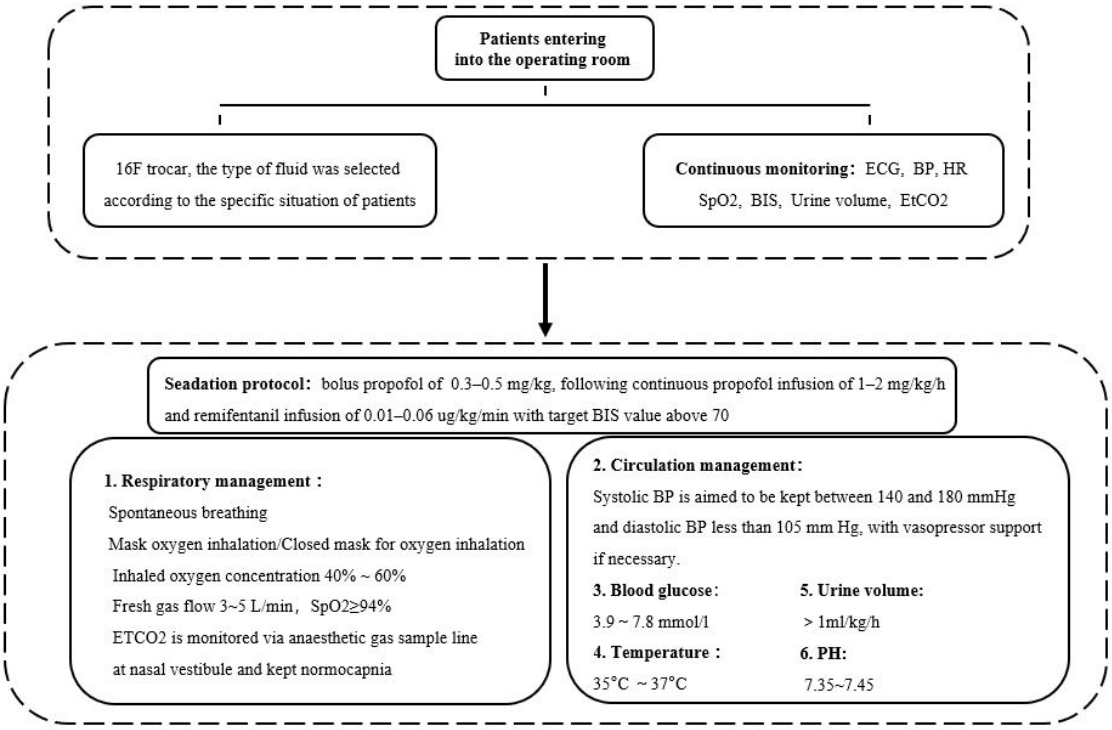
The study protocol specifies clinical criteria and procedures for the GA (see algorithm below).



Whether to remove endotracheal intubation immediately after operation is decided by the attending anesthesiologist and interventional physician according to the patient's situation.

4.3.4 Local anesthesia/conscious sedation

The study protocol specifies clinical criteria and procedures for the CS (see algorithm



below).

Indications for conversion

To ensure the clinical safety of patients, patients in the monitoring anesthesia group will be converted to general anesthesia intubation if the following conditions occur:

1) Unconscious.
2) Glasgow Coma Scale decrease to or less than 8.
3) Increase of end- tidal carbon dioxide (ETCO2) ≥60 mm Hg and/or a decrease in pulse oxygen saturation (SpO2) <94% despite oxygen supplementation.
4) Vomiting/dysphoria/agitation that cannot be controlled with sedation and/or restraint.
5) Seizure attack.

6) Recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage.

The decision to convert from CS to GA will be made by the neuroradiologist in charge and the attending anesthesiologists. The number of patients and reasons for the conversion will be recorded in detail.

4.4 Outcome measures

4.4.1 Primary outcome

The primary endpoint is the neurological disability at 90 days after EVT measured by mRS, which ranges from 0 (no symptoms) to 6 (death), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS ≤2[10, 14, 20]. The score will be evaluated by outcomes assessor who are blinded to allocation.

4.4.2 Secondary outcome

The secondary endpoints include the followings:

1) Change in NIHSS, from baseline to discharge 30 days and 3 months after randomization.
2) The score of mTICI will be evaluated before and after endovascular treatment.
3) All- cause mortality up to 3 months after randomization.
4) The incidence of complications up to 3 months after randomization.
5) Time-related outcomes, such as, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care unit after randomization.
6) The rate of conversion from CS to GA.
7) Work- flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.

8) All adverse events associated with this study will be recorded.

4.5 Recruitment and consent

4.5.1 Screening

Potentially eligible patients admitted/accepted for admission to the participating unit will be screened against the inclusion/exclusion criteria by the clinical team, supported by the Green Channel system. Both the attending neuroradiologist and interventional physician (the clinical team) must agree that the patient is suitable with either GA or CS management before recruiting. Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

Green channel system: In our hospital, we have built a multidisciplinary contact network through mobile app. When the potentially patient arrives at the emergency department, the interventional physician and anesthesiologist can quickly obtain the relevant information. Through communication with emergency physicians and the in-hospital electronic medical record system, clinical team can preliminarily determine whether the patient is suitable for surgical treatment or enrolled in this trial. When the potential patient arrives at the emergency room, the emergency doctor will conduct the initial assessment. After the diagnosis of acute stroke is confirmed, he/she will contact the interventional physician to determine whether intravascular treatment can be performed. Then, if the emergency EVT is necessary , the interventional physician will notify the anesthesiologist in advance for preoperative preparation. At least two designated anesthesiologists will arrive in the operating room or emergency room in advance to participate in the recruitment and research intervention. One is the attending physician, mainly responsible for the implementation of clinical anesthesia, and the other is a resident physician, mainly responsible for research recruitment and baseline data collection.

4.5.2 Consent

Patients with acute stroke often have consciousness changes and cannot fully understand the complex explanations. Therefore, it is difficult to involve study participants in the consenting process. Consent will be sought for the patients from their legal representatives as this is where the responsibility for deciding on medical treatment resides. However, if the patients with clear consciousness can express themselves, we must consider the patient's willingness. There are the following situations:

1) If the patient can clearly express their willingness not to participate, we will not enroll the patient
2) If the patient can clearly express their willingness to participate, we will further ask the families'/ legal representatives' consent and enroll the patient after they agree

The clinical team will screen the patients according to the inclusion and exclusion criteria. The designated resident anesthesiologist will introduce the detailed information of this trial to the patients (if possible) or their families/ legal representatives, including the purpose, the content and the intervention measures of this trial, the randomization method, potential risks and benefits of the patients after participating, participant confidentiality, use of personal data, data security, the future availability of the results of the study, etc.

After a detailed understanding, a Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection, to receive a follow-up questionnaire and for anonymized data to be shared with other researchers in the future. Families/ legal representatives will be given time to read the Consent Form and have an opportunity to

ask any questions they may have about patients 'participation in CAVANS-II and to discuss with other family members or friends or the patient (If possible) before confirming their decision.

After the person seeking consent has checked that the CAVANS-II trials and Consent Form have been understood, they will invite the families/ legal representatives to sign the Consent Form and will then add their own name and countersign it.

It is obviously impossible for patients with acute stroke to read and sign the informed consent form. Therefore, after simply introducing the CANVAS-II (if appropriate), only ask for their oral consent.

Refusal or withdrawals of consent: If informed consent is refused or withdrawn, this decision will be respected and abided by, and no further contact made. All data occurring up to the point of this decision will be retained in the trial unless the families/ legal representatives requests otherwise.

4.6 Randomization and masking

Randomization will be conducted via a computer- generated table. Patients will be randomly allocated to receive either GA or CS in a 1 to 1 ratio with a block of four. A designated staff who will neither be involved in anesthesia management nor follow- up will perform generation as well as allocation randomization sequence. The staff will implement the allocation sequence through opaque, sealed, and stapled envelopes. Each envelope has a fixed number to ensure that it is opened in the correct order and be kept in a special safe. Randomization occurs on the time of EVT when patients are admitted to the interventional neuroradiology suite, the decision for EVT has been made, the agreement from both the anesthesiologist and interventional physician has been reached, and written informed consent is obtained from patient's legal representatives. In order not to delay the

treatment time of patients, The designated resident anesthesiologist should arrive at the emergency room or operating room as early as possible for informed consent. The stored allocation randomization envelopes will be opened by the attending anesthesiologist in the operation room.

The endpoint assessors (detials in 4.8.1) for postoperative visiting are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. The anesthesiologist, neuroradiologist as well as attending doctors in neurological intensive care unit will not be blinded as they need to participate in the safe administration of GA or CS and related medical care. The enrolled patients and his/her legal representatives will not be blinded, either.

4.7 Sample size calculation

The PASS V.15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint—favorable outcome (mRS 0–2) at 3 months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only one indicated the association between anesthesia type and neurological outcome. In the case–control study of Jadhav et al, they reported the incidence of mRS≤2 at 90 days was 38.3% in CS and 31.1% in GA[17]. On the other hand, we reviewed posterior circulation AIS cases in our institution (Beijing Tiantan Hospital) and found that a higher incidence of favorable neurological outcome at 90 days in CS compared with GA group [64.7% (11/17) vs 34.9% (15/43)]. However, other factors including preoperative NIHSS score, preoperative intravenous thrombolysis treatment confound the results validity. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0–2 would

require 44 in each group to achieve power of 80% at a two- tailed significant level of 0.05, with a drop- out rate of 5%.

4.8 Follow-up information

4.8.1 Follow-up team

In this trial, follow-up work will be undertaken by the independent research team mainly composed of fixed graduate students, who are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. They must pass the examination before the implementation of the research to ensure that they accurately master the information collection skills, such as accurately scale evaluating, filing out CRF，etc. This team is only responsible for outcome data collection (details in 4.8.2). The resident anesthesiologist or attending anesthesiologist completes baseline and intraoperative data.

4.8.2 Data collection

1) Demographical data: gender, BMI, medical history (hypertension, atrial fibrillation, coronary artery disease [CAD], dyslipidemia, diabetes, (transient ischemic attack [TIA], past stroke), smoking, drinking, etiology (cardiogenic thrombosis, atherosclerosis), drug use (antiplatelet agent, anticoagulant agent, statin, hypoglycemic agent), American society of Anesthesiologists (ASA) physical status classification,
2) Stroke data: clinical status at admission (modified Rankin Scale, NIHSS score, Glasgow Coma Scale, systolic blood pressure, mean arterial pressure), lesion location (basilar artery, vertebral artery V4 segment or BA combined V4), IV-tPA pretreatment.

3) Work-flow time-related data: from onset to emergency, from onset to door, from onset to puncture, from onset to reperfusion, door to puncture, door to reperfusion, puncture to reperfusion, operating time.
4) Data measured during EVT: Perioperative vital signs including supine blood pressure, heart rate, saturation, EtCO2 et al will also be listed and summarized in each treatment group. The rate of conversion from CS to GA, EVT related information (operation method, mTICI score, etc.) and adverse events (AEs).
5) Outcome data：NIHSS (discharge, 30 days, 90 day), mRS (discharge, 30 days, 90day), mortality (up to 90 days), AEs (during hospitalization), time-related outcomes (length of assisted ventilation, stay in hospital, stay in the neurological intensive) and any complications (up to 90 days).

4.8.3 Visit 1(enrolment/randomization (Day 1)

Consenting patients are assessed to ensure they are eligible for the study (meet all inclusion criteria and none of the exclusion criteria), including by evaluation of CT and vessel imaging performed as standard of care. Patients who are not eligible must not be randomized in the study.

Patients should be enrolled, and consent informed as soon as possible and try to avoid delaying the start of the EVT. The randomization is completed after the patient enters the operating room, and the designated attending anesthesiologist opens the allocation envelope stored in the safe. The preoperative baseline, intraoperative data and grouping information of patients were recorded by the anesthesiologist or his/her assistant.

The following will occur during Visit 1, which is an on-site visit:

1) Obtaining of signed informed consent before any study-related procedures

2) Confirmation of patient eligibility:

-Randomization information （Code on the envelope）

-Collection of data in CRF (visit date; date of informed consent; eligibility criteria; demographical data; stoke date; work-flow time related date; EVT period data; AEs/SAEs; any complications)

3) Reason for patients not eligible

4.8.4 Visit 2 (during EVT)

The following will occur during Visit 2, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; work-flow time-related data; perioperative vital signs [e.g., HR, SBP]; conversion from CS to GA; EVT related information [e.g., operation method, mTICI score]; AEs/SAEs; any complications; perioperative medication)

If an AE/SAE is occurred during EVT, an unscheduled visit to evaluate the patient may be needed (at the Investigator's discretion).

4.8.5 Visit 5 （discharge）

The following will occur during Visit 5, which is an on-site visit:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; medications information; AEs/SAEs; any complications; time-related outcomes [length of assisted ventilation, stay in hospital, stay in the neurological intensive])

4.8.6 Visit 6 (Day 30±7 days)

The following will occur during Visit 6, which is a telephone contact:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; mRS; any complications)

4.8.7 Visit 7 (Day 90±14 days)

The following will occur during Visit 7, which is a telephone contact:

1) Collection of data in CRF (visit date; type of visit; NIHSS; GCS; mortality; mRS; any complications)

4.8.8 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits, e.g., to evaluate SAEs.

See details for definition of assessments/outcomes in Appendix B.

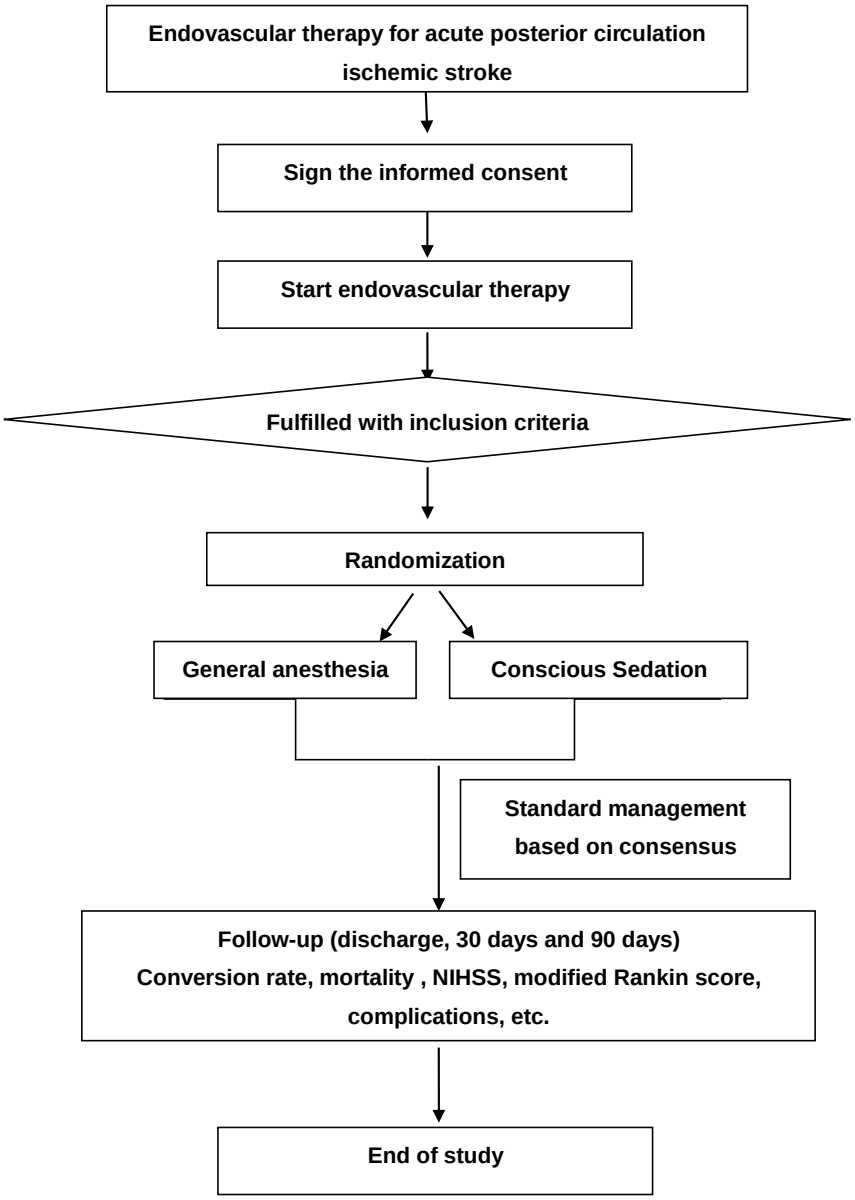
4.8.9 schedule of data collection

	STUDY PERIOD					
	Enrollment	Allocation	Post-allocation			
TIMEPOINT	At arrival	After evaluation	During treatment	Discharge	30±7 days after treatment	90±14 days after treatment
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS						
GA			X			
LA/CS			X			
ASSESSMENTS						
Demographical data	X					
Stroke data	X					
Work-flow time	X	X	X			
Peri-op vital signs			X			
EVT information			X			
mTICI			X			
mRS	X				X	X
NIHSS	X			X	X	X
GCS	X			X	X	X
AEs/SAEs			X	X		
All-cause mortality						X
Any complications			X	X	X	X
length of stay				X		
NICU stay and length				X		
Converting rate			X			

Tables marked in blue indicate completion by the independent follow-up team.

GA: general anesthesia; LA/CS: local anesthesia/conscious sedation; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; mTICI: modified Thrombolysis in Cerebral Infarction Scale

4.9 Participant timeline



4.10 Safety Monitoring and Reporting

4.10.1 Definition of AE

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to an intervention, whether considered causally related to the intervention. An undesirable medical condition can be

symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, abnormal breathing), or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an

AE can include an undesirable medical condition occurring at any time, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs. In this study, serious AEs (SAEs) will be collected.

4.10.2 Definition of SAE

An SAE is an AE occurring during any study phase, which fulfils one or more of the following criteria:

1) Results in death
2) Is immediately life-threatening
3) Requires in-patient hospitalization or prolongation of existing hospitalization
4) Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
5) Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further details, see Appendix C.

4.10.3 Recording and reporting of AEs

All adverse events associated with this study will be closely monitored until the adverse event is resolved, the situation is stable, or it can be confirmed that the adverse event is not related to this study. In the event of any adverse event, it should be reported to the study immediately, along with notification to the study principal, to determine the severity

of the adverse event and the impairment it caused. All adverse events related to this study will be recorded and reported to the Ethics Committee within one week as part of the annual report. The study principal is responsible for all adverse event reporting.

The possibility of missing patients during follow-up requires standardized training in follow-up and establish a network of patient contacts.

The following variables will be collected for each AE fulfilling SAE criteria:

1) AE (verbatim)
2) The date when the AE started and stopped
3) Maximum intensity
4) Whether the AE is serious or not
5) Outcome
6) In addition, the following variables will be collected for SAEs:
7) Date AE met criteria for SAE
8) Date Investigator became aware of SAE
9) AE is serious due to
10) Date of hospitalization
11) Date of discharge
12) Probable cause of death
13) Date of death
14) Autopsy performed
15) Causality assessment in relation to study procedure(s)
16) Causality assessment in relation to other procedure(s)
17) Description of AE

For further details, see Appendix C.

4.11 Data confidentiality management

All raw data will be placed in a dedicated locker. In addition, all researchers should follow the rules of professional confidentiality and must keep all personally identifiable and medical information of patients confidential. The paper clinical report form will be destroyed two years after the completion of the study. The electronic data will be encrypted and preserved after hiding the patient's personal information, and access to the database will be restricted. All the work of data confidentiality management shall be carried out by designated data management team which is established by the principal investigator (PI) and independent statisticians. The PI will regularly inspect the content of the forms and database to ensure accurate and timely data entry, follow-up, and recruitment progress, as well as count withdrawal and loss-to-follow-up rates. At the end of this study, at least 20% of the clinical report forms will be randomly selected by the research department for integrity and authenticity review.

4.12 Monitoring and auditing

The study center and all data, including raw data, must be monitored by the responsible unit. Data Monitoring Committee (DMC) will randomly select no less than 20% of enrolled patients from all case report forms in accordance with the monitoring plan and review the completeness and authenticity of the data against the registry's original documentation. All data corrections to the database will be electronically recorded in an audit trail. Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and good clinical practice (GCP)/regulatory compliance. A risk-based approach to monitoring will be applied. A mix of monitoring strategies will be implemented: on-site and remote monitoring (site-level monitoring activities performed at a location other than the

research center). Monitoring strategies will be tailored to risks, permit timely oversight, and will be focused on Critical Processes and Critical Data.

4.13 Statistical Analysis

Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. The data will be analyzed on intention-to-treat and per protocol, however, the conclusion will be drawn according to the intention- to- treat analysis. The intention- to-treat analysis will depend on our definition in *Statistical Analysis Plan* (The Intent-to-treat population will comprise of all subjects randomized to receive at least one type of anesthesia and with 90-days mRS score) while the per- protocol population will consist of all subjects in the ITT population not identified as protocol violators. Differences in the primary endpoint will be compared between groups using Cochran- Mantel- Haenszel test. STATA V.14.0 and SPSS 26.0 for windows will be used for all statistical analyses. The statistical significance will be declared at type I error of 0.05. See Statistical analysis plan for details.

5. Ethics, approvals, and dissemination

5.1 Research ethics

Clinical studies will follow the World Medical Assembly Declaration of Helsinki and other relevant regulations. The 18th World Medical Declaration and the Code of Practice for the Administration of Clinical Trials of Medicinal Products will guide all applications of the amendments. The clinical study will be implemented only after approval of the trial protocol by the Ethics Committee prior to the start of the study. Progress reports of the clinical trial

and a summary of clinical results after the clinical trial is completed should be submitted to the ethics committee annually.

5.2 Patient protection

Before each subject is enrolled in this study, it is the responsibility of the investigator to provide the subject or his or her representative with a complete and comprehensive description of the purpose, procedures and possible risks of the study and to sign a written informed consent, which should make the subject aware of their right to withdraw from the study at any time, and the informed consent should be retained as a clinical study document for review. The investigator should inform the subject about the study to the maximum extent possible in a language or terminology that the subject can understand. Subjects' personal privacy and data confidentiality will be protected during the study. Informed consent will be completed in a separate surgical interview room to avoid invasion/disclosure of patient privacy.

5.3 Informed Consent

Prior to participation in a clinical trial, the patient's legal representative should sign an informed consent form (name and date) with the investigator. If the legal representative is unable to read it, a witness is present throughout the informed process and signs it. The investigator should provide a copy of the signed informed consent form to the patient or the legal representative. The Principal Investigator(s) will:

1) Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
2) Ensure each patient is notified that they are free to discontinue from the study at any time

3) Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
4) Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
5) Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
6) Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

5.4 Protocol amendments

The principal investigator will be responsible for any decision to amend the protocol. If there is any modification (e.g., changes to eligibility criteria, outcomes, analyses), the principal investigator will communicate and gain approval from the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University prior to implementation and communicate with relevant parties.

5.5 Confidentiality

In accordance with GCP principles, the supervisory team (TSC/DMC) should verify the CRF against the original information. informed consent will include a statement that the patient is allowing authorized sponsors, ethics committees, and authorities direct access to relevant original information on the case report form (e.g., the patient's medical file, appointment records, original laboratory records, etc.). Researchers are expected to follow professional confidentiality rules and must keep all personally identifiable or medical information about the patient confidential.

5.6 Declaration of interests

CANVAS II Investigators report no conflicts of interest.

5.7 Dissemination policy

The findings of the study will be published in peer- reviewed journals and will be presented at national or international conferences.

5.8 Date sharing

The original research data can be shared only after contacting PI and obtaining the agreement of the research institution.

6. Trial closure

6.1 End of trial

The end of the trial will be defined as when the last participant has completed follow-up (Last participant, last follow-up). At this point, we will submit the 'Declaration of end of trial' to the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University.

6.2 Early discontinuation of the trial

This study has no interim analysis and no plan for early termination unless the data monitoring committee and the ethics committee stop it due to serious adverse events.

7. Trial management and oversight

7.1 Trial Management Group (TMG)

The TMG comprises the CANVAS II Trial Investigators – led by the Chief Investigator (PI). The day-to-day trial team will comprise the Chief Investigator, Clinical Trials Unit co-investigators (PX) alongside Trial Statisticians, Research Assistant. Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from another related research.

TMG members of this study are as follows:

PI: Ruquan Han (the chair), MD, PHD, Professor and Chairman of Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

PX: Fa Liang, MD, Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

PX: Xiaochuan Huo, MD, Professor of Department of Interventional Neurology, the Beijing Tiantan hospital, Capital Medical University

Data Manager: Youxuan Wu, MD, Minyu Jian, MD Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

Trial Statisticians: Anxin Wang, PHD, Department of Statistics, China National Clinical Research Centre for Neurological Diseases, Beijing

7.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established in line with the latest NIHR HTA guidelines. The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards. The TSC will be comprised by a majority of independent members (including the Chair) and include Patient and Public Involvement (PPI) representatives, in addition to the Chief Investigator. TSC members of this study are as follows:

Steering Committee:

Ruquan Han (the chair), MD, PHD, Professor and Chairman of Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University

Matthew TV. Chan, MD, PHD, Professor of Department of Anesthesia and Intensive Care, the Chinese University of Hong Kong

Zhongrong Miao, MD, PHD, Professor and Chairman of Department of Interventional Neurology, the Beijing Tiantan hospital, Capital Medical University

Haiyang Liu, MD, Department of Anesthesiology, the Beijing Tiantan hospital, Capital Medical University.

Anxin Wang, PHD, Department of Statistics, China National Clinical Research Centre for Neurological Diseases, Beijing.

7.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. The DMC will review all safety and efficacy data (endpoint data, SAEs), overall and by research center, on an ongoing basis. DMC members of this study are as follows:

Data Monitoring Committee:

Dongxin Wang MD, PhD, Professor and Chairman of Department of Anesthesiology and Critical Care Medicine, Peking University First Hospital, Beijing, China.

Nan Li MD, PhD, Professor, Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, China.

Liping Liu, MD, PHD, Professor and Chairman of Department of Neurointensive Care Unit, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

7.4 Patient and Public Involvement (PPI).

Not involved.

8. Sponsorship and funding

8.1 Sponsorship and indemnity

Beijing Tiantan Hospital, Capital Medical University

8.2 Funding

Clinical Medicine Development of Special Funding Support (ZYLX201708; DFL20180502) and the Beijing Municipal Science & Technology Commission (Z19110700660000).

9. Reference

1. Vos T, Barber RM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386:743-800.

2. Lee YY, Yoon W, Kim SK, et al. Acute Basilar Artery Occlusion: Differences in Characteristics and Outcomes after Endovascular Therapy between Patients with and without Underlying Severe Atherosclerotic Stenosis. AJNR Am J Neuroradiol 2017; 38:1600-1604.

3. Kim YW, Hong JM, Park DG, et al. Effect of Intracranial Atherosclerotic Disease on Endovascular Treatment for Patients with Acute Vertebrobasilar Occlusion. AJNR Am J Neuroradiol 2016; 37:2072-2078.

4. Gao F, Lo WT, Sun X, Mo DP, Ma N, Miao ZR. Combined Use of Mechanical Thrombectomy with Angioplasty and Stenting for Acute Basilar Occlusions with Underlying Severe Intracranial Vertebrobasilar Stenosis: Preliminary Experience from a Single Chinese Center. AJNR Am J Neuroradiol 2015; 36:1947-52.

5. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372:11-20.

6. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372:1019-30.

7. 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; 372:2285-95.

8. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372:1009-18.

9. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372:2296-306.

10. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015; 46:3020-35.

11. Gory B, Eldesouky I, Sivan-Hoffmann R, et al. Outcomes of stent retriever thrombectomy in basilar artery occlusion: an observational study and systematic review. J Neurol Neurosurg Psychiatry 2016; 87:520-5.

12. van Houwelingen RC, Luijckx GJ, Mazuri A, Bokkers RP, Eshghi OS, Uyttenboogaart M. Safety and Outcome of Intra-Arterial Treatment for Basilar Artery Occlusion. Jama Neurol 2016; 73:1225-1230.

13. Singer OC, Berkefeld J, Nolte CH, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. Ann Neurol 2015; 77:415-24.

14. Brinjikji W, Murad MH, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2015; 36:525-9.

15. Abou-Chebl A, Yeatts SD, Yan B, et al. Impact of General Anesthesia on Safety and Outcomes in the Endovascular Arm of Interventional Management of Stroke (IMS) III Trial. Stroke 2015; 46:2142-8.

16. Wang A, Abramowicz AE. Role of anesthesia in endovascular stroke therapy. Curr

Opin Anaesthesiol 2017; 30:563-569.

17. Jadhav AP, Bouslama M, Aghaebrahim A, et al. Monitored Anesthesia Care vs Intubation for Vertebrobasilar Stroke Endovascular Therapy. Jama Neurol 2017; 74:704-709.

18. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Republished: Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: Anesthetic management of endovascular treatment for acute ischemic stroke. Stroke 2014;45: e138-50.

19. Peng Y, Li Y, Jian M, et al. Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke: Protocol for a randomized controlled (CANVAS) trial. Int J Stroke 2017; 12:991-997.

20. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006; 37:922-8.

10. Appendices

Appendix A. Definition of stroke

Acute ischemic stroke:

The definition for acute stroke is based on the standardized definitions (Hicks et al 2015).

An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered to be an ischemic stroke:

1) Rapid onset (or existence on awakening) of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)

2) Rapid worsening of an existing focal neurological deficit (e.g., the index stroke event) that is judged by the investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non-ischemic etiology. The progression of original angiogenic ischemic stroke (i.e., NIHSS increase ≥ 4 on the basis of primary ischemic stroke, excluding post infarction hemorrhage transformation or symptomatic intracranial hemorrhage), accompanied by new ischemic changes on head MRI or CT.

Etiological typing will be carried out according to TOAST criteria.

Acute ischemic stroke in the posterior circulation:

According to the above-described criteria, it is diagnosed as acute ischemic stroke, and it is preliminarily determined through imaging evidence (CT/CTA or MR/MRA) that the responsible vessels are the following vessels:

1) Basilar artery

2) Vertebral artery

3) Posterior cerebral artery

In CANVAS-II, imaging evidence are mainly based on CT and CTA, and the onset time described above is limited to less than 24 hours.

TOAST criteria

Large atherosclerotic	The patient's acute cerebral infarction was caused by moderate stenosis of intracranial large vessels, or brain CT and MRI showed that the diameter of the focus of acute cerebral infarction was greater than 1.5cm.
Cardiogenic	The focus of acute cerebral infarction is bilateral and cannot be explained by a single blood vessel. It is necessary to check whether there are cardiac diseases such as atrial fibrillation and atrial myxoma.
Arteriole occlusion	Normal CT or MRI examination of the head or the diameter of the infarct is less than 1.5cm.
Other etiological	Acute cerebral infarction caused by causes other than the above

	three causes
Unexplained	Two or more causes or no cause has been found so far.

CANVAS-II focused on patients with large atherosclerotic and cardiogenic subtypes, which are the main types suitable for EVT intervention.

wake-up stroke

It refers to patients with acute cerebral infarction who have no new stroke symptoms before sleeping but are found to have stroke symptoms by the patient himself or witnesses after awakening.

Appendix B Efficacy and Safety assessment

Efficacy assessment

1.mRS score

mRS score will be used as the main assessment to evaluate the prognosis of neurological function. mRS scores will be collected for all patients at Visit 1 by the neuroradiologist with an on-site visit, and at Visit 6, Visit 7 by the independent follow-up team with a telephone contact. mRS≤2 is defined as neurological independence. The following questionnaire will be used to determine the mRS score:

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
	Derived from: the Internet Stroke Center at www.strokecenter.org

2.NIHSS score

NIHSS scores at the time of randomization will be collected for all patients to verify patient eligibility. The scores will also be used to assist in the analysis of the disability endpoint. NIHSS score will be collected for all patients at Visit 1by the interventional physician with an on-site visit and at Visit 5, Visit 6, Visit 7 by the independent follow-up team with an on-site visit or a telephone contact. The following questionnaire will be used to determine the NIHSS score:

Interval: [] Baseline [ ] discharge [ ] 23-37 days [ ] 76-104 days

[ ] Other _____ (___ ___) Time: ___ ___: ___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, notwhat the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube,	0 = Alert; keenly responsive 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond	

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.	2 = Not alert; requires repeated stimulation to attend, or isobtunded 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 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 him or her (pantomime), and the result scored (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 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	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	

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.		
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 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	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	

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 respond to item 11.		
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 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	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)	

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.	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 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.	0 = Absent 1 = Present in one limb 2 = Present in two limbs UN = Amputation or joint fusion, explain: _____	
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss; patient	

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	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	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	

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.	of speech and/or comprehension, however, makes conversation 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	0 = Normal 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty 2 = Severe dysarthria; patient's speech is so	

speech can be rated. Only if the 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.	slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthria UN = Intubated or another 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 anosognosia 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	

How to evaluate NIHSS score of comatose patients?

For patients with a score of less than 3 on item 1a, each item should be assessed according to the actual state. Item 1a is rated 3 only when the patient is completely unresponsive to any noxious stimuli (rubbing the sternum, pressing the orbit, etc.) and only has reflex activity.

If 1A = 3 points, other items shall be evaluated as:

1b. LOC Questions -2 **1c. LOC commands**-2 **2. Best Gaze** -1 (overcome by the head-eye reflex) or 2 (cannot overcome by the head-eye reflex) 3.**Visual**- assessment using visual threat **4. Facial Palsy**-3 **5. Motor Arm / 6. Motor Leg -** 4 for each limb **7. Limb Ataxia-** score can be given only when there is ataxia. If the patient's muscle strength decreases and cannot complete any examination of ataxia, 0 point will be given **8. Sensory**-2 **9. Best Language**-3 **10. Dysarthria**-2 **11. Extinction and Inattention (formerly Neglect)**-2

3.Glasgow Coma Score

Glasgow Coma scores at the time of randomization will be collected for all patients to verify patient eligibility. The scores will also be used to assist in the analysis of the disability endpoint. Glasgow Coma score will be collected for all patients at Visit 1 by the interventional physician with an on-site visit and at Visit 5, Visit 6, Visit 7 by the independent follow-up team with an on-site visit or a telephone contact. The following questionnaire will be used to determine the Glasgow Coma score:

Interval: [ ] Baseline [ ] discharge [ ] 23-37 days [ ] 76-104 days

[ ] Other _____ (___ ___) Time: ___ ___: ___ ___ [ ]am [ ]pm

Person Administering Scale _____

Eyes opening Response	Spontaneous--open with blinking at baseline	4
	To verbal stimuli, command, speech	3
	To pain only (not applied to face)	2
	No response	1
	Cannot open eyes due to swollen eyes, fractures, etc.	C
Verbal response	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
	Unable due to intubation or pneumotomy	T
Motor response	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension response in response to pain (decerebrate posturing)	2
	No response	1
Total score		

4.mTICI score

mTICI score will be used to evaluate vascular reperfusion and assist in the evaluation of two anesthesia methods. mTICI score will be collected for all patients at Visit 2 by the interventional physician with an on-site visit. The following questionnaire will be used to determine the mTICI score:

Time: ___ ___: ___ ___ [] am [] pm _____ / ____ / ___(Y /M / D)

Person Administering Scale _____

mTICI	Definitions
Grade o	No antegrade reperfusion at the occluded site and distal end of the responsible vessel
Grade I	antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade IIa	antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g., in one major division of the middle cerebral artery (MCA) and its territory)
Grade IIb	antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g., in two major divisions of the MCA and their territories)
Grade III	complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

5.Work-flow time:

Work-flow time will be recorded to compare the effect of the two anesthesia methods on the patient's time to achieve recanalization. It will be collected for all patients at Visit 2 by the resident anesthesiologist or the attending anesthesiologist with an on-site visit. The definitions of each time period are as follows:

From onset to emergency: It refers to the period from the symptom onset moment to the time when the patient arrives at emergency room after symptoms.

wake-up stroke: It refers to the period from the last asymptomatic moment to the time when the patient arrives at the emergency room after symptoms.

From onset to door: It refers to the period from the symptom onset moment to the time when the patient arrives at the operation room before EVT.

wake-up stroke: It refers to the period from the last asymptomatic moment to the time when the patient arrives at the operation room before EVT.

From onset to puncture: It refers to the period from the symptom onset moment to the time beginning of EVT for groin puncture.

Wake-up stroke: It refers to the period from the last asymptomatic moment to the time beginning of EVT for groin puncture.

Door to puncture: It refers to the period from the moment arriving at the operation room to the time beginning of EVT for groin puncture.

Door to reperfusion: It refers to the period from the moment arriving at the operation room to the time of first-time recanalization (maintenance time > 10min). For patients who need thrombectomy or stent placement due to re-occlusion after 10 minutes of reperfusion, the Door to reperfusion time is calculated according to the time achieving first recanalization. For patients

who have not achieved recanalization (mTICI=0), the Door to reperfusion time is calculated according to the time starting femoral artery suturing.

Puncture to reperfusion: It refers to the period from the moment beginning of EVT for groin puncture to the time of first-time recanalization (maintenance time > 10min). For patients who need thrombectomy or stent placement due to re-occlusion after 10 minutes of reperfusion, the Puncture to reperfusion time is calculated according to the time achieving first recanalization. For patients who have not achieved recanalization (mTICI=0), the Puncture to reperfusion time is calculated according to the time starting femoral artery suturing.

Operating time: It refers to the time from the moment beginning groin puncture to the moment completing femoral artery suture.

6. Other safety outcomes:

Death

All deaths occurring post-randomization and up to 90 days (Visit 7) will be considered endpoints. Relevant data is mainly completed by the independent follow-up team with a telephone contact.

There are three causes of death: 1. Cardiovascular death 2. Non-cardiovascular death 3. Unknown cause

Cardiovascular death: Death from vascular causes includes death from stroke, sudden cardiac death, death from acute myocardial infarction, death from heart failure, pulmonary embolism, death from cardiac / cerebrovascular intervention or surgery (unrelated to acute MI), and death from other cardiovascular causes [such as arrhythmias unrelated to sudden cardiac death, rupture of aortic aneurysm, or peripheral arterial disease].

Any death with unknown / unclear cause within 90 days after stroke, myocardial infarction or cardio cerebrovascular operation / operation will be regarded as death caused by stroke, myocardial infarction or cardio cerebrovascular operation / operation, respectively.

Non-Cardiovascular death: include deaths due to bleeding (including gastrointestinal bleeding), pulmonary causes (respiratory failure, pneumonia), malignant tumors, trauma, suicide, infection / sepsis, or any other well-defined (such as liver failure or renal failure)

Time-related outcomes

Relevant data is mainly completed by the independent follow-up team by an on-site visiting at discharge (Visit 5).

Length of assisted ventilation: The length of time that the patient needs endotracheal intubation to assist breathing during hospitalization. Patients may need endotracheal intubation if they have the following conditions:

1) Endotracheal intubation was performed during EVT treatment. After treatment, retain endotracheal intubation and continue treatment in the neurological intensive care unit.

- During EVT with CS, it is suspected that the disease is progressing, respiratory dysfunction (SpO2 cannot be maintained, or serious reflux aspiration) occurs, and the CS is converted to GA. It is expected that it will not recover in a short time after treatment, and retaining tracheal tube is required for a period of time.

- During EVT with GA, a large amount of gastric contents were aspirated through intubation, which confirmed that the patient had been complicated with serious

aspiration before operation.

- During EVT with GA, the patient's respiratory status could not meet the extubation criterion (Spontaneous breathing, tidal volume ≥ 300ml, breath rate≥12 times/min, SpO2 maintained at ≥90% under oxygen concentration of 30-40%, EtCO2 maintain ≤ 45mmHg) and a long time of attempts (>1 hour) even had been tried.

- Requirements of the attending neurointerventional physician

2) In the neurointensive care unit, the patient developed respiratory failure and required endotracheal intubation assistance as the disease progressed. Patients may develop severe respiratory dysfunction in the following conditions.

- severe cerebral edema

- intracerebral hemorrhagic transformation

- Infarct enlargement/ new infarct

- severe pneumonia

- Obstruction of upper airway (e.g., gloss coma, laryngospasm) due to various causes (e.g., coma, excessive secretions)

Whether or when to remove endotracheal intubation is decided by the competent neurocritical care physician according to the patient's condition

Length of Staying in the neurological intensive care unit (NICU) or hospital:

Hospital stays: the time from EVT (date and time) to discharge.

NICU stay time: including the time of first and second entry into NICU.

The criteria for leaving NICU or discharge shall be determined by the competent neurocritical care physician.

Complication:

The following complications occurring post-randomization and up to 90 days (Visit 7) will be considered endpoints. Relevant data is mainly completed by the independent follow-up team with a telephone contact and review electronic medical records.

Post infarction hemorrhagic transformation

Hemorrhage may be a consequence of an ischemic stroke (the index event or a subsequent stroke), i.e., a hemorrhagic transformation. Hemorrhagic transformations may be either symptomatic or asymptomatic.

Symptomatic hemorrhagic transformation of an ischemic stroke must have imaging evidence of extravascular blood within an area of known acute/subacute infarction that is judged to be nontraumatic and at least partially responsible for the patient's clinical neurological deterioration with neurological symptoms out of proportion to what would be expected for the size and location of the infarction.

Asymptomatic hemorrhagic transformation of an ischemic stroke must have imaging evidence of any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, with no detected worsening of neurological symptoms related to the hemorrhage.

myocardial infarction (MI)

Criteria for acute myocardial infarction: general definition of the Third Edition (Thygesen 2012).

If there is clinical evidence of myocardial necrosis consistent with acute myocardial ischemia, MI should be diagnosed. MI is diagnosed when any of the following criteria are met:

Cardiac biomarkers (preferably troponin [cTn]) are detected to be elevated or then decreased after elevated, with at least one value greater than the 99% upper limit of the reference value (URL), and at least one of the following:

1) Clinical symptoms of myocardial ischemia

2) New myocardial ischemia changes on the ECG, namely new ST-segment changes or left bundle branch block (LBBB) [according to whether there is ST-segment elevation on the ECG, it is divided into acute ST-segment elevation myocardial infarction (STEMI) and non-acute ST-segment elevation myocardial infarction (NSTEMI)]

3) Pathological Q waves on the ECG

4) Imaging suggests new deactivated myocardium or new segmental wall motion abnormalities

5) Angiographic or autopsy-proven coronary thrombosis

Pulmonary embolism (PE)

Gold standard: radionuclide pulmonary ventilation/perfusion (V/Q) imaging scan is highly suspected, or confirmed by pulmonary angiography or spiral CT, or confirmed by autopsy.

Other aids in diagnosis:

Signs and symptoms of pulmonary embolism comprise sudden onset of dyspnea or deterioration of existing dyspnea, chest pain, syncope or dizziness due to hypotension or shock, hemoptysis, tachycardia, or tachypnoea.

Abnormalities on chest radiography, electrocardiography, or blood gas analysis are not specific for pulmonary embolism but might be useful in the differential diagnosis.

About 70% of patients with symptomatic pulmonary embolism have concomitant deep vein thrombosis, which is symptomatic in up to a quarter of cases. Conversely, silent pulmonary embolism is present in at least a third of patients with symptomatic deep vein thrombosis.

D-dimer abnormally increase (>500 µg/L).

Pneumonia

Hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) are the main type observed. According to the guidelines, the diagnosis of HAP and VAP requires all of the following:

- New lung infiltrates on chest imaging
- Respiratory decline
- Fever
- Productive cough

Absence of a new infiltrate significantly lowers the probability of VAP and can guide the clinician to alternative causes of inpatient respiratory decline, including pulmonary

embolism. Once an infiltrate is observed and HAP or VAP is suspected as the cause of respiratory decline, several noninvasive tests are recommended to assist in diagnosis.

- Blood cultures
- Sputum cultures
- Polymerase chain reaction
- Procalcitonin testing

Deep venous thrombosis (DVT)

Clinical manifestations of deep vein thrombosis of the legs include swelling or pitting oedema, redness, tenderness, and presence of collateral superficial veins. The compression ultrasonography confirms mid-echoic, or hypoechoic filling of the veins.

Indicators during treatment

The follow indicators during treatment (Visit 2) will be completed by the attending anesthesiologist with an on-site visit:

Hypotension: intraoperative systolic blood pressure lower than 120mmHg. When hypotension occurs, timely administration of vasoactive drugs to raise blood pressure

Dysphoria or motion: physical movement that interferes with the operator's operation, requiring a brief cessation of the operation or increased sedation

Conversion rate from CS to GA: detail in section 4.34

Intraoperative physiological parameters :

BP：monitoring noninvasive pressure, which is measured every 5 minutes.

HR: continuous monitoring through ECG monitoring and recording every 5 minutes.

SpO2: Continuous monitoring through oxygen monitoring and recording every 5 minutes.

EtCO2: monitored via anesthetic gas sample line at nasal vestibule in CS group and via endotracheal intubation at trachea in GA group.

Oxygen concentration: in CS group, recorded the oxygen flow value when the mask inhaled oxygen and the inhaled oxygen concentration was calculated by the formula:

Oxygen concentration (%) = 21 + Inhaled oxygen flow （L/min）× 4

in GA group, recorded the output oxygen concentration from the anesthesia machine.

Appendix C Additional safety information

Further guidance on the definition of a serious adverse event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the interventions would result in the patient's death (e.g., In CS group, sudden body movement caused vascular perforation and massive intracranial hemorrhage).'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., pneumonia resolved without respiratory failure).

Hospitalization

Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. (e.g., combined with chronic arterial stenosis, stenting was performed during follow-up).

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect intervention does not mean that it is an important medical

event; medical judgement must be used.

Possible serious adverse event and emergency plans during perioperative period

1) Respiratory dysfunction

Closely monitor the patient's respiratory function. Once the patient has respiratory dysfunction (EtCO2 exceeds 60mmHg or SpO2<92%), immediately stop the surgical operation and give the patient assisted ventilation. And converse from CS to GA, tracheal intubation, to ensure airway safety. At the same time, analyze the reasons and record in detail.

2) Severe hypotension

Closely monitor the patient's circulatory system and strictly control blood pressure according to the consensus of AIS intravascular anesthesia management. Once patients have severe hypotension (SBP < 120mmHg), they should be actively treated with vasoactive drugs. Analyze the reasons and deal with them.

3) respiratory and cardiac arrest:

Stop the operation immediately; Immediately perform external cardiac compression and electric defibrillation; Endotracheal intubation and mechanical ventilation; Intratracheal or intravenous administration of resuscitation drugs (epinephrine and vasoactive drugs, antiarrhythmic drugs and others); analyze the reasons and deal with them.

4) Acute myocardial infarction:

Prompt and definite diagnosis; suspend the operation or complete the operation as soon as possible; Sufficient oxygen supply; Apply inotropic drugs (dopamine, norepinephrine, etc.); Intensive intraoperative monitoring (MBA, CVP, T, urine output); Coronary expansion treatment, and reduce myocardial preload and myocardial oxygen consumption.

5) Acute pulmonary embolism:

Suspect diagnosis; Immediately carry out cardiopulmonary resuscitation when necessary; Endotracheal intubation to ensure adequate oxygen supply and analgesia; Control the treatment of heart failure and arrhythmia; Anti shock and anticoagulation therapy.

6) Arrhythmia

Clarify the type and cause of arrhythmia; Treat the cause immediately; Prevent the recurrence of arrhythmia while terminating the attack of arrhythmia and striving for radical cure; Pay attention to the side effects caused by treatment while actively treating.

7) Intracranial hemorrhage

Keep the airway unobstructed; Give respiratory support; Maintain hemodynamic stability; Give drug support when necessary; Patients with significant intracranial pressure increase were treated with hyperventilation, osmotic diuretics and hormone therapy to reduce brain edema.

8) Malignant hyperthermia

Stop all anesthetic drugs and operations immediately, hyperventilate with pure oxygen, and promote CO2 emission; Active cooling treatment; Correct acidosis; Rehydration and diuresis; Use a lot of hormones; Apply anti skeletal muscle contracture drugs.

9) Hypertensive crisis

When the blood pressure reaches 220/140-150mmhg, it can be regarded as a crisis. Rapid blood pressure reduction is the only effective method to prevent further damage to important organs such as heart, brain and kidney; Artificial hibernation to prevent hypertensive convulsion; Reduce intracranial pressure.

10) Bronchospasm

Clear incentives and eliminate stimulating factors; If the anesthesia is too shallow, the anesthesia should be deepened; Inhale oxygen, assist or control breathing; Symptomatic treatment, intravenous infusion of corticosteroids, aminophylline, etc.

11) Adverse drug reactions

Stop administration immediately and treat symptomatically; Patients with severe allergy may have bronchospasm, airway edema, hypotension, etc., and should be treated with antispasmodic, fluid infusion and pressor drugs. If there is airway obstruction, all methods should be used to ensure effective ventilation; Use diazepam to prevent convulsion. In case of convulsion, immediately use drugs to relieve convulsion and protect patients from accidental injury.

This plan should be adjusted according to the actual condition of the subjects.

*Ch*oice of *AN*esthesia for Endo-*VAS*cular treatment of acute ischemic stroke in the posterior circulation (CANVAS II)

Statistical Analysis Plan

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Contents

1 Introduction

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2 Study Objective(s) and Endpoint(s)

2.1 Study Objective(s)

The primary objective of this study is to detect the difference of the post-procedural neurological function in patients with posterior circulation AIS under general anesthesia (GA) and conscious sedation (CS), and hence to observe the effect of anesthesia type on outcomes after endovascular treatment (EVT).

The secondary objectives of this study include:

- To assess secondary outcome including:
  - Change in NIHSS (National Institutes of Health Stroke Scale).
  - The score of mTICI (modified Thrombolysis in Cerebral Infarction).
  - All- cause mortality.
  - Time intervals and time-related outcomes, such as from onset to emergency, from onset to door, from onset to puncture, from onset to reperfusion, door to puncture, door to reperfusion, puncture to reperfusion, operating time, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care

unit, so on.

- Adverse events during treatment, such as hypotension, dysphoria, or motion.
- Complications after treatment, such as pulmonary infection, deep venous thrombosis and hemorrhagic transformation.
- The rate of conversion from CS to GA

- To assess whether there are differential treatment effects in predefined subgroups:
  - age.
  - sex.
  - Baseline NIHSS score.
  - Time from onset of stroke to EVT.
  - Site of arterial occlusion.
  - mTICI score.

2.2 Study Endpoint(s)

For definitions and measurements of outcomes, see appendices at the end of protocol version 1.4.

2.2.1 Primary Outcome

The primary endpoint is the neurological disability at 90 days after EVT measured by mRS, which ranges from 0 (no symptoms) to 6 (death), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS ≤2. The score will be evaluated by outcomes assessor who are blinded to allocation.

2.2.2 Secondary Outcome

- Change in NIHSS, from baseline to 24 hours, 7 days (or at discharge), 30 days and 3 months after randomization.
- Score of mTICI will be evaluated before and after endovascular treatment.
- All- cause mortality up to 3 months after randomization.
- Time intervals, such as from onset to emergency, from onset to door, from onset to puncture, from onset to reperfusion, door to puncture, door to reperfusion, puncture to reperfusion, operating time.
- Time-related outcomes, such as, length of assisted ventilation, length of stay in hospital, length of stay in the neurological intensive care unit after randomization.
- Incidence of adverse events associated with this study, such as hypotension, dysphoria or motion.
- Incidence of complications up to 3 months after randomization.
- Rate of conversion from CS to GA.

3 Statistical Hypotheses

The primary endpoint for this study will be the favorable neurological outcome at 3 months (mRS ≤2) after treatment.

The null hypothesis of no difference in this rate between the two treatment groups will be tested using a two-sided test at the 5% level of significance.

H0: $\lambda 1/\lambda 2 = 1$

H1: λ1/λ2 ≠1

Where λ1 is the rate of 3 months favorable neurological outcome in the GA group and λ2 is the same endpoint in the CS group.

4 Study Design

This randomized, parallel-group, exploratory trial was carried out at Beijing Tiantan Hospital, Capital Medical University, China, from January 2018 to December 2020, and was also approved by the Ethics Committee (KY2017-074-02).The primary null hypothesis of this single-center, randomized, parallel-group, exploratory trial clinical trial is, there is no difference in 90-day favorable neurological outcome rate between general anesthesia and conscious sedation in patients with acute posterior circulation stroke undergoing endovascular therapy.

Posterior circulation AIS patients who deemed suitable for recanalization of the culprit's vessels will be considered for recruitment in the study. The inclusion criteria are vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CT angiography (CTA)/magnetic resonance angiography (MRA), the modified Thrombolysis in Cerebral Infarction (mTICI) score ≤1, age ≥18 years, stroke onset to treatment time ≤24 hours and modified Rankin score ≤2 before onset. Patients with unclear radiological image to identify infarction and vessel occlusion, with intracranial hemorrhage (ICH), anterior circulation occlusion, Glasgow coma score (GCS)≤8, NIHSS score <6 or >30, post circulation Alberta Stroke Program Early CT Score (pc- ASPECTS) <6, pons- midbrain index ≥3, severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission, intubated before EVT, unconsciousness and known allergy to anesthetics or analgesics will be excluded from

the study. Patients whose legal relative refuses to participate will be excluded. Both the neuroradiologists and the attending anesthesiologists must agree that the patient is suitable with either GA or CS management before recruiting. Reasons why eligible patients are not recruited to the trial will be documented.

Patients meeting the inclusion criteria and exclusion criteria and offering informed content will be randomized into two group. In the conscious sedation group, patients received propofol (0.3–0.5 mg/kg) and then continuous infusion remifentanil (0.01–0.06 ug/kg/min) and propofol (1–2 mg/kg/h). In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask insertion with propofol (1–2 mg/kg), remifentanil (0.2–0.8 ug/kg) and muscle relaxant (rocuronium ,0.6 mg/kg), and then maintained with propofol (4–6 mg/kg/h) and remifentanil (0.05 to 0.1 ug/kg/min). This study is expected to be completed in two years, with 88 subjects recruited from Beijing Tiantan Hospital, Capital Medical University, China. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

5 Planned Analyses

The analyses that are detailed in this SAP will be performed only when the database has been frozen, all protocol violators identified, and treatment allocations have been unblinded. Membership of the Intent-to-Treat and Per Protocol populations will be determined using the rules set out in this SAP and will be determined prior to unblinding the treatment allocation. At a date to be agreed within the project team, a data look will be performed. This will involve production of all data displays on a subset of the data using dummy treatment codes. These are produced purely as an aide to the pre-programming of the study and no unblinding will

occur.

6 Sample Size Considerations

The PASS V.15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint—favorable outcome (mRS 0–2) at 3 months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only one indicated the association between anesthesia type and neurological outcome. In the case–control study of Jadhav et al, they reported the incidence of mRS≤2 at 90 days was 38.3% in CS and 31.1% in GA[1]. On the other hand, we reviewed posterior circulation AIS cases in our institution (Beijing Tiantan Hospital) and found that a higher incidence of favorable neurological outcome at 90 days in CS compared with GA group [64.7% (11/17) vs 34.9%(15/43)]. However, other factors including preoperative NIHSS score, preoperative intravenous thrombolysis treatment confound the results validity. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0–2 would require 44 in each group to achieve power of 80% at a two- tailed significant level of 0.05, with a drop- out rate of 5%.

7 Analysis populations

7.1 Intent-to-Treat Population

The Intent-to-treat (ITT) population will comprise of all subjects randomized to receive at least one type of anesthesia and with 90-days mRS score. Randomized subjects will be assumed to

have received trial treatment unless definitive evidence to the contrary exists.

The ITT Population will be used for tables of efficacy, demography, safety, health outcomes, listings of withdrawals after randomization, and all relevant listings. This population will be the primary population for analyses of all outcomes.

7.2 Per Protocol population

The Per Protocol (PP) population will consist of all subjects in the ITT population not identified as protocol violators. The decision to exclude a subject from the PP population will be made prior to breaking the blind. This population will be used for secondary analyses of all outcomes. For the Per Protocol Population, subjects will be analyzed according to the treatment received. If study treatment was changed then the subject will be considered a protocol violator (from the point of change onwards).

8 Treatment comparisons

The treatment comparison of interest in this study is the favorable neurological outcomes between general anesthesia and conscious sedation at 90-days, based on the ITT population.

9 General considerations for data analyses

STATA V.14.0 for windows will be used for all statistical analyses. Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data, skewed continuous data, and counts (percentage) for categorical data. Unless otherwise specified all significance tests will be two-sided at the alpha=0.05 level and all confidence intervals will be

95%.

10 Data handling conventions

10.1 Premature Withdrawal and Missing Data

If any subject withdraws prematurely from the study (prior to the final telephone follow-up at 3 months -/+ 2 weeks, they are required to complete the withdrawal record in the CRF. The reasons for withdrawal will be presented in a summary table.

Subjects who withdraw before the end of the study, but who do provide at least one postoperative measure for a particular endpoint, will be included in the analysis.

Subjects who do not be assessed at any timepoint after randomization will be excluded from analysis of rate of disability-free survival, recovery quality and safety outcomes, as no post-baseline data will be available.

11 Study Population

11.1 Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the per protocol population will be listed, and the total number of subjects being assessed at each timepoint will also be summarized by treatment group.

The number of subjects randomized, completed, and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.

A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or Randomized into the trial.

11.2 Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol. Subjects who commit protocol violations will be included in the ITT population but excluded from the per protocol population. These protocol violations will be shown in a listing. For subjects who violated the protocol in conscious sedation due to: unconscious; Glasgow Coma Scale decrease to or less than; increase of end- tidal carbon dioxide (ETCO2) ≥60 mm Hg and/or a decrease in pulse oxygen saturation (SpO2) <94% despite oxygen supplementation; agitation that cannot be controlled with sedation and/or restraint; seizure attack; vomiting; recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage, the analysis will only use data recorded prior to the violation.

A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from the per protocol population will be agreed by the study team prior to unblinding the study.

11.3 Demographic and Baseline Characteristics:

The following demographic information will be listed and summarized for subjects in each group: age, gender, BMI, medical history (hypertension, atrial fibrillation, coronary artery disease

(CAD), dyslipidemia, diabetes, (transient ischemic attack(TIA),past stroke), smoking, drinking, etiology (cardiogenic thrombosis, atherosclerosis) ,drug use(antiplatelet agent, anticoagulant agent, statin, hypoglycemic agent), American society of Anesthesiologists (ASA) physical status classification, premorbid modified Rankin Scale (mRS), clinical status at admission(modified Rankin Scale, NIHSS score, Glasgow Coma Scale, systolic blood pressure, mean arterial pressure),lesion location(basilar artery, vertebral artery V4 segment or BA combined V4), IV-tPA pretreatment.

Perioperative vital signs including preoperative supine blood pressure, heart rate, pulse saturation, PetCO2 et al. will also be listed and summarized in each treatment group.

12 Outcome analyses

STATA V.14.0 for windows will be used for all statistical analyses. Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data, skewed continuous data, and counts (percentage) for categorical data. Unless otherwise specified all significance tests will be two-sided at the alpha=0.05 level and all confidence intervals will be 95%.

12.1 Primary Analysis

Differences in the primary endpoint will be compared between groups using Cochran- Mantel-Haenszel test. Furthermore, primary outcome will be analyzed in the following subgroups: age, sex, baseline NIHSS score, time from onset of stroke to EVT, site of arterial occlusion, and mTICI score.

12.2 Secondary Analysis

Other categorical variables will be analyzed by $\chi 2$ test and continuous variables using the Student- t-test or Mann- Whitney U test.

12.3 Other Analysis

To allow for a varying number of follow-up measurements, for example, systolic blood pressure, the repeated measure analysis of variance methods with a mixed-model approach (treating time as a random effect and other covariates as fixed effects) will be utilized. The specific comparison of the change in each of those measurements between baseline and any specific post-baseline time point can be tested using linear contrast.

13 REFERENCES

1. Jadhav AP, Bouslama M, Aghaebrahim A, et al. Monitored Anesthesia Care vs Intubation for Vertebrobasilar Stroke Endovascular Therapy. *JAMA Neurol*. Jun 1 2017;74(6):704-709. doi:10.1001/jamaneurol.2017.0192

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Statistical Analysis Plan

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H0: $\lambda 1/\lambda 2 = 1$

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Where λ1 is the rate of 3 months favorable neurological outcome in the GA group and λ2 is the same endpoint in the CS group.

4 Study Design

This double-center, randomized, parallel-group, exploratory trial was carried out at Beijing Tiantan Hospital, Capital Medical University, and Baiyun Hospital, Guizhou Medical University, China, from January 2018 to December 2021 and was also approved by the Ethics Committee in the hospitals (KY2017-074-02; No. 8 in 2020).The primary null hypothesis is that, there is no difference in 90-day favorable neurological outcome rate between general anesthesia and conscious sedation in patients with acute posterior circulation stroke undergoing endovascular therapy.

Posterior circulation AIS patients who deemed suitable for recanalization of the culprit's vessels will be considered for recruitment in the study. The inclusion criteria are vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CT angiography (CTA)/magnetic resonance angiography (MRA), age ≥18 years, stroke onset to treatment time ≤24 hours and modified Rankin score ≤2 before onset. Patients with unclear radiological image to identify infarction and vessel occlusion, with intracranial hemorrhage (ICH), anterior circulation occlusion, Glasgow coma score (GCS)≤8, NIHSS score <6 or >30, post circulation Alberta Stroke Program Early CT Score (pc- ASPECTS) <6, pons- midbrain index ≥3, severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission, intubated before EVT, unconsciousness and known allergy to anesthetics or analgesics will be excluded from the study. Patients whose legal relative refuses to participate will be excluded. Both the

neuroradiologists and the attending anesthesiologists must agree that the patient is suitable with either GA or CS management before recruiting. Reasons why eligible patients are not recruited to the trial will be documented.

Patients meeting the inclusion criteria and exclusion criteria and offering informed content will be randomized into two group. In the conscious sedation group, patients received propofol (0.3–0.5 mg/kg) and then continuous infusion remifentanil (0.01–0.06 ug/kg/min) and propofol (1–2 mg/kg/h). In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask insertion with propofol (1–2 mg/kg), remifentanil (0.2–0.8 ug/kg) and muscle relaxant (rocuronium ,0.6 mg/kg), and then maintained with propofol (4–6 mg/kg/h) and remifentanil (0.05 to 0.1 ug/kg/min). This study is expected to be completed in three years, with 88 subjects recruited from Beijing Tiantan Hospital, Capital Medical University, and Baiyun Hospital, Guizhou Medical University, China. A Data and Safety Monitoring Board (DSMB) will regularly monitor safety during the study.

5 Planned Analyses

The analyses that are detailed in this SAP will be performed only when the database has been frozen, all protocol violators identified, and treatment allocations have been unblinded. Membership of the Intent-to-Treat and Per Protocol populations will be determined using the rules set out in this SAP and will be determined prior to unblinding the treatment allocation. At a date to be agreed within the project team, a data look will be performed. This will involve production of all data displays on a subset of the data using dummy treatment codes. These are produced purely as an aide to the pre-programming of the study and no unblinding will

occur.

6 Sample Size Considerations

The PASS V.15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint—favorable outcome (mRS 0–2) at 3 months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only one indicated the association between anesthesia type and neurological outcome. In the case–control study of Jadhav et al, they reported the incidence of mRS≤2 at 90 days was 38.3% in CS and 31.1% in GA[1]. On the other hand, we reviewed posterior circulation AIS cases in our institution (Beijing Tiantan Hospital) and found that a higher incidence of favorable neurological outcome at 90 days in CS compared with GA group[64.7% (11/17) vs 34.9%(15/43)]. However, other factors including preoperative NIHSS score, preoperative intravenous thrombolysis treatment confound the results validity. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0–2 would require 44 in each group to achieve power of 80% at a two- tailed significant level of 0.05, with a drop- out rate of 5%.

7 Analysis populations

7.1 Intent-to-Treat Population

The Intent-to-treat (ITT) population will comprise of all subjects randomized to receive at least one type of anesthesia and with 90-days mRS score. Randomized subjects will be assumed to

have received trial treatment unless definitive evidence to the contrary exists.

The ITT Population will be used for tables of efficacy, demography, safety, health outcomes, listings of withdrawals after randomization, and all relevant listings. This population will be the primary population for analyses of all outcomes.

7.2 Per Protocol population

The Per Protocol (PP) population will consist of all subjects in the ITT population not identified as protocol violators. The decision to exclude a subject from the PP population will be made prior to breaking the blind. This population will be used for secondary analyses of all outcomes. For the Per Protocol Population, subjects will be analyzed according to the treatment received. If study treatment was changed then the subject will be considered a protocol violator (from the point of change onwards).

8 Treatment comparisons

The treatment comparison of interest in this study is the favorable neurological outcomes between general anesthesia and conscious sedation at 90-days, based on the ITT population.

9 General considerations for data analyses

STATA V.14.0 and SPSS 26.0 for windows will be used for all statistical analyses. Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data, skewed continuous data, and counts (percentage) for categorical data. Unless otherwise specified all significance tests will be two-sided at the alpha=0.05 level and all confidence

intervals will be 95%.

10 Data handling conventions

If any subject withdraws prematurely from the study (prior to the final telephone follow-up at3 months -/+ 2 weeks,, they are required to complete the withdrawal record in the CRF. The reasons for withdrawal will be presented in a summary table.

Subjects who withdraw before the end of the study, but who do provide at least one postoperative measure for a particular endpoint, will be included in the analysis.

Subjects who do not be assessed at any timepoint after randomization will be excluded from analysis of rate of disability-free survival, recovery quality and safety outcomes, as no post-baseline data will be available.

11 Study Population

11.1 Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the per protocol population will be listed, and the total number of subjects being assessed at each timepoint will also be summarized by treatment group.

The number of subjects randomized, completed, and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.

A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or Randomized into the trial.

11.2 Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol. Subjects who commit protocol violations will be included in the ITT population but excluded from the per protocol population. These protocol violations will be shown in a listing. For subjects who violated the protocol in conscious sedation due to: unconscious; Glasgow Coma Scale decrease to or less than; increase of end- tidal carbon dioxide (ETCO2) ≥60 mm Hg and/or a decrease in pulse oxygen saturation (SpO2) <94% despite oxygen supplementation; agitation that cannot be controlled with sedation and/or restraint; seizure attack; vomiting; recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage, the analysis will only use data recorded prior to the violation.

A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from the per protocol population will be agreed by the study team prior to unblinding the study.

11.3 Demographic and Baseline Characteristics:

The following demographic information will be listed and summarized for subjects in each group: age, gender, BMI, medical history (hypertension, atrial fibrillation, coronary artery disease (CAD), dyslipidemia, diabetes, (transient ischemic attack(TIA),past stroke), smoking, drinking, etiology (cardiogenic thrombosis, atherosclerosis) ,drug use(antiplatelet agent, anticoagulant agent, statin, hypoglycemic agent), American society of Anesthesiologists (ASA) physical

status classification, premorbid modified Rankin Scale (mRS), clinical status at admission(modified Rankin Scale, NIHSS score, Glasgow Coma Scale, systolic blood pressure, mean arterial pressure),lesion location(basilar artery, vertebral artery V4 segment or BA combined V4), IV-tPA pretreatment.

Perioperative vital signs including preoperative supine blood pressure, heart rate, pulse saturation, PetCO2 et al. will also be listed and summarized in each treatment group.

12 Outcome analyses

STATA V.14.0 and SPSS 26.0 for windows will be used for all statistical analyses. Descriptive statistics will be reported as means with SD and medians with IQR for normally distributed data, skewed continuous data, and counts (percentage) for categorical data. Unless otherwise specified all significance tests will be two-sided at the alpha=0.05 level and all confidence intervals will be 95%.

12.1 Primary Analysis

Differences in the primary endpoint will be compared between groups using Cochran- Mantel-Haenszel test.

12.2 Secondary Analysis

Other categorical variables will be analyzed by $\chi 2$ test and continuous variables using the Student- t-test or Mann- Whitney U test.

12.3 Other Analysis

Baseline NIHSS score, occlusion site, age, and intravenous tissue plasminogen activator (IV-tPA) use were included in the logistic regression model and modified Poisson regression to estimate the adjusted odds ratio (OR) and risk ratio. The modified Poisson regression with robust (sandwich) estimation was an extra analysis based on the original protocol. $P < .05$ was regarded as statistically significant[2].

To allow for a varying number of follow-up measurements, for example, systolic blood pressure, the repeated measure analysis of variance methods with a mixed-model approach (treating time as a random effect and other covariates as fixed effects) will be utilized. The specific comparison of the change in each of those measurements between baseline and any specific post-baseline time point can be tested using linear contrast.

13 REFERENCES

1. Jadhav AP, Bouslama M, Aghaebrahim A, et al. Monitored Anesthesia Care vs Intubation for Vertebrobasilar Stroke Endovascular Therapy. JAMA Neurol. Jun 1 2017;74(6):704-709. doi:10.1001/jamaneurol.2017.0192

2. Shu D, Young JG, Toh S. Privacy-protecting estimation of adjusted risk ratios using modified Poisson regression in multi-center studies. BMC Med Res Methodol. Dec 5 2019;19(1):228. doi:10.1186/s12874-019-0878-6