

Intra-arterial tenecteplase during thrombectomy for acute stroke (BRETIS-TNK II): rationale and design

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ABSTRACT

Background Our recent pilot study suggests intra-arterial tenecteplase (TNK) during the first pass of endovascular treatment (EVT) seems safe, may increase first-pass reperfusion and good outcome in acute ischaemic stroke (AIS) patients with large-vessel occlusion (LVO).

Aims To determine the efficacy and safety of intra-arterial TNK administration during EVT in AIS-LVO patients presenting up to 24 hours from symptom onset.

Sample size estimates A maximum of 380 patients are required to test the superiority hypothesis with 80% power according to a two-side 0.05 level of significance, stratified by age, gender, baseline systolic blood pressure, prestroke modified Rankin Scale (mRS), baseline National Institute of Health stroke scale, baseline ASPECTS, time from onset to groin puncture, intravenous thrombolysis before EVT, stroke territory and stroke aetiology.

Design Intra-arterial TNK during thrombectomy for acute stroke (BRETIS-TNK II) study is a prospective, randomised, adaptive enrichment, open-label, blinded end point, multicentre study. Eligible AIS-LVO patients are randomly assigned into the experimental group and control group with a ratio of 1:1. The experimental group will be treated with intra-arterial infusion of TNK during EVT. The control group will be treated with standard EVT.

Outcome The primary end point is a favourable outcome, defined as an mRS score of 0–2 at 90 days. The primary safety end point is symptomatic intracranial haemorrhage within 48 hours, which is defined as an increase in the National Institutes of Health Stroke Scale score of ≥4 points as a result of the intracranial haemorrhage.

Conclusions The results of BRETIS-TNK II will provide evidence for the efficacy and safety of intra-arterial TNK administration during EVT in AIS patients with LVO.

INTRODUCTION AND RATIONALE

Acute ischaemic stroke (AIS) is one of the leading causes of morbidity and mortality worldwide, especially in patients with large-vessel occlusion (LVO).¹ Endovascular treatment (EVT) has been approved as the standard treatment for LVO stroke. Rapid and complete reperfusion is the most important modifiable predictor of good clinical outcome. With the development of endovascular thrombectomy techniques, recanalisation of the occluded vessel can be achieved in 59%–88% of LVO patients.^{2–3} However, only

46%–51% of AIS-LVO patients who attain successful reperfusion after EVT achieve functional independence at 90 days.^{4,5}

Several studies have indicated that clinical outcomes are most favourable in patients achieving successful reperfusion after the first retrieval attempt.^{6–7} Multiple retrieval attempts were reported to be negatively associated with good clinical outcome.⁸ First-pass complete reperfusion was shown to be an independent factor for a favourable outcome with 2–3 fold higher odds for favourable clinical outcome.⁷ In addition, residual clot burden in the microcirculation or distal circulation after mechanical thrombectomy may also influence the outcome after recanalisation,⁹ which may be dissolved by intra-arterial thrombolysis.¹⁰ Previous studies suggest that intra-arterial thrombolysis can increase reperfusion in patients with middle cerebral artery occlusion and improve clinical outcomes.¹⁰ The CHOICE trial indicated that among AIS-LVO patients with successful reperfusion following thrombectomy, the use of adjunct intra-arterial alteplase compared with placebo resulted in a greater likelihood of excellent neurological outcome at 90 days.⁹

Tenecteplase (TNK) is a genetic variant of alteplase with higher fibrin specificity, greater conservation of fibrinogen, greater resistance to inhibitors of tissue plasminogen activator, more rapid thrombolysis and longer half-life.^{11–12} In this context, our primary hypothesis is that intra-arterial TNK during EVT may increase the rate of first-pass reperfusion and improve neurological outcome in AIS-LVO patients. The hypothesis was supported by our recent BRETIS-TNK study, which was a prospective, single-arm, single-centre study, indicating that intra-arterial TNK administration as an adjunct to mechanical thrombectomy seemed safe and feasible, with the potential to increase first-pass reperfusion rates (53.8% vs 36.0%) and good clinical outcome (50% vs 34.6%), compared with

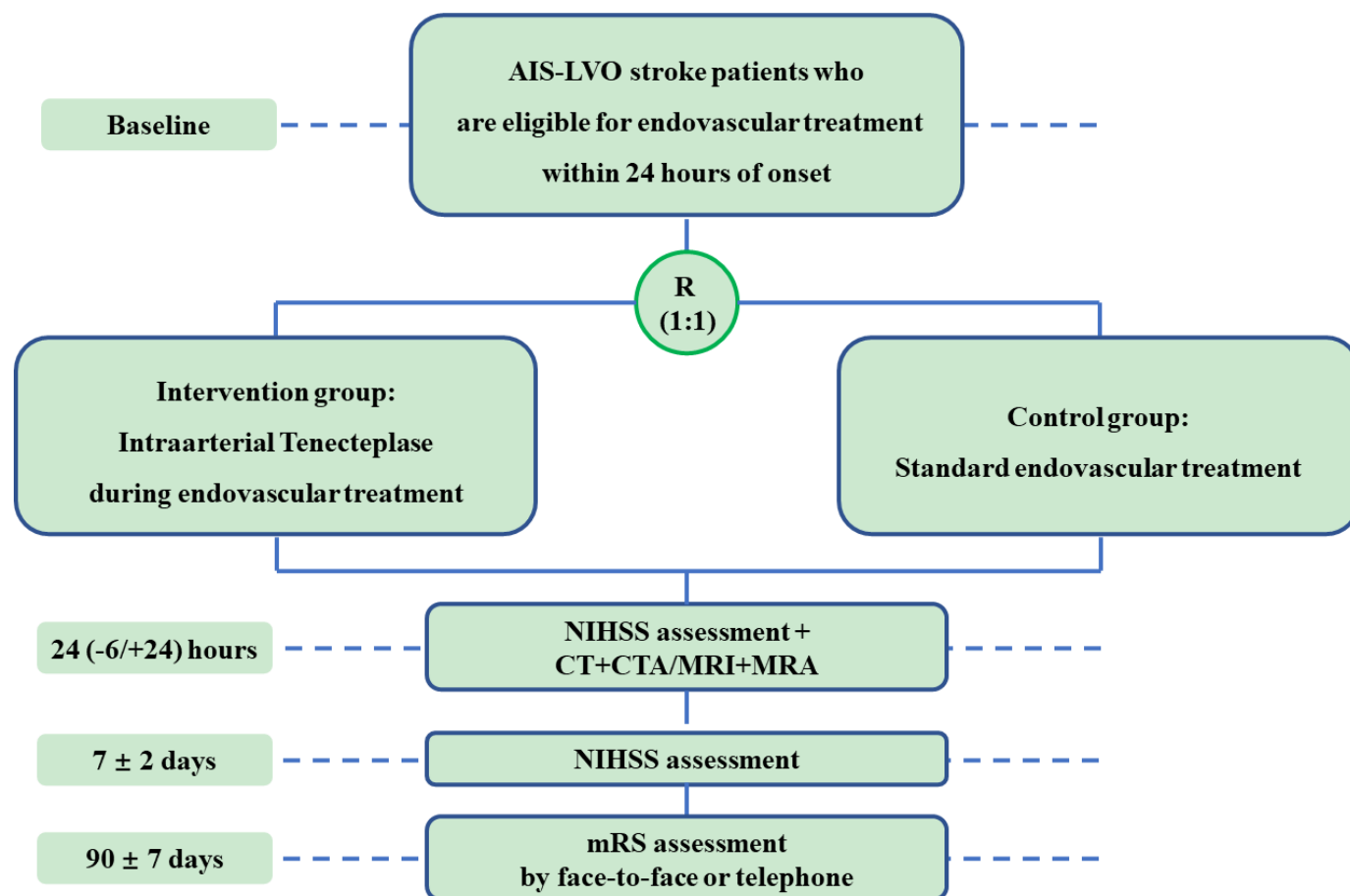


Figure 1 Trial flow chart. AIS, acute ischaemic stroke; LVO, large-vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; R, randomisation.

historical control patients.¹³ Based on these pilot results, we designed this trial to determine the efficacy and safety of intra-arterial TNK administration during EVT in AIS-LVO patients.

METHODS

Design

The intra-arterial TNK during thrombectomy for acute stroke (BRETIS-TNK II) study is a prospective, randomised, adaptive-enrichment, open-label, blinded-end point, multicentre study in China, aiming to determine the efficacy and safety of intra-arterial TNK administration during thrombectomy. The trial flow chart is shown in [figure 1](#).

Study population

Eligible participants are AIS-LVO patients who are planned for EVT according to current guidelines,^{14 15} as judged by the investigator. They will be enrolled at approximately 30 sites in China between March 2023 and March 2025. The detailed inclusion/exclusion criteria are listed in [box 1](#).

Trial registration number

The BRETIS-TNK II trial is registered on www.clinical-trial.gov (NCT05657444).

Randomisation and intervention

The eligible patients treated with EVT will be assigned into an experimental and control group as a ratio of 1:1 using central and computerised random sequence generation as stratified by centre. The type of anaesthesia, including local anaesthesia, sedation or general anaesthesia, will be decided by the team that performs the procedure. The EVT procedure will be performed according to the usual practice of each centre, including stent retrievers, contact aspiration, balloon angioplasty, stenting or a combination of these approaches.

The intra-arterial TNK strategy in the experimental group is as follows ([figure 2](#)): intra-arterial administration of 4 mg TNK is given distal to the clot after microcatheter navigation across the clot. Then, intra-arterial continuous administration of TNK with 0.4 mg/min is given manually or by an infusion pump via the intermediate or guide catheter for 5 min after release of the first stent retriever and while waiting for the stent retriever to be enmeshed with the clot, followed by slow withdrawal of the stent retriever. A digital subtraction angiography (DSA) will then be performed to judge whether the LVO is recanalised. If successful recanalisation (Modified Treatment in Cerebral Ischaemia (mTICI) 2b–3) is achieved, intra-arterial TNK with 0.2 mg/min (0.15 mg/min if the patient received or is also receiving intravenous thrombolysis) is

Box 1 Inclusion and exclusion criteria**Inclusion criteria**

1. Age ≥ 18 years.
2. Patient who had a stroke with large-vessel occlusion (LVO) (internal carotid artery, M1 or M2 of middle cerebral artery, basilar artery or intracranial segment of vertebral artery) who meets criteria for endovascular treatment within 24 hours of stroke onset*.
3. The modified Rankin Scale score before onset ≤ 2 .
4. ASPECTS 6 or greater on CT.
5. Signed informed consent.

Exclusion criteria

1. Haemorrhagic stroke.
2. Tandem occlusion.
3. Coagulation disorders, systematic haemorrhagic tendency, thrombocytopenia ($<100\,000/\text{mm}^3$).
4. Severe hepatic or renal dysfunction, increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (more than 2 times of upper limit of normal value), elevated serum creatinine (more than 1.5 times of upper limit of normal value) or requiring dialysis.
5. Severe uncontrolled hypertension (systolic blood pressure over 200 mm Hg or diastolic blood pressure over 110 mm Hg).
6. Patients with contraindication or allergic to any ingredient of drugs in our study.
7. Pregnancy, or plan to get pregnant or during active lactation.
8. Suspected septic embolus or infective endocarditis.
9. The estimated life expectancy is less than 6 months due to other serious disease(s).
10. Other conditions unsuitable for this clinical study as assessed by researcher.

*When selecting patients with AIS within 6–24 hours of last known normal who have LVO in the anterior circulation, CT perfusion or diffusion-weighted MRI, with or without MRI perfusion will be performed according to current guidelines.^{14 15} Some patients may be selected based on the comprehensive adjudication of the non-contrast CT and the patients' clinical symptoms.³⁰ AIS, acute ischaemic stroke.

continuously administered for 20 min via the relocated intermediate, aspiration or guide catheter proximal to the site of occlusion (the highest dose of TNK: 9–10 mg). If successful recanalisation (mTICI 2b–3) is not achieved, intra-arterial TNK with 0.4 mg/min is given again as above for 5 min after the release of the second stent retriever, followed by DSA to judge whether the LVO is fully recanalised. If successful recanalisation is achieved, intra-arterial TNK with 0.2 mg/min (0.15 mg/min if receiving intravenous thrombolysis) is continuously administered for 15 min via the relocated intermediate, aspiration or guide catheter proximal to the site of occlusion (the highest dose of TNK: 10–11 mg). If successful recanalisation (mTICI 2b–3) is not achieved, the third attempt and intra-arterial TNK as above will be performed followed by DSA to judge whether the LVO is fully recanalised. If successful recanalisation is achieved, intra-arterial TNK with 0.2 mg/min (0.15 mg/min if receiving intravenous thrombolysis) is continuously administered for 10 min via the relocated intermediate, aspiration or guide catheter proximal to the site of occlusion (the highest dose of TNK:

11.5–12 mg). If successful recanalisation (mTICI 2b–3) is not achieved, then the subsequent procedure will be determined by the local investigator. The control group will be treated by standard EVT procedure. If contact aspiration is used, the TNK strategy (0.4 mg/min for 5 min) will not be administrated during this attempt. Intravenous thrombolysis with alteplase, urokinase or TNK will be administrated according to the current guidelines in China.¹⁵

To minimise the risk of intracranial haemorrhage (ICH), several strategies are in place: (1) Aside from procedurally administered heparinised saline (a continuous drip of 2000 IU heparin in 1000 mL saline into femoral artery sheaths), which will be used if intravenous thrombolysis was not given before EVT, intravenous heparin is prohibited until after the 24 hours after EVT when neuroimaging has been performed; (2) Blood pressure will be tightly controlled to less than 185/110 mm Hg during the first 24 hours. If TICI >2 b reperfusion is achieved and the systolic blood pressure is persistently above 140 mm Hg, a blood pressure of 120–160/70–90 mm Hg would be targeted by continuous monitoring after EVT¹⁶; (3) Blood glucose level will be controlled to less than 160 mg/dL; (4) If contrast extravasation occurs during the procedure which may indicate active bleeding, the TNK infusion will be stopped immediately; (5) If ICAD-LVO is highly suspected and rescue balloon angioplasty and/or stenting will be performed, the dose of intra-arterial TNK will be reduced to half of the recommended dose, or stop, as determined by the local investigator and (6) If there is a concern for change in the patient's neurological condition, a CT scan (flat panel CT in the angio suite permitted) will be performed to rule out haemorrhage and if present, TNK will be immediately stopped. Hypotension and hypovolaemia will be corrected or avoided according to current guidelines.^{14 15} A CT scan will be performed before and after the EVT procedure in all patients.

Rescue treatment with balloon angioplasty and/or stenting will be performed according to the following criteria: (1) intracranial atherosclerotic stenosis is highly suspected as a cause of LVO; (2) repeat reocclusion shortly after recanalisation with EVT and (3) flow compromise because of residual stenosis after EVT. Considering stent patency was shown to be associated with the use of glycoprotein IIb/IIIa inhibitor during or after the EVT procedure,¹⁷ the safety and potential benefit of low-dose rescue tirofiban during mechanical thrombectomy on clinical outcome of patients with ICAD,^{17 18} an intra-arterial bolus (0.4–0.6 mg), followed by intravenous maintenance dose of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ tirofiban for a 12–24 hours will be administered. After dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) overlap, tirofiban will then be stopped.

Outcomes

The primary end point is a favourable outcome, defined as modified Rankin Scale (mRS) score of 0–2 at 90 $\pm$ 7 days.

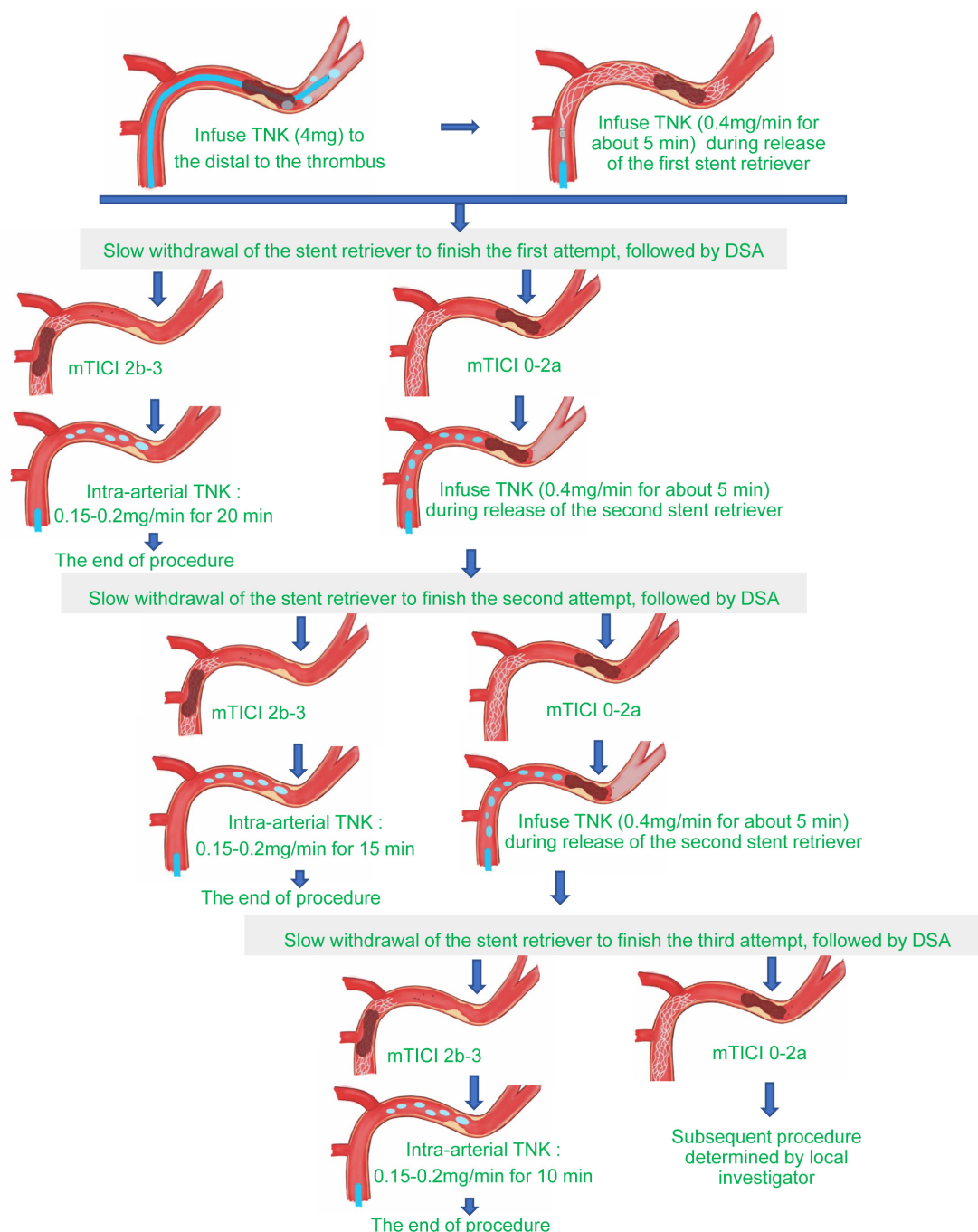


Figure 2 Flow chart of endovascular treatment procedures. DSA, digital subtraction angiography; mTICI, Modified Treatment in Cerebral Ischaemia; TNK, tenecteplase.

The secondary end points include the proportion of patients with successful reperfusion after the first pass or final pass of EVT, defined as mTICI 2b–3; excellent outcome (defined as mRS 0–1) at 90±7 days; ordinal distribution of mRS at 90±7 days; change in cerebral circulation time after the intervention¹⁹; early neurological improvement (ENI), which is defined as a 4 point or greater decrease in National Institutes of Health Stroke Scale (NIHSS) within 24 (–6/+24) hours²⁰; change in NIHSS at 24 (–6/+24) hours; the composite of nonfatal

stroke, nonfatal myocardial infarction and other cardiovascular events within 90±7 days.

The primary safety end point is symptomatic ICH (sICH) within 24 (–6/+24) hours, which is defined as an increase in the NIHSS score of ≥4 points as a result of the ICH.²¹ The secondary end points include parenchymal haemorrhage (PH1, PH2)²¹ within 24 (–6/+24) hours; percentage of severe adverse events (AEs) within 24 (–6/+24) hours; cerebral oedema within 24 (–6/+24) hours; death due to all causes within 7±2 days or during

hospitalisation; distal embolisation after the first pass, determined by DSA; extracranial haemorrhage.

Follow-up procedure

Study visits will be performed at 24 (−6/+24) hours, 7±2 days and 90±7 days after randomisation. Patient demographic characteristics, baseline NIHSS, routine laboratory tests and neuroimaging will be collected and 90-day mRS will be evaluated. The last known normal to puncture time, door-to-puncture time, puncture-to-reperfusion time, onset-to-reperfusion time, location of arterial occlusion on angiography, retrieval and recanalisation techniques, number of passes, recanalisation status and neuroimaging will be recorded. To reduce bias, the follow-up NIHSS scores will be obtained by the same neurologist. To prevent bias on the primary results, the 90-day clinical assessments including mRS will be evaluated by one qualified personnel blinded to treatment allocation according to a standardised procedure manual in each study centre. To ensure the validity, consistency and reproducibility of the evaluation, we will have a training course for all investigators at each centre. The primary endpoint will be evaluated by in-person or by telephone interview if an in-person evaluation is not possible. Concomitant medications and AEs within 90 days after randomisation will be recorded in detail by investigators and adjudicated by certified assessors. The duration of this trial is expected to be approximately 36 months.

Data management and quality control

All data will be entered using MedSci (<http://BRETIS-TNK2.medsci.cn>) which includes the patient case report form. The data will be downloaded from MedSci with a dedicated person for statistical analysis. The independent Data Safety and Monitoring Committee (iDSMC) will perform data checking for this study in an unblinded manner for safety reasons. A central core lab for imaging was created to judge intracranial bleeding events (ECASS²¹ and HBC definitions²²) and assess neuroimaging data. The trial will have an adaptive design. An interim analysis will be performed after 150 patients have been followed up completely by an independent statistician of the DSMC, who is not involved in managing the trial. The stopping rule or sample size adjusting rule will be prespecified by the DSMC. Based on this analysis, the DSMC can recommend to the steering committee to adjust the sample size, reduce the study drug dosage, remove a patient subgroup or early termination of the study (eg, a subgroup at high risk of sICH are patients who received intravenous thrombolysis before EVT or antiplatelet therapy for rescue angioplasty/stenting). If a subgroup is recommended for removal, these patients will be retained in the primary intention-to-treat (ITT) analysis. No formal analysis of the primary endpoint will be conducted during the interim analysis, to avoid the occurrence of a type-I error.

All AEs monitoring

AEs include any adverse medical events that occur during the study. All information about AEs will be recorded,

and whether the unexpected AE is associated with a pre-existing condition, the study disease, intra-arterial TNK administration, the EVT procedure, intercurrent condition, incidental finding or other, will be adjudicated by the iDSMC.

Sample size determination

Based on our cohort data, the proportion of expected favourable functional outcome (mRS 0–2) at 90 days in eligible patients (control group) was approximately 30%–40%. According to our pilot study, the proportion of favourable functional outcome in the experimental group is estimated to be 15% higher compared with the control group. Using a power of 80% and α level of 0.05 to carry out the two-sided test, the calculated sample size to test the superiority hypothesis is 320–342. In consideration of 10% of patients lost to follow-up, the total sample size is adjusted to 356–380. Finally, this study plans to include 380 patients, with 190 patients in each group.

Statistical analysis

ITT analysis will be used to analyse the therapeutic effects of the two groups. All data will be analysed with SPSS V.26.0 (SPSS Software, IBM). The mean±SD will be used if the data are normally distributed; the median and IQR will be used if the data are non-normally distributed. Count data are expressed as n (%). Comparisons of baseline demographic, clinical, imaging and procedural characteristics will be evaluated by one-way analysis of variance on ranks followed by Dunn's method for discontinuous or non-normal variables, or student t-test followed by Bonferroni post hoc test for continuous and normally distributed variables or χ^2 tests. The primary and secondary outcomes such as mRS (0–2) at 90 days, successful reperfusion, ENI, proportion of sICH within 24 hours, proportion of PH, serious AEs within 24 hours, cerebral oedema within 24 hours, mortality at 7 days will be estimated using a binary logistic regression adjusted for the admission NIHSS, age, baseline ASPECTS and prior intravenous thrombolytic use. Change in NIHSS score and cerebral circulation time between two groups will be compared using a general linear model. Time to events of stroke recurrence, other vascular events and death within 90 days will be compared using Cox regression. A p value of 0.05 is considered statistically significant.

The primary endpoint will further be stratified by age (≤ 65 vs > 65), gender (male vs female), baseline SBP (< 140 vs ≥ 140 mm Hg), baseline NIHSS (6–12 vs > 12), baseline ASPECTS (8–10 vs 6–7), prestroke mRS (0–1 vs 2), time from onset to groin puncture (0–6 vs 6–24 hours), intravenous thrombolysis before EVT (yes vs no), stroke territory (anterior vs posterior circulation infarction), stroke aetiology (large-artery atherosclerosis vs cardioembolism), mTICI (2b vs 2c/3) and type of anaesthesia (general anaesthesia vs conscious sedation or local anaesthesia).

Study organisation and funding

The protocol was designed by Hui-Sheng Chen and discussed with the trial steering committee. The trial steering committee is composed of external scientific advisors, who will monitor the research and blinded iDSMC report. The trial steering committee will organise teleconference or physical meetings to provide recommendations about the trial. Neuroimaging associated with clinical events will be collected centrally and interpreted by two independent neuroradiologists. The trial is initiated by the Cerebrovascular Disease Collaboration & Innovation Alliance of Liaoning and supported by grants from the Science and Technology Project Plan of Liao Ning Province (2022JH2/101500020). TNK was donated by CSPC Recomen Pharmaceutical (Guangzhou).

Current status

At the time of the first submission of this article, the trial has not begun recruitment of patients. Recruitment will be continued until the complete sample size is achieved, which is expected to be March 2025 at the latest.

DISCUSSION

Rapid and complete reperfusion is closely related to good clinical outcome of AIS-LVO patients. Successful reperfusion within the first three retrieval attempts was found to be associated with improved clinical outcome,²³ while additional retrieval manoeuvres are associated with a risk for distal embolisation and endothelial injury, hence decreasing the likelihood of successful reperfusion.^{24 25} Many efforts have been made to improve thrombectomy techniques to achieve a higher first-pass reperfusion rate.

The BRETIS-TNK II (Boosting REcanalization of Thrombectomy for Ischemic Stroke by Intra-arterial TNK II) is the first prospective, multicentre trial to test the hypothesis that intra-arterial TNK during EVT can improve the first-pass reperfusion rate, with improved clinical outcome in AIS-LVO patients. This trial is designed based on two considerations. First, theoretically, adjunctive intra-arterial TNK during EVT would increase the possibility of first successful recanalisation. Intra-arterial thrombolysis was reported in several studies to increase recanalisation and improve clinical outcomes in AIS patients.^{10 26} Second, our pilot study has preliminarily validated the feasibility and safety of this treatment strategy as well as the possible efficacy. We found that intra-arterial infusion of TNK during the first retrieval attempt increased the first-pass successful reperfusion rate and the proportion of functional independence at 90 days, compared with a historical control group of patients with a safe profile.

This trial has two distinct characteristics. First, TNK was chosen in this trial given its higher fibrin specificity and greater resistance to inhibitors of tissue plasminogen activator, and its high recanalisation rate^{11 12 27} compared with alteplase. Second, the unique strategy of intra-arterial thrombolysis will be tested in this trial. The first step is an

infusion of 4 mg TNK after the microcatheter navigation across the clot, aiming to dissolve the thrombus in situ as well as possible microthrombus after recanalisation. The second step is intra-arterial administration of TNK via the intermediate or guide catheter during the release of the stent retriever, which can dissolve the thrombus in situ to help increase the successful reperfusion rate without interfering with the EVT procedure. If successful recanalisation is achieved after the stent retriever, intra-arterial TNK will be given similar to the CHOICE (CHemical OptImization of Cerebral Embolectomy in Patients With Acute Stroke Treated With Mechanical Thrombectomy) design.

In the design of this trial, two major concerns were considered in advance: the dose of intra-arterial TNK and the sample size of the trial. A study on intra-arterial TNK for the treatment of AIS indicated that administration of intra-arterial TNK with a dose ranging from 1.5 mg to 10 mg had similar safety and favourable outcomes compared with intra-arterial alteplase or reteplase in AIS patients.²⁸ Furthermore, intra-arterial 0.4 mg/min TNK seemed safe and showed potential benefit in the BRETIS-TNK study. Given these results and the potential risk of sICH across different subgroups, different doses of intra-arterial TNK were chosen in this trial after discussion with the steering committee, with the aim to minimise sICH risk. The second major concern of the trial was the sample size. Given the potential for removal of a subgroup in the event of a safety concern, an adaptive increase in sample size would be performed with statistician support when the interim results are reported.²⁹

CONCLUSIONS

The results of the BRETIS-TNK II randomised trial will provide important evidence for the efficacy and safety of intra-arterial TNK administration during EVT in AIS-LVO patients.

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Contributors Z-AZ and JQ wrote the first draft of the manuscript. WL, TN, SW, HS, FW, MW and DL critically revised the manuscript. H-SC designed the study and critically revised the manuscript.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by the ethics committee of General Hospital of Northern Theatre Command (IRB-Y (2022) 168). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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