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Stroke & Vascular Neurology

Tirofiban combined with Aspirin in the Treatment of Acute Penetrating Artery Territory Infarction (STRATEGY): protocol for a multicentre, randomised controlled trial

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ABSTRACT

Background Perforating artery territorial infarction (PAI) caused by branch atheromatous disease (BAD) is prone to recurrence and early progression without an effective and well-documented antiplatelet treatment regimen. Tirofiban, an adjunctive antiplatelet agent, has shown great potential to treat acute ischaemic stroke. However, whether the combination of tirofiban and aspirin can improve the prognosis of PAI remains unclear.

Aim To explore an effective and safe antiplatelet regimen for reducing the risk of recurrence and early neurological deterioration (END) in PAI caused by BAD by comparing the tirofiban and aspirin combination with placebo and aspirin combination.

Methods Tirofiban combined with Aspirin in the Treatment of Acute Penetrating Artery Territory Infarction (STRATEGY) trial is an ongoing multicentre, randomised, placebo-controlled trial in China. Eligible patients shall be randomly assigned to receive standard aspirin with tirofiban or placebo on the first day and standard aspirin from days 2 to 90. The primary endpoint is a new stroke or END within 90 days. The primary safety endpoint is severe or moderate bleeding within 90 days.

Discussion The STRATEGY trial will assess whether tirofiban combined with aspirin is effective and safe in preventing recurrence and END in patients with PAI.

Trial registration number NCT05310968.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Perforating artery territorial infarction (PAI) caused by branch atheromatous disease (BAD) is prone to recurrence and early progression. Tirofiban could promote vascular recanalisation and improve the long-term prognosis of ischaemic stroke, usually as an adjunct therapy alongside conventional treatment, while its efficacy and safety in PAI caused by BAD remain unknown.

WHAT THIS STUDY ADDS
⇒ The STRATEGY trial will provide high-quality evidence for the efficacy and safety of tirofiban combined with aspirin in reducing the risk of recurrent stroke and early progression in patients with PAI caused by BAD within 90 days of acute PAI occurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ The study could provide insights into the pathogenesis of PAI and offer a new, efficient prevention and treatment strategy for PAI caused by BAD.

INTRODUCTION AND RATIONALE

Perforating artery territorial infarction (PAI) is a single small deep infarct caused by a perforating artery. This accounts for 15.3%–25% of all stroke cases. The annual recurrence and disability rates range between 2%–12% and 18%–33%, respectively.[1 2] Apart from arterial dissection, embolism and other rare cases, PAI is mainly attributed to conditions involving the small artery with three different pathophysiological mechanisms, including lipohyalinosis, large parent artery plaque and microatheroma.[3] Lipohyalinosis, a cerebral small-vessel disease, usually causes a true 'lacunar infarct' (diameter <15 mm).[4] Large parent artery plaques involve perforating artery embolisms originating from unstable plaques of the parent artery with severe stenosis. Finally, branch atheromatous disease (BAD), caused by microatheroma, is indirectly defined by the radiological characteristics of ischaemic lesions identifiable by a diameter ≥15 mm, without severe stenosis of the parent artery.[5]

Early neurological deterioration (END) and recurrence of stroke play important roles in adverse outcomes of PAI.[6 7] Compared with lipohyalinosis, infarcts consequent to atherosclerosis are more likely to progress or recur, usually accompanied by increased infarct volume.[8 9] Hence, effective antithrombotic therapy is essential for PAI prognosis. Dual

antiplatelet therapy is widely accepted as the first choice for infarcts with intracranial and extracranial artery stenosis of >30%.[10 11] However, the efficacy of antithrombotic therapy for single infarcts without severe stenosis of the parent artery, that is, BAD-related PAI, is still uncertain. Based on the Secondary Prevention of Small Subcortical Strokes trial, aspirin-added clopidogrel could not significantly prevent the recurrence of lacunar infarctions measuring ≤20 mm, including lipohyalinosis and BAD.[12] Moreover, the intervention time was within 6 months of stroke, which might exceed the END period. According to an analysis of a 'Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events' subgroup, for single infarctions (caused by large-artery atherosclerosis, small-artery occlusion and undetermined causes), dual antiplatelet therapy (clopidogrel plus aspirin) did not significantly reduce recurrence more than aspirin alone.[13] Without refining the pathological and pathogenesis mechanisms, these studies could not prove the efficacy of antiplatelet drug monotherapy against PAI. A small, multicentre study found that in BAD, an ultra-early cilostazol combined with an oral antiplatelet agent could better restrain the clinical progression than that with single cilostazol, aspirin or clopidogrel.[14] For atherosclerotic occlusion of small arteries, early tirofiban plus one oral antiplatelet drug could significantly reduce the National Institutes of Health Stroke Scale (NIHSS) score of patients who had disease progression.[15 16] These studies have highlighted the effectiveness of dual antiplatelet treatment in PAI caused by BAD, especially for END. However, they also have obvious limitations, such as a small sample size, retrospective or observational design, and inconsistent or inexplicit definitions of BAD. Therefore, a well-designed randomised controlled trial with sufficient samples is urgently required to explore better antithrombotic treatments for PAI caused by BAD.

Tirofiban, a selective and reversible antagonist of the glycoprotein (GP) IIb/IIIa receptor on the platelet, has been increasingly used to treat acute ischaemic stroke in recent years. The efficacy of intra-arterial injection of tirofiban was comparable with that of intracranial angioplasty/stenting for acute atherosclerotic occlusion of large artery.[17] For acute middle cerebral artery infarction, recombinant tissue plasminogen activator (rt-PA) with tirofiban could reduce more lesions than rt-PA alone, suggesting tirofiban's impact on thrombi in small vessels, induced by the recanalisation of upstream vessels.[18] Meanwhile, aspirin is the first-line antiplatelet treatment in patients with atherosclerotic stroke, particularly in Asia. Combining tirofiban with aspirin stabilises platelet activation and inhibits thrombosis expansion by acting on various targets. Therefore, based on the hypothesis that tirofiban and aspirin combination could safely reduce the risk of stroke recurrence and END of acute PAI due to BAD within 90 days, compared with single aspirin, we designed the 'Tirofiban combined with Aspirin in the Treatment of Acute Penetrating Artery Territory Infarction (STRATEGY)' trial.

METHODS

Design

This is a randomised, double-blind, parallel, placebo-controlled, multicentre trial (figure 1). Within 48 hours of onset, all participants shall be randomly assigned to one of two groups, and tirofiban plus aspirin or tirofiban placebo plus aspirin will be administered, with a 90-day follow-up. This study is expected to last for 24 months. We have checked the design through the Standard Protocol Items: Recommendations for Interventional Trials checklist for standardisation.

Participants

Participants are being recruited from 39 centres in China. Patients with persistent neurological deficits will be screened by study criteria (box 1).
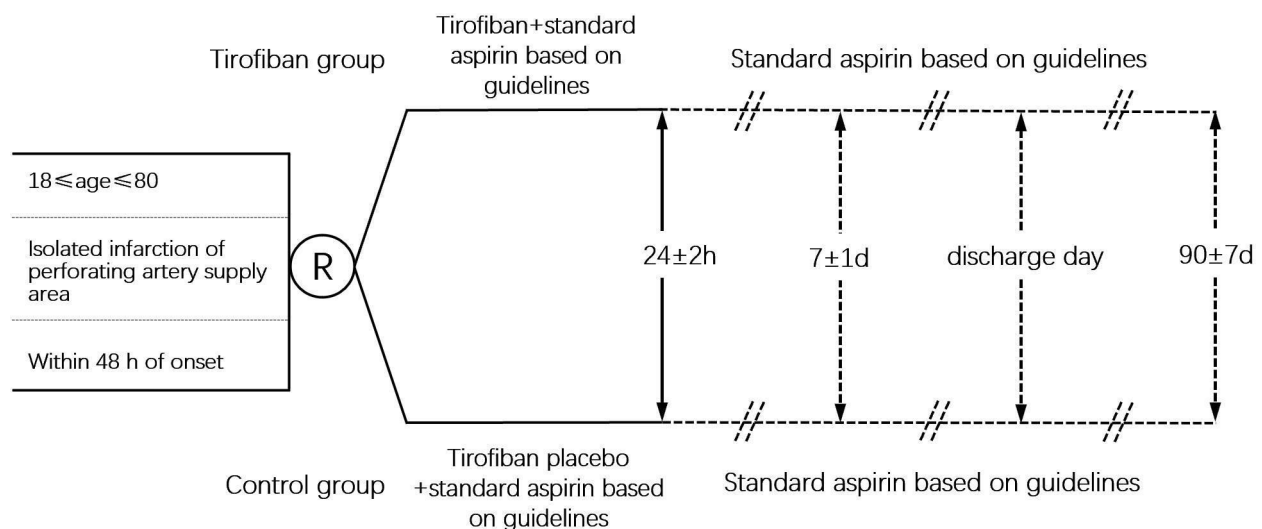

Figure 1 STRATEGY study design. STRATEGY, Tirofiban combined with Aspirin in the Treatment of Acute Penetrating Artery Territory Infarction.

Box 1 Inclusion and exclusion criteria

Inclusion criteria
1. Eighteen to 80 years old.
2. Male or female.
3. No more than 48 hours after onset.
4. Clinical manifestations indicating infarction of penetrating artery territory (no cortical or multiple infarctions, NIHSS score ≤10 and consciousness-1a score ≤1).
5. Diffusion-weighted image suggesting single infarction (maximum diameter <30 mm) of penetrating artery territory, which involves two or more transverse layers, or whose maximum diameter ≥15 mm, or connected to the ventral surface of the pons but not crossing the midline.
6. With stenosis of <70% of the parent artery.
7. Signed informed consent by the patient or his/her legal agent.

Exclusion criteria
1. History of intracranial haemorrhage.
2. History of intracranial tumours, vascular malformation or aneurysm.
3. Emergency intravascular intervention or intravenous thrombolysis before randomisation.
4. Being on dual antiplatelet therapy, or having received dual antiplatelet therapy within 14 days prior to randomisation (excluding use of aspirin with non-loaded clopidogrel after onset).
5. Having received other antiplatelet drugs, or anticoagulant drugs, or defibrase treatments after onset.
6. Indications for long-term use of antiplatelet drugs (not for research) or non-steroidal anti-inflammatory drugs.
7. With stenosis of >70% of the parent artery.
8. Definite indications for anticoagulant treatment (eg, suspected cardioembolism) or dual antiplatelet treatment (eg, recent endovascular stent implantation).
9. Severe hepatic dysfunction (ALT or AST >three times the normal upper limit) or severe renal dysfunction (creatinine clearance rate <30 mL/min) before randomisation.
10. Haemorrhagic tendency (such as platelet count <100×10^9/L; heparin treatment within 48 hours; activated partial thromboplastin time ≥35 s; current use of warfarin, international normalised ratio >1.7; current use of novel oral anticoagulants; current use of direct thrombin or factor Xa inhibitor).
11. Resistant hypertension (SBP >180 mm Hg or DBP >110 mm Hg after antihypertensive therapy).
12. History of obvious head trauma within 3 months of randomisation.
13. History of intracranial or intraspinal surgery within 3 months of randomisation.
14. History of major surgery or severe physical trauma within 1 month of randomisation.
15. Severe neurological defects (modified Rankin Scale ≥2) before onset.
16. Acute pericarditis.
17. Haemorrhagic retinopathy.
18. Women of childbearing age without effective contraceptive methods and negative pregnancy tests.
19. Known to be allergic to tirofiban.
20. Discontinuance of trial drugs due to planned surgical or interventional treatment within 3 months.
21. Expected survival time within 6 months due to any terminal illness.
22. Undergoing other trial drugs or instruments.
23. Other conditions unsuitable for this study, such as having mental diseases, cognitive or mood disturbance, and could not comply with research procedures or with MRI contraindications.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Randomisation

The drugs were packed according to the random code list, which was generated by random permuted blocks with fixed size. Each centre will assign random codes and corresponding treatment kits to eligible patients in an ascending order. Patients will be treated with tirofiban or placebo, and the ratio of the random probability of being assigned to the two groups is 1:1.

To ensure blinding, drug assignments are concealed in sealed envelopes. The treatment and control drugs are identical in appearance. The research centres are equipped with specific personnel injecting drugs, who will not participate in drug administration. The personnel involved in the subject screening, efficacy and safety evaluation, and clinical research organisation data processing will be blinded to the randomisation, preparation and drug administration processes. Unblinding is permitted when an endpoint or adverse event occurs if knowing the composition of the drug is necessary for subsequent treatment. Investigators could open the envelope with approval of the sponsor.

Interventions

Patients who have passed the criteria screening will be included in the trial (table 1). The tirofiban group (tirofiban plus aspirin group) will receive tirofiban continuously for 24.5 hours and 100–300 mg aspirin on the first day of enrolment (to ensure that 300 mg aspirin is administered on the day of onset or the first day of enrolment). Tirofiban hydrochloride will be injected intravenously at

Table 1 Treatment administered to the participants

Group	Time	Treatment
Tirofiban	The first day after randomisation	Tirofiban (weight-dependent dose)+aspirin 100–300 mg*
	Days 2–90	Aspirin 100 mg
Control	The first day after randomisation	Tirofiban placebo+aspirin 100–300 mg*
	Days 2–90	Aspirin 100 mg

*To ensure that 300 mg aspirin is administered on the day of onset or the first day of enrolment.

0.4 µg/kg/min for the first 30 min and 0.1 µg/kg/min for the next 24 hours. From days 2 to 90, the patients will receive 100 mg aspirin per day.

The control group (tirofiban placebo plus aspirin group) will receive tirofiban placebo for 24.5 hours continuously, and 100–300 mg aspirin on the first day of enrolment (to ensure that 300 mg aspirin is administered on the day of onset or the first day of enrolment). A weight-dependent dose tirofiban placebo will be injected intravenously similar to that of tirofiban. From days 2 to 90, the patients will receive 100 mg aspirin per day.

In addition to the study medication, other necessary treatment and concomitant care will be permitted in all participants.

Study organisation

In-person visits with participants will be performed separately at baseline, 24±2 hours, 7±1 days, discharge day and 90±7 days. Participants with newly occurring neurological clinical symptoms or suspicious events, including deterioration of the original ischaemic event and transient or persistent neurological symptoms, will undergo additional interviews. The NIHSS scores will be recorded at baseline, 24±2 hours, 7±1 days and 90±7 days. The modified Rankin Scale (mRS) scores will be recorded at baseline and 90±7 days. Fasting venous blood samples at early morning will be collected within 24±2 hours of randomisation. MRI should be completed at baseline and event interviews. In the high-resolution MRI (HR-MRI) or 7T-MRI subgroup, special sequences of MRI will be conducted on 7±1 days. The study plan is detailed in online supplemental table 1.

Endpoints
Primary endpoints
1. New-onset stroke within 90±7 days.
2. END within 90±7 days.

Secondary endpoints
1. New-onset stroke or END within 7±1 days and 24±2 hours.

2. Composite vascular events (recurrence of symptomatic stroke, myocardial infarction and vascular death) within 90±7 days.
3. Disability or death (mRS score between 2 and 6 points) within 90±7 days.
4. Improvement of neurological function (decrease of NIHSS score by ≥4 points compared with the baseline or NIHSS score of 0–1 point) within 90±7 days, 7±1 days and 24±2 hours.
5. The score based on the EuroQol-5 dimension-5 Level Scale on 90±7 days.

Safety endpoints
The safety endpoints include the occurrence of the following events within 90±7 days:
1. Moderate or severe bleeding events defined by Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Criteria.[19]
2. Symptomatic and asymptomatic intracranial haemorrhage defined by Heidelberg Bleeding Classification.[20]
3. Vascular death.
4. Overall death.
5. Adverse event and serious adverse events (platelet count ≤100×10^9/L, hypersensitivity, renal failure).

Relevant detailed definitions for all above events are shown in online supplemental table 2.

Sample size calculation
We assumed the incidence of the primary endpoint rate to be 20% and 13.3% in the control group[7 21] and tirofiban group,[22–24] respectively, which implied a 30% reduction in relative risk. Considering a testing power of 80% and a significance level of 5%, 970 patients (485 in each group) will be required, allowing for a 5% dropout rate. We used Power Analysis and Sample Size software V.11.0 (NCSS, Kaysville, Utah, USA) to calculate.

Statistical analyses
According to intention-to-treat principle, participants with at least one record of medication and efficacy evaluation will be included in the full analysis set. Whenever a participant is lost to follow-up, or dropped out of the study, the last observed value is substituted as each value of subsequent time points. The proportion of participants with new-onset stroke or END at 90±7 days will be presented as frequency (percentage) and compared using the χ^2 test. The ORs and 95% CIs will be calculated by logistic regression. The cumulative risk of stroke or vascular events at 90±7 days will be characterised by Kaplan-Meier survival curves. The risk factors, the HR and 95% CI will be explored and calculated by Cox proportional hazards model. Efficacy will be evaluated using the log-rank test. The influence of age, sex, comorbidity, stenosis of parent artery, intracranial microhaemorrhage, inflammatory markers and sites of infarction on treatment will be assessed through the subgroup

analyses. Changes in NIHSS scores between every visit and the baseline will be summarised for the two groups and tested by Student's t-test or Mann-Whitney U test. Statistical analyses will be accomplished using SAS software V.9.4 (SAS Institute).

Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) is comprised of academic experts and statisticians independent of the trial implementation process. DSMB charters, including membership, roles and responsibilities, will be certified by its members and executive committee. The DSMB will regularly monitor to ensure ethical procedures and patient safety, and have access to the final trial dataset.

Data management and quality control

Data will be transmitted through the electronic data capture system (http://study.ericure.com) based on the electronic case report forms (CRFs) of this study, after proofreading and correction by data managers. The principal investigators of all subcentres should be certified in Good Clinical Practice. Clinical inspectors shall visit the subcentres regularly to ensure strict adherence to the protocol and consistency of the original and CRF data.

Criteria for study withdrawal

Participants are able to withdraw voluntarily without any justification at any time. If the participants develop conditions unfit for the further study, investigators shall decide to withdraw them from the trial.

DISCUSSION

The STRATEGY Study is the first large sample, multicentre, randomised controlled trial to evaluate the efficacy and safety of tirofiban–aspirin versus aspirin antiplatelet therapy for PAI caused by BAD, using MRI-based evaluation.

There are few studies on PAI, and even fewer studies on BAD-related factors. In prior studies, the various definitions of MRI-based BAD might indirectly doubt the efficacy of antiplatelet therapy.[12 14] Considering the pathogenesis, this study will define BAD based on the MRI characteristics and try to exclude infracts caused by hyaline arterioles which did not require dual antiplatelet therapy and those accompanied by obvious stenosis requiring dual antiplatelet or interventional therapy.

The administration of dual or triple antiplatelet[14 16] or antiplatelet combined with anticoagulant therapies[25] at an early stage can inhibit the episode of stroke warning syndrome or END of patients with BAD; however, a generally accepted antithrombotic regimen is unavailable. Recently, tirofiban has been used to treat ischaemic stroke, sometimes in combination with oral antiplatelet drugs, intravenous thrombolytic therapy and endovascular

therapy. It can reversibly combine with GPIIb/IIIa receptors, inhibiting platelet aggregation rather than dissolving thrombi, thereby effectively suppressing microthrombi.[26] According to the result of the Safety of Tirofiban in Acute Ischaemic Stroke trial, tirofiban administration within 3–22 hours of ischaemic stroke onset could reduce the mortality rate over the next 5 months without increasing the risk of intracranial haemorrhage.[27] For stroke warning syndrome, which tends to develop into PAI, tirofiban plus oral antiplatelet drugs can stop early symptomatic fluctuations and promote neurological function recovery as soon as possible.[16] Notably, in progressive stroke, the improvement in neurological symptoms is more significant in small-vessel occlusion than that in large-vessel occlusion after tirofiban treatment.[15] Therefore, early intensive dual antiplatelet therapy can potentially prevent the progression or recurrence of PAI caused by BAD, with tirofiban being a suitable antiplatelet drug. The incidence of symptom progression was 13.5%–41% within 3 days–3 weeks of stroke onset,[6 8 9] and 23.9%–38.1% within 48 hours,[28–30] indicating that most END happened within 48 hours after stroke onset. According to studies of tirofiban in ischaemic stroke, the risk of bleeding increased with the duration of medication (see online supplemental table 3). In the STRATEGY Study, tirofiban is used to prevent stroke progression. Considering the time window for progression and bleeding risk, we suggest combining intravenous tirofiban with oral aspirin for 24 hours at an early stage (within 48 hours of onset). Meanwhile, due to the high risk of PAI progression, both recurrent stroke and END were considered as primary endpoints in this study, thus allowing a more rigorous evaluation of efficacy.

The strengths of this study are as follows: first, the sample size was calculated based on conservative data, making it larger than that used in similar previous studies. In addition, confounding and selection biases are well controlled through randomisation and multicentre implementation. Second, the participants will be screened using MRI-based inclusion criteria, thus excluding patients without BAD. The aetiology and pathogenesis of acute progressive PAI and the different efficacies of tirofiban intensive antiplatelet therapy for different types of PAI will be assessed using HR-MRI and 7T-MRI. Finally, we will continue to follow up until 3 months after the onset, which will allow us to examine both early progression and long-term recurrence of the disease, particularly using dual antiplatelet therapy.

BAD is encountered frequently, but existing treatment strategies lack evidence-based clinical practice, and efficient antithrombotic therapy has not yet been established. The results of the STRATEGY trial will be expected to help find an effective and safe dual antiplatelet treatment option for PAI caused by BAD.

Project management

The steering committee will be responsible for trial design and executing guidance. The executive committee will supervise the progress of the study, especially data collection. The adjudication committee is comprised of external experts who will review the endpoints and adverse events and make the final decision. The site study investigators will recruit patients, collect data and report clinical events. The National Clinical Research Center for Neurological Diseases of China will conduct randomisation, data quality control and statistical analysis.

Trial status

This trial was recruiting patients when the manuscript was submitted. The first patient was enrolled on 15 November 2022.

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Disclaimer The principal investigator and executive committee will have full access to the entire dataset at trial completion and will be responsible for analysis and publication, in collaboration with the sponsor.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY 2021-089-08). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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