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# BMJ Open

## **Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic Disease(BAD)-Related Stroke (BRANT): Protocol for a randomized controlled trial**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082141
Article Type:	Protocol
Date Submitted by the Author:	15-Nov-2023
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Keywords:	Stroke < NEUROLOGY, Prognosis, THERAPEUTICS

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4 **Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic**  
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6 **Disease(BAD)-Related Stroke (BRANT): Protocol for a randomized controlled**  
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56 **Total word count: 3720**  
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### Strengths and limitations of this study

1. Most published clinical studies classed BAD into small-vessel occlusion or undetermined etiology based on TOAST system. This study focuses on patients with acute BAD-related stroke, with the aid of magnetic resonance imaging.
2. Currently, there is no effective regimen to treat BAD-related stroke, and reduce disability. This study aims to addressing the current treatment dilemma in acute phase. Intervention will be prescribed within 48 hours after onset. 90-day modified Rankin Scale is set as primary outcome.
3. Lack of double blinded design is a limitation, but the endpoints are measured in a blind manner. An independent Clinical Event Committee is established to assess clinical events.

## Abstract

**Introduction:** Branch atheromatous disease (BAD)-related stroke is increasingly becoming a clinical entity and prone to early neurological deterioration (END) and poor prognosis. There are no effective regimen in acute phase to reduce the disability caused by BAD-related stroke. Recent studies have indicated the efficacy of tirofiban in acute ischemic stroke, but have not been validated in patients with BAD-related stroke. Thus, we aim to test whether intravenous tirofiban initiated within 48 hours after onset would safely improve the functional outcome in patients with acute BAD-related stroke, in comparison with standard antiplatelet therapy based on guideline.

**Methods and analysis:** BRANT is a multicenter, randomized, open-label, blinded endpoint, parallel controlled phase III trial in China. Participants with acute BAD-related stroke are randomized 1:1 to tirofiban or control group. The primary outcome is the excellent functional outcome (modified Rankin Scale score: 0-1) at 90 days. Secondary outcomes include END, major bleeding, stroke, death, functional status, serious adverse events, and change in bleeding-related markers. A total of 516 participants assuming the rates of primary outcome to be 74% in the tirofiban group and 62% in the control group are needed for 0.8 power (two-sided 0.05 alpha).

**Discussion:** BRANT aims to provide direct evidence on the efficacy and safety of early intravenous tirofiban in acute BAD-related stroke, thus addressing the current treatment dilemma for improving functional outcome.

**Ethics and dissemination:** BRANT study has been approved by the Ethics Committee of Peking Union Medical College Hospital. Written informed consent is required for

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4 all patients before enrollment. Results of the study will be published in a peer-reviewed  
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6 journal.  
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11 **Keywords:** Branch Atheromatous Disease, Acute ischemic stroke, Early neurological  
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13 deterioration, Functional outcome, Tirofiban, Treatment  
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## Introduction

Branch atheromatous disease (BAD), first described by Caplan in 1989 as a concept, is becoming a clinical entity with the aid of advanced neuroimaging.<sup>1-3</sup> BAD-related stroke, characterized by subcortical single infarcts without severe stenosis of large artery, accounts for 20.4% of all ischemic stroke cases in Asian population.<sup>2</sup> Different from lacunar infarct due to lipohyalinosis, BAD-related stroke is caused by parent arterial plaque occlusion of the perforating orifice or proximal atherosclerotic occlusion of the perforating artery.<sup>1-3</sup>

High incidence of early neurological deterioration (END) was observed in BAD-related stroke, and was strongly associated with poor prognosis.<sup>4 5</sup> The rate of END is higher in BAD-related stroke than that in lacunar infarct (26.8-37.5% vs. 6.3-18.6%), and thrombolysis itself cannot prevent the occurrence of END.<sup>4-6</sup> In addition, it remains unclear whether the intravenous thrombolysis could improve the clinical outcome in BAD-related stroke.<sup>7</sup> Its rate of disability could reach 61%.<sup>2</sup> However, there are no high-level recommendations for acute-phase treatment of BAD-related stroke, and no RCT has examined BAD as a separate disease. Current practice-based on limited observational data and expert opinion-is heterogeneous, including anticoagulants and dual antiplatelet therapy, whose efficacy is uncertain for BAD-related stroke.<sup>8 9</sup>

Historical evidence suggests that intravenous tirofiban, a selective and reversible antagonist of GP IIb/IIIa inhibitors on platelet, increases recanalization rate and improves functional prognosis in stroke patients with endovascular therapy, without increased bleeding risk<sup>10-12</sup>. A large randomized trial of stroke without large or

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4 medium-sized vessel occlusion also reported the efficacy of tirofiban<sup>13</sup>. Though  
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6 atherosclerotic mechanism is presumed between BAD and large artery atherosclerosis,  
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8 this evidence may not generalize to BAD-related stroke, for selection bias, retrospective  
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10 data or small sample.<sup>10 14</sup> Another limitation is that tirofiban was often prescribed after  
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12 END, which might cause irreversible ischemic lesion and neurologic deficit.<sup>10 13</sup>  
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14 Randomized controlled trials of acute BAD-related stroke are therefore needed, and  
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16 have been called for by researchers.<sup>3 15</sup>  
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18 The BTANT trial aims to establish the efficacy and safety of intravenous tirofiban in  
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20 improving functional outcome in patients with acute BAD-related stroke.  
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## 30 **Methods**

### 31 **Design**

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33 This is a multicenter, randomized, open label, blinded endpoint, parallel controlled  
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35 phase III trial. BRANT study has started enrollment on November 9, 2023, and the  
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37 anticipated date of study completion is October 31, 2025. This protocol has been  
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39 registered at ClinicalTrials.gov (NCT06037889).  
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### 45 **Patient population**

46  
47 BRANT will enroll 516 participants with BAD-related stroke within 48 hours of onset,  
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49 from 21 centers in China.  
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### 52 **Inclusion criteria**

- 53 ● Age: 18-75 years old
  - 54 ● Acute ischemic stroke
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- Time from onset to randomization  $\leq 48\text{h}$ ; if onset time is unknown, time from last known well to randomization  $\leq 48\text{h}$

- Meet the following BAD Diagnostic Imaging Criteria

1. DWI infarcts: single (isolated) deep (subcortical) infarcts;

2. The culprit arteries are either Lenticulostriate artery (LSA) or Paramedian pontine artery (PPA), and the infarct lesion on DWI conforms to one of the following characteristics (A/B):

- A. LSA: “Comma-like” infarct lesions with “Fan-shaped” extension from bottom to top in the coronary position; or  $\geq 3$  layers (layer thickness 5– 7 mm) on axial DWI brain images;

- B. PPA: The infarct lesion extends from the deep pons to the ventral pons on the axial DWI brain images;

- No more than 50% stenosis on the parent artery of the criminal artery (i.e. corresponding basilar or middle cerebral artery) (Confirmed by MRA/CTA/DSA)
- Signed informed consent by the patient or legally authorized representatives.

#### **Exclusion criteria**

- Transient ischemic attack (TIA)
- Intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain abscesses, malignant space-occupying lesions, or other non- ischemic intracranial lesions detected by baseline CT/MRI, or MRA/CTA/ DSA

- Presence of  $\geq 50\%$  stenosis in extracranial artery in tandem relationship ipsilateral to the lesion
- Cardiogenic embolism: atrial fibrillation, myocardial infarction, heart valve disease, dilated cardiomyopathy, infective endocarditis, atrioventricular block disease, heart rate less than 50 beats per minute
- Have received or plan to receive endovascular therapy or thrombolysis after onset
- Stroke of other clear causes, e.g., moyamoya disease, arterial entrapment, vasculitis, etc.
- modified Rankin Scale  $\geq 2$  before onset
- Use of tirofiban within 1 week before or after onset
- Low platelets ( $<100 \times 10^9/L$ ), or prothrombin time  $>1.3$  times of the upper normal limit, or INR  $>1.5$ , or other systemic hemorrhagic tendencies such as hematologic disorders
- Elevation of ALT or AST more than 1.5 times the upper normal limit
- Glomerular filtration rate  $<60$  ml/min/1.73m<sup>2</sup>
- Known malignant tumors
- History of trauma or major surgical intervention within 6 weeks prior to onset
- History of intracranial hemorrhage
- Active or recent history (within 30 days prior to onset) of clinical bleeding (e.g., gastrointestinal bleeding)

- Malignant hypertension (systolic blood pressure >200 mmHg, or diastolic blood pressure >120 mmHg)
- Life expectancy  $\leq$  6 months
- Contraindications of 3 T MRI examination
- Pregnant or lactating women
- Have participated in another clinical trial within 3 months prior to the date of informed consent, or are participating in another clinical trial

### **Randomization**

Participants will be randomized at a ratio of 1:1 using a dynamic block randomization method via an independent central website. Block sizes were set to 6, 8, and 12. The allocation sequence was stored in the central website and the participant was issued to intervention or control group by 1:1 ratio according to the order of enrollment time.

### **Intervention**

Tirofiban group: Intravenous tirofiban will be administered immediately after randomization for a total duration of 48 hours with a loading dose of 0.4ug/kg/min\*30min, followed by a maintenance dose of 0.1ug/kg/min\*47.5h (Figure 1).

Control group: Standard antiplatelet therapy based on Chinese stroke guideline will be initiated after randomization for a total duration of 48 hours, as the two following types:

1) aspirin 150-300 mg qd, or 2) aspirin 100 mg qd plus clopidogrel 75 mg qd<sup>16</sup>. Its

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4 initiation will be determined based on the last administration time of antithrombotic  
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6 drugs, but the drug should be given as soon as possible.  
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### 10 11 **Primary outcomes**

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14 The primary outcome is excellent functional outcome at 90 days, defined as modified  
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16 Rankin Scale score: 0-1. Primary outcome will be measured by the qualified evaluators,  
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18 who are blinded to all procedures.  
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### 24 25 **Secondary outcomes**

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27 Secondary efficacy outcomes include END, National Institutes of Health Stroke Scale  
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29 (NIHSS) score, Barthel index score, ischemic stroke, stroke, TIA, and a composite  
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31 event of new-onset stroke, myocardial infarction, and all-cause death. The safety  
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33 outcomes include the proportion of major bleeding defined by the PLATO criteria,  
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35 adverse events, all-cause death, and changes in bleeding-related markers<sup>17</sup>. Evaluators  
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37 after randomization are not aware of treatment assignment. All the clinical and safety  
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39 events will be re-examined by the independent Clinical Event Committee (CEC), who  
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41 are blinded during all procedures.  
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48 The presence of END is determined by an increase of  $\geq 4$  points in the NIHSS or an  
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50 increase of  $\geq 2$  points in the NIHSS motor score. In addition, NIHSS motor score refers  
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52 to bilateral upper and lower extremity mobility scores. The baseline NIHSS score for  
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54 the calculation of END is the first clinician-evaluated and recorded NIHSS score after  
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56 onset. The time frame for post-randomization END is within 7 days of randomization.  
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## Study protocol and data management

A study flow is shown in Figure 1 and Table S1. At visit 1, trained investigators will recruit the patient by screening age, onset time, magnetic resonance imaging, and other enrollment criteria (ie, intracranial artery, and electrocardiogram). Then, the investigator will explain the BRANT study in details, including contents of each visits and interventions to patients. After obtaining written informed consent, participants will be assigned to tirofiban or control group via a central website-based randomization system. Patients are encouraged to undergo on-site follow-up at 90 days. Demographic, clinical, radiological, laboratory and clinical event data at each visit (Table S1) will be collected and stored in electronic case report form via a website (<http://117.78.2.36:5010/>). All CRFs will be checked by local investigators for completeness and correction before data entry. Data will be checked dynamically by investigator (Jun Ni), with the aid of research assistants.

## Data Monitoring Board

An independent Data Security Monitoring Board (DSMB), including academic experts and statisticians, has been established to protect the interests of the participants during the study. The DSMB needs to review the overall implementation of the clinical study, and assess the risks and benefits regularly and dynamically, especially unexpected adverse event. DSMB reports to the Executive Committee and provides professional advice.

### Sample size estimates

Based on previous studies and clinical practice, we assumed the rates of primary outcome to be 62% and 74% in the control group and tirofiban group, respectively.<sup>2</sup>  
10-12 14 18-20 Thus, 234 per arm is needed for a two-sided test at alpha 0.05 and power 0.8. Considering a 10% dropout rate, 516 patients will be required.

### Statistical analyses

According to the principle of intention-to-treat analysis, all subjects randomized into the groups with more than one efficacy evaluation will be included in the full analysis set. The estimation of missing values will be conducted by the carry-over based on last observation carried forward (LOCF) estimation method. The proportion of excellent outcome at 90 days will be compared using the chi-square tests, and shown as frequency (percentage). Most secondary outcome analyses will also use the primary outcome analysis strategy. Survival data will be calculated by Kaplan-Meier method to estimate its survival rate in each group and the efficacy are assessed by Log-rank test. Hazard ratio and 95% CI will be calculated by cox proportional hazards model. Non-survival data will be calculated by chi-square test and odds ratios and 95%CI also will be calculated. Continuous variables will be compared by Student t -test or Wilcoxon rank sum test between the two groups. The influence of covariables will be evaluated via the subgroup analyses. All analysis will be performed using SAS 9.4 and a two-sided P < 0.05 is considered significant.

## Patient and public involvement statement

None.

**Ethics and dissemination:** BRANT study has been approved by the Ethics Committee of Peking Union Medical College Hospital on July 20, 2023. Written informed consent is required for all patients before enrollment. BRANT is carried out according to Good Clinical Practice and the Declaration of Helsinki. Protocol amendments will be reported to the institutional ethics committee. The trial sponsor is Peking Union Medical College Hospital. Trial results will be published in a peer-reviewed journal.

## Discussion

The BRANT trial is a multicenter RCT, addressing the important treatment dilemma that how to improve the functional outcome of BAD-related stroke.

BAD was first described by Caplan in 1989, when BAD was just a concept, distinct from lacuna infarct.<sup>1</sup> However, in past three decades, most clinical studies classed BAD into small-vessel occlusion or undetermined etiology based on TOAST system.<sup>15 21</sup> Few studies focused on acute BAD-related stroke, probably due to discrepant definitions.<sup>3</sup> Recently, increasing observational studies found distinct clinical, radiologic, and prognostic features that BAD-related stroke were prone to END and poor prognosis.<sup>2</sup>

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Due to the limitation of neuroimaging technique, there were no direct visualization of perforating artery, such as LSA and PPA. Radiological diagnosis was based on vascular

territory, dimension, or shape of the lesion,<sup>3 23</sup> which resulted in a huge variation among BAD definitions. With the aid of neuroimaging and clinical practice, Asian neurologists proposed radiological diagnosis criteria for BAD.<sup>24 25</sup> Our previous study also found that  $\geq 4$  consecutive slices on axial view was more effective than transversal diameter to differentiate atherosclerotic mechanisms of single subcortical infarction in LSA territory.<sup>26</sup> Considering generalization and diagnostic accuracy of our study, we used  $\geq 3$  consecutive layers on axial DWI series instead of lesion diameter to define BAD-related stroke in LSA territory.<sup>27</sup> As direct evidence of LSA and PPA are not technically feasible at present, our inclusion criteria based on MRI shows considerable accuracy and representativeness.

About 78.6%-90.9% of END occurred within 48 hours after onset.<sup>28 29</sup> Our preliminary results of BAD-related stroke cohort found that the median hours from onset to END was 38<sup>30</sup>. We hypothesize that early tirofiban could improve functional prognosis via preventing the occurrence of END. Thus, tirofiban should be initiated within 48 hours after onset. Considering the predictive value of END, we adopted the widely used and conservative definition of END in BRANT study.<sup>31</sup> The effect of tirofiban on reducing END risk is a key secondary outcome.

We set 90-day excellent outcome instead of END or new-onset stroke as the primary outcome for: 1) historical evidence indicated that tirofiban improved the functional outcome of ischemic stroke;<sup>10 13</sup> 2) END is an intermediate indicators;<sup>4</sup> 3) 90-day rate of recurrent stroke is 1.8% in our preliminary analysis of BAD-related stroke cohort, and probably less than 3.8% in other cohorts,<sup>22</sup> which is relatively low. Thus, BRANT



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4 study would provide direct evidence on how to reduce disability caused by BAD, which  
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6 is the major challenge in current clinical practice.  
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9 As oral mono antiplatelet therapy is unethical and against Chinese stroke guidelines for  
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11 patients with NIHSS  $\leq 3$ , there are two types of antiplatelet therapy in control group.<sup>16</sup>  
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13 Double-blind design would markedly increase the complexity of the trial procedure.  
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15 Therefore, we selected PROBE design for BRANT. We trained independent senior  
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17 neurologists for the evaluation of primary outcome blinded to the procedure  
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19 information. Independent CEC was established to centrally re-examine all clinical  
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21 events after randomization. Some local investigators may know the treatment allocation,  
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23 but all evaluators of subjective indicators are blinded to treatment allocation.  
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## 32 **Conclusions**

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34 BRANT is designed to test the efficacy and safety of early intravenous tirofiban in  
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36 patients with acute BAD-related stroke, aiming at effectively improving the functional  
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38 outcome.  
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45 **Contributors:** Shengde Li, and Jun Ni designed the study. Shengde Li drafted the  
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47 manuscript. Dingding Zhang designed the statistical method. Yuhui Sha, Lixin Zhou,  
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49 Yicheng Zhu, and Bin Peng critically revised the study protocol and the manuscript.  
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51 The entire project will be supervised by Jun Ni.  
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55 **Funding:** This study is funded by the National High Level Hospital Clinical Research  
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57 Funding (2022-PUMCH-D-007).  
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4 **Disclaimer:** The funder has no role in this study.  
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6 **Competing interests:** None declared.  
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**Figure I. Study Flow**

For peer review only

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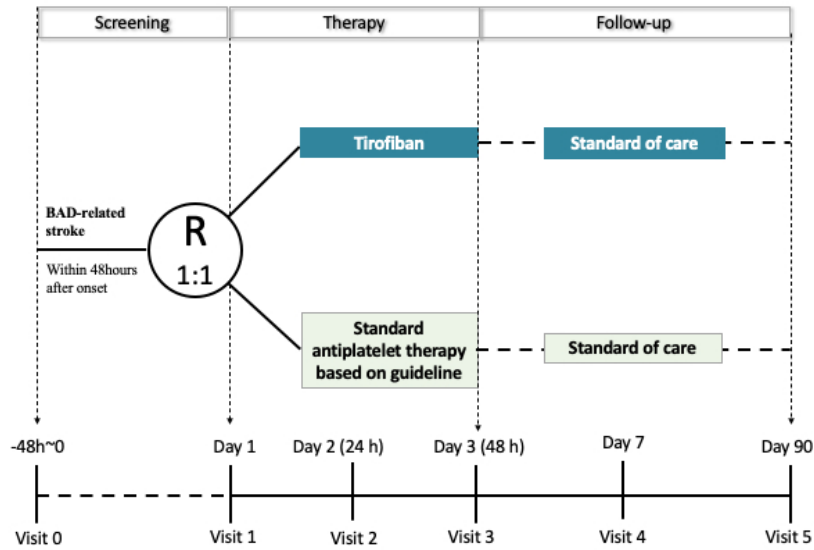


Figure 1. Study Flow

338x190mm (54 x 54 DPI)

## Supplementary materials

Table S1. Study Procedure of STRATEGY trial

Measurement	Day 1	Day 2	Day 3	Day 7	Day 90
Demographic characteristics	X				
Current medical history taking	X				
Body temperature measurement	X				
Physical examination	X			X	X
Past medical history	X				
Pre-randomization medication after onset	X				
Regular blood pressure monitoring	X	X			
NIHSS score	X			X	X
mRS score	X			X	X
Barthel index score	X				X
Magnetic resonance image	X				
Evaluation of Intracranial vessels	X				
Evaluation of extracranial vessels	X				
Laboratory tests*	X				
ECG*	X			X	
Verification of inclusion/exclusion criteria	X				
Signed informed consent	X				
Randomization	X				
Blood tests after enrollment		X	X		

Urine and fecal examination			<b>X</b>		
Compliance			<b>X</b>		
Concomitant medication				<b>X</b>	<b>X</b>
Early neurological deterioration				<b>X</b>	
Major bleeding				<b>X</b>	<b>X</b>
Adverse Events/ Serious Adverse Events				<b>X</b>	<b>X</b>
*Remarks: ECG and laboratory data performed within 48 hours of onset before signing the informed consent form can be used as trial data.					



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Clinical Trials.gov
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	Clinical Trials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5

1				
2	Objectives	7	Specific objectives or hypotheses	6
3				
4	Trial design	8	Description of trial design including type of trial (eg, parallel	6
5			group, crossover, factorial, single group), allocation ratio, and	
6			framework (eg, superiority, equivalence, noninferiority,	
7			exploratory)	
8				
9				
10	<b>Methods: Participants, interventions, and outcomes</b>			
11				
12	Study setting	9	Description of study settings (eg, community clinic, academic	6
13			hospital) and list of countries where data will be collected.	
14			Reference to where list of study sites can be obtained	
15				
16	Eligibility	10	Inclusion and exclusion criteria for participants. If applicable,	6-9
17	criteria		eligibility criteria for study centres and individuals who will perform	
18			the interventions (eg, surgeons, psychotherapists)	
19				
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow	9
22			replication, including how and when they will be administered	
23				
24		11b	Criteria for discontinuing or modifying allocated interventions for a	In
25			given trial participant (eg, drug dose change in response to	Protocol,
26			harms, participant request, or improving/worsening disease)	not
27				shown in
28				article
29				
30				
31		11c	Strategies to improve adherence to intervention protocols, and	In
32			any procedures for monitoring adherence (eg, drug tablet return,	Protocol,
33			laboratory tests)	not
34				shown in
35				article
36				
37				
38		11d	Relevant concomitant care and interventions that are permitted or	In
39			prohibited during the trial	Protocol,
40				not
41				shown in
42				article
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45	Outcomes	12	Primary, secondary, and other outcomes, including the specific	10
46			measurement variable (eg, systolic blood pressure), analysis	
47			metric (eg, change from baseline, final value, time to event),	
48			method of aggregation (eg, median, proportion), and time point	
49			for each outcome. Explanation of the clinical relevance of chosen	
50			efficacy and harm outcomes is strongly recommended	
51				
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53	Participant	13	Time schedule of enrolment, interventions (including any run-ins	Figure
54	timeline		and washouts), assessments, and visits for participants. A	1
55			schematic diagram is highly recommended (see Figure)	
56				
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2	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
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6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	In
7				Protocol,
8				not
9				shown in
10				article
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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16				
17	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
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25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
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31	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
32				
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34	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
35				
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
40				
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42				

### Methods: Data collection, management, and analysis

43				
44				
45	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
46				
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53		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
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2	Data	19	Plans for data entry, coding, security, and storage, including any	11
3	management		related processes to promote data quality (eg, double data entry;	
4			range checks for data values). Reference to where details of data	
5			management procedures can be found, if not in the protocol	
6				
7	Statistical	20a	Statistical methods for analysing primary and secondary	12
8	methods		outcomes. Reference to where other details of the statistical	
9			analysis plan can be found, if not in the protocol	
10				
11				
12		20b	Methods for any additional analyses (eg, subgroup and adjusted	12
13			analyses)	
14				
15		20c	Definition of analysis population relating to protocol non-	112
16			adherence (eg, as randomised analysis), and any statistical	
17			methods to handle missing data (eg, multiple imputation)	
18				
19				

### Methods: Monitoring

20				
21	Data	21a	Composition of data monitoring committee (DMC); summary of its	11
22	monitoring		role and reporting structure; statement of whether it is	
23			independent from the sponsor and competing interests; and	
24			reference to where further details about its charter can be found,	
25			if not in the protocol. Alternatively, an explanation of why a DMC	
26			is not needed	
27				
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30		21b	Description of any interim analyses and stopping guidelines,	NA
31			including who will have access to these interim results and make	
32			the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited	11
35			and spontaneously reported adverse events and other	
36			unintended effects of trial interventions or trial conduct	
37				
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39	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and	11
40			whether the process will be independent from investigators and	
41			the sponsor	
42				

### Ethics and dissemination

43				
44				
45	Research	24	Plans for seeking research ethics committee/institutional review	13
46	ethics		board (REC/IRB) approval	
47	approval			
48				
49				
50	Protocol	25	Plans for communicating important protocol modifications (eg,	13
51	amendments		changes to eligibility criteria, outcomes, analyses) to relevant	
52			parties (eg, investigators, REC/IRBs, trial participants, trial	
53			registries, journals, regulators)	
54				
55				
56	Consent or	26a	Who will obtain informed consent or assent from potential trial	13
57	assent		participants or authorised surrogates, and how (see Item 32)	
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2		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
3			NA
4			
5	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
6			In
7			protocol
8			, not
9			shown in
10			article
11			
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
13			15
14			
15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
16			15
17			
18			
19	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
20			In
21			protocol
22			, not
23			shown in
24			article
25			
26	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
27			13
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33		31b	Authorship eligibility guidelines and any intended use of professional writers
34			In
35			protocol
36			, not
37			shown in
38			article
39			
40		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
41			NA
42			
43			
44	<b>Appendices</b>		
45			
46	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
47			Consent form
48			has
49			been
50			approved.
51			
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53			
54	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable
55			NA
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the



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protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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# BMJ Open

## Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082141.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Feb-2024
Complete List of Authors:	Li, Shengde; Peking Union Medical College Hospital, dingding, zhang; peking union medical college hopspital Sha, Yuhui; Peking Union Medical College, Department of Neurology yicheng, zhu; Peking Union Medical College Hospital, Neurology Zhou, Lixin; Peking Union Medical College, Department of Neurology Peng, Bin; Peking Union Medical College Hospital Ni, Jun; Peking Union Medical College, Department of Neurology
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Prognosis, THERAPEUTICS

SCHOLARONE™  
Manuscripts

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4 **Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic**  
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6 **Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled**  
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9 **Trial**  
10

11 **Authors:** Shengde Li, MD;1 Dingding Zhang, PhD;2 Yuhui Sha, MD;1 Yicheng Zhu,  
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29 Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and  
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56 **Total word count: 4077**  
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## Abstract

**Introduction:** Branch atheromatous disease (BAD)-related stroke is increasingly becoming a clinical entity and prone to early neurological deterioration (END) and poor prognosis. There are no effective regimens to reduce the disability caused by BAD-related stroke in acute phase. Recent studies have indicated the efficacy of tirofiban in acute ischemic stroke, however, its efficacy has not been validated in patients with BAD-related stroke. Thus, we aim to test whether intravenous tirofiban initiated within 48 hours after onset would safely improve the functional outcome in patients with acute BAD-related stroke, in comparison with standard antiplatelet therapy based on the current guideline.

**Methods and analysis:** BRANT is a multicenter, randomized, open-label, blinded endpoint, parallel-controlled, phase III trial conducted in 21 hospitals in China. Participants aged 18-75 years with acute BAD-related stroke within 48 h after stroke onset are randomized in a 1:1 ratio to the tirofiban or control group. The treatment period is 48 hours in both groups. The primary outcome is the excellent functional outcome (modified Rankin Scale score: 0-1) at 90 days. The secondary outcomes include END, major bleeding, stroke, death, functional status, serious adverse events, and change in bleeding-related markers. Assuming the rates of the primary outcome to be 74% in the tirofiban group and 62% in the control group, a total of 516 participants are needed for 0.8 power (two-sided 0.05 alpha).

**Ethics and dissemination:** BRANT study has been approved by the Ethics Committee of the Peking Union Medical College Hospital. Written informed consent is required

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4 for all patients before enrollment. The results of the study will be published in a peer-  
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6 reviewed journal.  
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9 **Trial registration number** ClinicalTrials.gov (NCT06037889)  
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11 **Keywords:** Branch Atheromatous Disease, Acute ischemic stroke, Early neurological  
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13 deterioration, Functional outcome, Tirofiban, Treatment  
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### Strengths and limitations of this study

1. With the aid of magnetic resonance imaging, this study focuses on patients with acute BAD-related stroke, which had been inappropriately classified as small-vessel occlusion or an undetermined aetiology by the TOAST system in previous studies.
2. This study is designed to test the efficacy of tirofiban initiated within 48 h of onset, with the aim of addressing the current treatment dilemma in the acute phase.
3. Lack of double-blinded design is a limitation, but the endpoints are measured in a blinded manner.

## Introduction

Branch atheromatous disease (BAD), first described conceptually by Caplan in 1989, is being confirmed as a clinical entity with the aid of advanced neuroimaging.[1-3] BAD-related stroke, characterized by subcortical single infarcts in penetrating artery territories without severe stenosis of the large parent artery, accounts for 20.4% of all ischaemic stroke cases in Asian populations[2 4]. Differing from lacunar infarct due to lipohyalinosis, BAD-related stroke is caused by parent arterial plaque occlusion of the perforating orifice or proximal atherosclerotic occlusion of the perforating artery[1-3], which could be identified from small-vessel occlusion or stroke of undetermined source in the TOAST system[5 6].

High incidence of early neurological deterioration (END) has been observed in BAD-related stroke and is strongly associated with poor prognosis[7 8]. The rate of END is higher in BAD-related stroke than lacunar infarct (26.8-37.5% vs. 6.3-18.6%), and thrombolysis itself cannot prevent the occurrence of END[7-9]. In addition, it remains unclear whether intravenous thrombolysis could improve the clinical outcome in BAD-related stroke[10]. The rate of disability can reach 61%[2]. However, there are no high-level recommendations for acute-phase treatment of BAD-related stroke, and no RCT has examined BAD as a separate disease. Current practice—based on limited observational data and expert opinion—is heterogeneous, including anticoagulant and mono/dual antiplatelet therapy, the efficacy of which is uncertain for BAD-related stroke[11 12].

Tirofiban, a selective and reversible antagonist of glycoprotein IIb/IIIa inhibitors on

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4 platelets, might be more effective than conventional agents (such as aspirin or  
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6 clopidogrel) by blocking the final common pathway of platelet aggregation at the  
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8 pathophysiological level[13]. In clinical studies, historical evidence has also reported  
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10 that tirofiban increases the recanalization rate and improves functional prognosis in  
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12 stroke patients with endovascular therapy without increasing bleeding risk[14-16]. A  
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14 large randomized trial of patients with stroke without large or medium-sized vessel  
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16 occlusion also reported the efficacy of tirofiban[17]. However, though an  
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18 atherosclerotic mechanism is presumed to exist between BAD and large artery  
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20 atherosclerosis, this evidence may not be generalized to BAD-related stroke, as  
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22 retrospective data or small samples may introduce selection bias[14 18]. Moreover,  
23  
24 about 78.6%-90.9% of END occurs within 48 h after onset[19 20]. Our preliminary  
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26 results of a cohort with BAD-related stroke found that the median time from onset to  
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28 END was 38 h. We hypothesised that early tirofiban administration could improve  
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30 functional prognosis by preventing the occurrence of END. However, tirofiban was  
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32 often prescribed after END in previous studies, which might cause irreversible ischemic  
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34 lesions and neurologic deficits[14 17]. Thus, randomised controlled trials of acute  
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36 BAD-related stroke are needed and have been requested by researchers[3 4]. In addition,  
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38 we speculated that tirofiban should be initiated within 48 h after onset to prevent the  
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40 occurrence of END.  
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53 The BRANT trial aims to establish the efficacy and safety of intravenous tirofiban for  
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55 improving functional outcome in patients with acute BAD-related stroke.  
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## Methods

### Design

This is a multicenter, randomized, open-label, blinded-endpoint, parallel-controlled phase III trial. The BRANT study began enrolment on November 9, 2023, and the anticipated date of study completion is October 31, 2025.

### Patient population

BRANT will enroll 516 participants with BAD-related stroke within 48 hours of onset, from 21 centers in China.

### Inclusion criteria

- Age: 18-75 years old [21 22]
- Acute ischemic stroke
- Time from onset to randomization  $\leq 48\text{h}$ ; if onset time is unknown, time from last known well to randomization  $\leq 48\text{h}$
- Meet the following BAD Diagnostic Imaging Criteria
  1. Diffusion Weighted Imaging (DWI) infarcts: single (isolated) deep (subcortical) infarcts;
  2. The culprit arteries are either lenticulostriate artery (LSA) or paramedian pontine artery (PPA), and the infarct lesion on DWI conforms to one of the following characteristics (A/B):
    - A. LSA: “Comma-like” infarct lesions with “fan-shaped” extension from bottom to top in the coronal position; or  $\geq 3$  layers (layer thickness 5–7 mm) on axial DWI brain images;

1  
2  
3  
4 B. PPA: The infarct lesion extends from the deep pons to the ventral pons on  
5  
6 the axial DWI brain images;

- 7  
8  
9 ● No more than 50% stenosis on the parent artery of the criminal artery (i.e.  
10  
11 corresponding basilar or middle cerebral artery) (Confirmed by magnetic  
12  
13 resonance angiography[MRA]/ computed tomography angiography [CTA]/  
14  
15 digital subtraction angiography [DSA])  
16  
17  
18 ● Signed informed consent by the patient or legally authorized representatives.  
19  
20  
21

### 22 **Exclusion criteria**

- 23  
24 ● Transient ischemic attack (TIA)  
25  
26  
27 ● Intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain  
28  
29 abscesses, malignant space-occupying lesions, or other non- ischemic  
30  
31 intracranial lesions detected by baseline computed tomography(CT)/ magnetic  
32  
33 resonance imaging (MRI), or MRA/CTA/ DSA  
34  
35  
36 ● Presence of  $\geq 50\%$  stenosis in extracranial artery in tandem relationship  
37  
38 ipsilateral to the lesion  
39  
40  
41  
42 ● Cardiogenic embolism: atrial fibrillation, myocardial infarction, heart valve  
43  
44 disease, dilated cardiomyopathy, infective endocarditis, atrioventricular block  
45  
46 disease, heart rate less than 50 beats per minute  
47  
48  
49  
50 ● Have received or plan to receive endovascular therapy or thrombolysis after  
51  
52 onset  
53  
54  
55 ● Stroke of other clear causes, e.g., moyamoya disease, arterial entrapment,  
56  
57 vasculitis, etc.  
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60

- modified Rankin Scale  $\geq 2$  before onset
- Use of tirofiban within 1 week before or after onset
- Low platelets ( $<100 \times 10^9/L$ ), or prothrombin time  $>1.3$  times of the upper normal limit, or international normalised ratio (INR)  $>1.5$ , or other systemic hemorrhagic tendencies such as hematologic disorders
- Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 1.5 times the upper normal limit
- Glomerular filtration rate  $<60$  mL/min/1.73m<sup>2</sup>
- Known malignant tumors
- History of trauma or major surgical intervention within 6 weeks prior to onset
- History of intracranial hemorrhage
- Active or recent history (within 30 days prior to onset) of clinical bleeding (e.g., gastrointestinal bleeding)
- Malignant hypertension (systolic blood pressure  $>200$  mmHg, or diastolic blood pressure  $>120$  mmHg)
- Life expectancy  $\leq 6$  months
- Contraindications of 3 T MRI examination
- Pregnant or lactating women
- Have participated in another clinical trial within 3 months prior to the date of informed consent or are participating in another clinical trial

## Randomization

1  
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4 Participants will be randomized in a 1:1 ratio using a dynamic block randomization  
5  
6 method via an independent central website. The block sizes were set to 6, 8, and 12.  
7  
8  
9 The allocation sequence is stored on the central website and the participant will be  
10  
11 assigned to the intervention or control group in a 1:1 ratio according to the order of  
12  
13 enrolment.  
14  
15

### 16 17 18 19 **Intervention**

20  
21  
22 Tirofiban group: Intravenous tirofiban will be administered immediately after  
23  
24 randomization for a total duration of 48 hours with a loading dose of 0.4µg  
25  
26 /kg/min×30min, followed by a maintenance dose of 0.1µg /kg/min×47.5h (Figure1).  
27  
28

29  
30 Control group: Standard antiplatelet therapy based on Chinese stroke guideline will be  
31  
32 initiated after randomization for a total duration of 48 hours, as the two following types:  
33  
34 (1) aspirin 150-300 mg qd, or (2) aspirin 100 mg qd plus clopidogrel 75 mg qd.[23] Its  
35  
36 initiation will be determined based on the last administration time of antithrombotic  
37  
38 drugs; however, the drug should be administered as soon as possible.  
39  
40

41  
42 After a 48-hour treatment period in both groups, the standard of care, including an  
43  
44 antithrombotic regimen, will be performed based on current guidelines and recorded in  
45  
46 detail (Figure 1).  
47  
48

### 49 50 **Primary outcomes**

51  
52 The primary outcome is excellent functional outcome at 90 days, defined as modified  
53  
54 Rankin Scale score of 0-1.[24] Primary outcome will be measured by the qualified  
55  
56 evaluators who are blinded to all procedures.  
57  
58  
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## Secondary outcomes

Secondary efficacy outcomes include END, National Institutes of Health Stroke Scale (NIHSS) score, Barthel index score, ischemic stroke, stroke, TIA, and a composite event of new-onset stroke, myocardial infarction, and all-cause death. Safety outcomes include the proportion of major bleeding as defined by the PLATO criteria, adverse events, all-cause death, and changes in bleeding-related markers[25]. The evaluators will not be aware of the treatment assignment after randomization. All the clinical and safety events will be re-examined by the independent Clinical Event Committee (CEC), who will be blinded during all procedures.

Considering the predictive value of END, we adopted the widely used and conservative definition of END for the BRANT study[26]. The presence of END is determined by an increase of  $\geq 4$  points in the NIHSS or an increase of  $\geq 2$  points in the NIHSS motor score. The NIHSS motor score refers to bilateral upper and lower extremity mobility scores. The baseline NIHSS score for the calculation of END is the first clinician evaluated and recorded NIHSS score after onset. The time frame for post-randomisation END is within 7 days of randomization.

## Study protocol and data management

A study flowchart is shown in Figure 1 and Table S1. At visit 1, trained investigators will recruit patients based on screening age, onset time, MRI, and other enrolment criteria (i.e. intracranial artery and electrocardiogram). The investigator will then explain the BRANT study to the patient in detail, including the contents of each visit

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3  
4 and the interventions. After obtaining written informed consent, the participants will be  
5  
6 assigned to the tirofiban or control groups via a central website-based randomization  
7  
8 system. Patients are encouraged to undergo on-site follow-up at 90 days. Demographic,  
9  
10 clinical, radiological, laboratory, and clinical event data at each visit (Table S1) will be  
11  
12 collected and stored in an electronic case report form (CRF) via a secure website. All  
13  
14 CRFs will be checked by local investigators for completeness and correction prior to  
15  
16 data entry. The data will be checked dynamically by the principal investigator (Jun Ni)  
17  
18 with the aid of research assistants.  
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### 27 **Data Monitoring Board**

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29 An independent Data Security Monitoring Board (DSMB), including academic experts  
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31 and statisticians, has been established to protect the interests of the participants during  
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33 the study. The DSMB will review the overall implementation of the clinical study and  
34  
35 regularly and dynamically assess the risks and benefits, particularly unexpected adverse  
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37 events. The DSMB reports to the Executive Committee and provides professional  
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39 advice.  
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### 48 **Sample size estimates**

49  
50 Based on previous studies and clinical practice, we assumed the rates of the primary  
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52 outcome to be 62% and 74% in the control and tirofiban groups, respectively[2 14-16  
53  
54 18 27-29]. Thus, 234 participants per arm are needed for a two-sided test at alpha 0.05  
55  
56 and power 0.8. Considering a dropout rate of 10%, 516 patients will be required.  
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## Statistical analyses

According to the principle of intention-to-treat analysis, all participants who are randomized into groups with more than one efficacy evaluation will be included in the full analysis set. The estimation of missing values will be conducted by the carry-over based on last observation carried forward (LOCF) estimation method. The proportion of excellent outcomes at 90 days will be compared using the chi-square tests, and shown as frequency (percentage). Most secondary outcome analyses will also use the primary outcome analysis strategy. Survival data will be calculated using the Kaplan-Meier method to estimate the survival rate in each group, and efficacy will be assessed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CI) will be calculated using the Cox proportional hazards model. Non-survival data will be analysed using the chi-square test, and odds ratios and 95% CIs will be calculated. Continuous variables will be compared between the two groups using the Student's t-test or Wilcoxon rank-sum test. The influence of covariables will be evaluated using subgroup analysis. All analyses will be performed using SAS 9.4, and a two-sided  $P < 0.05$  is considered significant.

## Patient and public involvement statement

None.

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4 **Ethics and dissemination:** The BRANT study was approved by the Ethics Committee  
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6 of Peking Union Medical College Hospital on July 20, 2023. Written informed consent  
7  
8 is required from all patients before enrolment. BRANT will be carried out according to  
9  
10 Good Clinical Practice and the Declaration of Helsinki. Protocol amendments will be  
11  
12 reported to the institutional ethics committee. The trial sponsor is Peking Union  
13  
14 Medical College Hospital. The trial results will be published in a peer-reviewed journal.  
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## 22 **Discussion**

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24 The BRANT trial is a multicentre RCT that addresses the important treatment dilemma  
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26 of improving the functional outcomes of BAD-related stroke.  
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29  
30 BAD was first proposed by Caplan in 1989 to be distinct from lacunar infarct[1].  
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32 However, in the past three decades, most clinical studies have classified BAD as small-  
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34 vessel occlusion or undetermined etiology based on the TOAST system[4 30]. Few  
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36 studies focused on acute BAD-related stroke, probably due to discrepant definitions[3].  
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38 Recently, an increasing number of observational studies found distinct clinical,  
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40 radiologic, and prognostic features that patients with BAD-related stroke are prone to  
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42 END and poor prognosis[2 31].  
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48 Owing to the limitations of neuroimaging techniques, the perforating artery, such as the  
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50 LSA or PPA, cannot be directly visualized. Radiological diagnosis is based on the  
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52 vascular territory, dimension, or shape of the lesion[3 32], which results in a huge  
53  
54 variations among BAD definitions. With the aid of neuroimaging and clinical practice,  
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56 Asian neurologists proposed radiological diagnosis criteria for BAD[33 34]. Our  
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4 previous study also found that  $\geq 4$  consecutive slices on axial view are more effective  
5  
6 than transversal diameter to differentiate atherosclerotic mechanisms of single  
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8 subcortical infarction in the LSA territory[35]. Considering the generalisation and  
9  
10 diagnostic accuracy of our study, we used  $\geq 3$  consecutive layers on axial DWI series  
11  
12 instead of lesion diameter to define BAD-related stroke in the LSA territory[36].  
13  
14 Because obtaining direct evidence of the LSA and PPA is currently not technically  
15  
16 feasible, our inclusion criteria based on MRI show considerable accuracy and  
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18 representativeness.  
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24 In addition, our study uses simplified operationalised criteria to exclude cardiogenic  
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26 embolism, and patients with these comorbidities will not be included. Some conditions  
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28 seem general, which is a limitation of our study; however, this facilitates the  
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30 researcher's ability to complete screening within a limited timeframe with low  
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32 inconsistency.  
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37 We set a 90-day excellent outcome instead of END or new-onset stroke as the primary  
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39 outcome for the following reasons: (1) historical evidence indicated that tirofiban  
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41 improved the functional outcome of ischemic stroke[14 17]; (2) END is an intermediate  
42  
43 indicators[7]; (3) the 90-day rate of recurrent stroke is 1.8% in our preliminary analysis  
44  
45 of a BAD-related stroke cohort and probably less than 3.8% in other cohorts[31], which  
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47 is relatively low. Thus, the BRANT study will provide direct evidence on how to reduce  
48  
49 disability caused by BAD, which is the major challenge in current clinical practice.  
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54 As oral mono antiplatelet therapy is unethical and against Chinese stroke guidelines for  
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56 patients with NIHSS  $\leq 3$ , there are two types of antiplatelet therapy in the control  
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4 group[23]. A double-blind design would markedly increase the complexity of the trial  
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6 procedure. Therefore, we selected a prospective randomized open blinded end-point  
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8 design (PROBE) for BRANT. Independent senior neurologists who will be blinded to  
9  
10 the procedure information have been trained to evaluate the primary outcome. An  
11  
12 independent CEC has been established to centrally re-examine all clinical events after  
13  
14 randomization. Some local investigators may know the treatment allocation; however,  
15  
16 all evaluators of the subjective indicators will be blinded to the treatment allocation.  
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25 **Contributors:** Shengde Li, and Jun Ni designed the study. Shengde Li drafted the  
26  
27 manuscript. Dingding Zhang designed the statistical method. Yuhui Sha, Lixin Zhou,  
28  
29 Yicheng Zhu, and Bin Peng critically revised the study protocol and the manuscript.  
30  
31 The entire project will be supervised by Jun Ni.  
32  
33  
34

35 **Funding:** This study is funded by the National High Level Hospital Clinical Research  
36  
37 Funding (2022-PUMCH-D-007).  
38  
39

40 **Disclaimer:** The funder has no role in this study.  
41  
42

43 **Competing interests:** None declared.  
44

#### 45 **Data Availability Statement**

46  
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48 The data that support the findings of this study are available from the corresponding  
49  
50 author on reasonable request.  
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**Figure I. Study Flow**

For peer review only

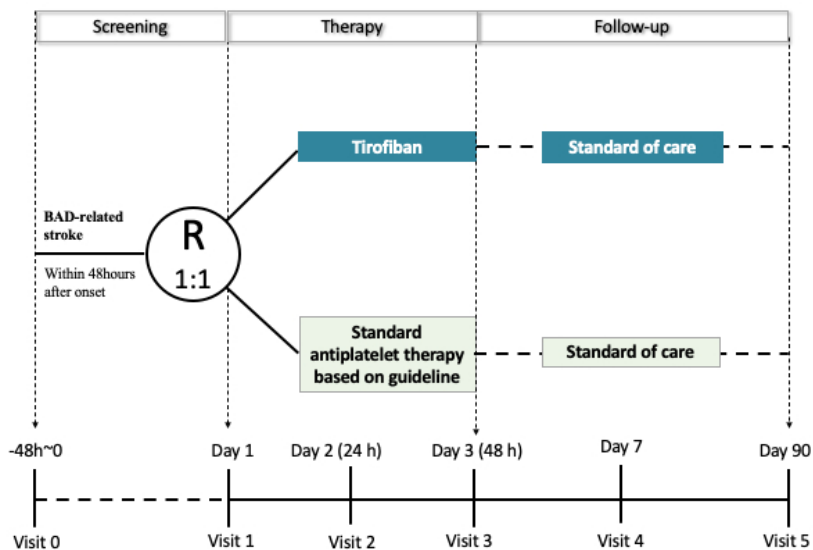


Figure 1. Study Flow

338x190mm (54 x 54 DPI)



## Supplementary materials

**Table S1. Study Procedure of BRANT trial**

Measurement	Day 1	Day 2	Day 3	Day 7	Day 90
Demographic characteristics	X				
Current medical history taking	X				
Body temperature measurement	X				
Physical examination	X			X	X
Past medical history	X				
Pre-randomization medication after onset	X				
Regular blood pressure monitoring	X	X			
NIHSS score	X			X	X
mRS score	X			X	X
Barthel index score	X				X
Magnetic resonance image	X				
Evaluation of Intracranial vessels	X				
Evaluation of extracranial vessels	X				
Laboratory tests*	X				
ECG*	X			X	
Verification of inclusion/exclusion criteria	X				
Signed informed consent	X				
Randomization	X				
Blood tests after enrollment		X	X		

Urine and fecal examination			<b>X</b>		
Compliance			<b>X</b>		
Concomitant medication				<b>X</b>	<b>X</b>
Early neurological deterioration				<b>X</b>	
Major bleeding				<b>X</b>	<b>X</b>
Adverse Events/ Serious Adverse Events				<b>X</b>	<b>X</b>
*Remarks: ECG and laboratory data performed within 48 hours of onset before signing the informed consent form can be used as trial data.					



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2-3
	2b	All items from the World Health Organization Trial Registration Data Set	Clinical Trials.gov
Protocol version	3	Date and version identifier	In Protocol, not shown in article
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	Clinical Trials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

**Introduction**

1				
2	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
3				
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6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
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15				
16	<b>Methods: Participants, interventions, and outcomes</b>			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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23	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
24				
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27	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
28				
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30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	In Protocol, not shown in article
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37		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	In Protocol, not shown in article
38				
39				
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43				
44		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	In Protocol, not shown in article
45				
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50				
51	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
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1				
2	Participant	13	Time schedule of enrolment, interventions (including any run-ins	Figure
3	timeline		and washouts), assessments, and visits for participants. A	1
4			schematic diagram is highly recommended (see Figure)	
5				
6	Sample size	14	Estimated number of participants needed to achieve study	12
7			objectives and how it was determined, including clinical and	
8			statistical assumptions supporting any sample size calculations	
9				
10	Recruitment	15	Strategies for achieving adequate participant enrolment to reach	In
11			target sample size	Protocol,
12				not
13				shown in
14				article
15				
16				
17				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21				
22	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9-10
23	generation		generated random numbers), and list of any factors for	
24			stratification. To reduce predictability of a random sequence,	
25			details of any planned restriction (eg, blocking) should be	
26			provided in a separate document that is unavailable to those who	
27			enrol participants or assign interventions	
28				
29				
30	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9-10
31	concealme		telephone; sequentially numbered, opaque, sealed envelopes),	
32	nt		describing any steps to conceal the sequence until interventions	
33	mechanism		are assigned	
34				
35				
36	Implement	16c	Who will generate the allocation sequence, who will enrol	9-10
37	ation		participants, and who will assign participants to interventions	
38				
39	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10-11
40	(masking)		participants, care providers, outcome assessors, data analysts),	
41			and how	
42				
43		17b	If blinded, circumstances under which unblinding is permissible,	NA
44			and procedure for revealing a participant's allocated intervention	
45			during the trial	
46				
47				

### Methods: Data collection, management, and analysis

49				
50	Data	18a	Plans for assessment and collection of outcome, baseline, and	11-12
51	collection		other trial data, including any related processes to promote data	
52	methods		quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known. Reference	
55			to where data collection forms can be found, if not in the protocol	
56				
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1			
2		18b	Plans to promote participant retention and complete follow-up, 11-12
3			including list of any outcome data to be collected for participants
4			who discontinue or deviate from intervention protocols
5			
6	Data	19	Plans for data entry, coding, security, and storage, including any 11-12
7	management		related processes to promote data quality (eg, double data entry;
8			range checks for data values). Reference to where details of data
9			management procedures can be found, if not in the protocol
10			
11			
12	Statistical	20a	Statistical methods for analysing primary and secondary 13
13	methods		outcomes. Reference to where other details of the statistical
14			analysis plan can be found, if not in the protocol
15			
16		20b	Methods for any additional analyses (eg, subgroup and adjusted 13
17			analyses)
18			
19		20c	Definition of analysis population relating to protocol non- 13
20			adherence (eg, as randomised analysis), and any statistical
21			methods to handle missing data (eg, multiple imputation)
22			
23			
24	<b>Methods: Monitoring</b>		
25			
26	Data	21a	Composition of data monitoring committee (DMC); summary of its 12
27	monitoring		role and reporting structure; statement of whether it is
28			independent from the sponsor and competing interests; and
29			reference to where further details about its charter can be found,
30			if not in the protocol. Alternatively, an explanation of why a DMC
31			is not needed
32			
33			
34		21b	Description of any interim analyses and stopping guidelines, NA
35			including who will have access to these interim results and make
36			the final decision to terminate the trial
37			
38	Harms	22	Plans for collecting, assessing, reporting, and managing solicited 12
39			and spontaneously reported adverse events and other
40			unintended effects of trial interventions or trial conduct
41			
42			
43	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and 12
44			whether the process will be independent from investigators and
45			the sponsor
46			
47			
48	<b>Ethics and dissemination</b>		
49			
50	Research	24	Plans for seeking research ethics committee/institutional review 3
51	ethics		board (REC/IRB) approval
52	approval		
53			
54	Protocol	25	Plans for communicating important protocol modifications (eg, 3
55	amendments		changes to eligibility criteria, outcomes, analyses) to relevant
56			parties (eg, investigators, REC/IRBs, trial participants, trial
57			registries, journals, regulators)
58			
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1				
2	Consent or	26a	Who will obtain informed consent or assent from potential trial	3
3	assent		participants or authorised surrogates, and how (see Item 32)	
4				
5		26b	Additional consent provisions for collection and use of participant	NA
6			data and biological specimens in ancillary studies, if applicable	
7				
8	Confidentiality	27	How personal information about potential and enrolled	In
9			participants will be collected, shared, and maintained in order to	protocol
10			protect confidentiality before, during, and after the trial	, not
11				shown in
12				article
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14				
15	Declaration of	28	Financial and other competing interests for principal investigators	16
16	interests		for the overall trial and each study site	
17				
18	Access to	29	Statement of who will have access to the final trial dataset, and	16
19	data		disclosure of contractual agreements that limit such access for	
20			investigators	
21				
22				
23	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	In
24	post-trial care		compensation to those who suffer harm from trial participation	protocol
25				, not
26				shown in
27				article
28				
29				
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	See
31	policy		to participants, healthcare professionals, the public, and other	consent
32			relevant groups (eg, via publication, reporting in results	from
33			databases, or other data sharing arrangements), including any	
34			publication restrictions	3
35				
36				
37		31b	Authorship eligibility guidelines and any intended use of	In
38			professional writers	protocol
39				, not
40				shown in
41				article
42				
43				
44		31c	Plans, if any, for granting public access to the full protocol,	NA
45			participant-level dataset, and statistical code	
46				
47	<b>Appendices</b>			
48				
49	Informed	32	Model consent form and other related documentation given to	We
50	consent		participants and authorised surrogates	provide
51	materials			a model
52				consent
53				from
54				
55				
56	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
57	specimens		biological specimens for genetic or molecular analysis in the	
58			current trial and for future use in ancillary studies, if applicable	
59				
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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
2 Explanation & Elaboration for important clarification on the items. Amendments to the  
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
4 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"  
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# BMJ Open

## Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082141.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Mar-2024
Complete List of Authors:	Li, Shengde; Peking Union Medical College Hospital, dingding, zhang; peking union medical college hospital Sha, Yuhui; Peking Union Medical College, Department of Neurology yicheng, zhu; Peking Union Medical College Hospital, Neurology Zhou, Lixin; Peking Union Medical College, Department of Neurology Peng, Bin; Peking Union Medical College Hospital Ni, Jun; Peking Union Medical College Hospital Department of Neurology, Department of Neurology
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Prognosis, THERAPEUTICS

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Manuscripts

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4 **Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic**  
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6 **Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled**  
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9 **Trial**  
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56 **Total word count: 4102**  
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## Abstract

**Introduction:** Branch atheromatous disease (BAD)-related stroke is increasingly becoming a clinical entity and prone to early neurological deterioration (END) and poor prognosis. There are no effective regimens to reduce the disability caused by BAD-related stroke in acute phase. Recent studies have indicated the efficacy of tirofiban in acute ischemic stroke, however, its efficacy has not been validated in patients with BAD-related stroke. Thus, we aim to test whether intravenous tirofiban initiated within 48 hours after onset would safely improve the functional outcome in patients with acute BAD-related stroke, in comparison with standard antiplatelet therapy based on the current guideline.

**Methods and analysis:** BRANT is a multicenter, randomized, open-label, blinded endpoint, parallel-controlled, phase III trial conducted in 21 hospitals in China. Participants aged 18-75 years with acute BAD-related stroke within 48 h after stroke onset are randomized in a 1:1 ratio to the tirofiban or control group. The treatment period is 48 hours in both groups. The primary outcome is the excellent functional outcome (modified Rankin Scale score: 0-1) at 90 days. The secondary outcomes include END, major bleeding, stroke, death, functional status, serious adverse events, and change in bleeding-related markers. Assuming the rates of the primary outcome to be 74% in the tirofiban group and 62% in the control group, a total of 516 participants are needed for 0.8 power (two-sided 0.05 alpha).

**Ethics and dissemination:** BRANT study has been approved by the Ethics Committee of the Peking Union Medical College Hospital (I-23PJ1242). Written informed consent

1  
2  
3  
4 is required for all patients before enrollment. The results of the study will be published  
5  
6 in a peer-reviewed journal.  
7

8  
9 **Trial registration number** ClinicalTrials.gov (NCT06037889)  
10

11 **Keywords:** Branch Atheromatous Disease, Acute ischemic stroke, Early neurological  
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13 deterioration, Functional outcome, Tirofiban, Treatment  
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### Strengths and limitations of this study

1. With the aid of magnetic resonance imaging, this study focuses on patients with acute BAD-related stroke, which had been inappropriately classified as small-vessel occlusion or an undetermined aetiology by the TOAST system in previous studies.
2. Intervention will be initiated within 48 hours of onset, which is more in line with the timeliness of BAD treatment.
3. Lack of double-blinded design is a limitation, but the endpoints are measured in a blinded manner.

## Introduction

Branch atheromatous disease (BAD), first described conceptually by Caplan in 1989, is being confirmed as a clinical entity with the aid of advanced neuroimaging.[1-3] BAD-related stroke, characterized by subcortical single infarcts in penetrating artery territories without severe stenosis of the large parent artery, accounts for 20.4% of all ischaemic stroke cases in Asian populations[2 4]. Differing from lacunar infarct due to lipohyalinosis, BAD-related stroke is caused by parent arterial plaque occlusion of the perforating orifice or proximal atherosclerotic occlusion of the perforating artery[1-3], which could be identified from small-vessel occlusion or stroke of undetermined source in the Trial Org 10172 in Acute Stroke Treatment (TOAST) system[5 6].

High incidence of early neurological deterioration (END) has been observed in BAD-related stroke and is strongly associated with poor prognosis[7 8]. The rate of END is higher in BAD-related stroke than lacunar infarct (26.8-37.5% vs. 6.3-18.6%), and thrombolysis itself cannot prevent the occurrence of END[7-9]. In addition, it remains unclear whether intravenous thrombolysis could improve the clinical outcome in BAD-related stroke[10]. The rate of disability can reach 61%[2]. However, there are no high-level recommendations for acute-phase treatment of BAD-related stroke, and no Randomized Controlled Trial (RCT) has examined BAD as a separate disease. Current practice—based on limited observational data and expert opinion—is heterogeneous, including anticoagulant and mono/dual antiplatelet therapy, the efficacy of which is uncertain for BAD-related stroke[11 12].

Tirofiban, a selective and reversible antagonist of glycoprotein IIb/IIIa inhibitors on

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4 platelets, might be more effective than conventional agents (such as aspirin or  
5  
6 clopidogrel) by blocking the final common pathway of platelet aggregation at the  
7  
8 pathophysiological level[13]. In clinical studies, historical evidence has also reported  
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10 that tirofiban increases the recanalization rate and improves functional prognosis in  
11  
12 stroke patients with endovascular therapy without increasing bleeding risk[14-16]. A  
13  
14 large randomized trial of patients with stroke without large or medium-sized vessel  
15  
16 occlusion also reported the efficacy of tirofiban[17]. However, though an  
17  
18 atherosclerotic mechanism is presumed to exist between BAD and large artery  
19  
20 atherosclerosis, this evidence may not be generalized to BAD-related stroke, as  
21  
22 retrospective data or small samples may introduce selection bias[14 18]. Moreover,  
23  
24 about 78.6%-90.9% of END occurs within 48 h after onset[19 20]. Our preliminary  
25  
26 results of a cohort with BAD-related stroke found that the median time from onset to  
27  
28 END was 38 h. We hypothesised that early tirofiban administration could improve  
29  
30 functional prognosis by preventing the occurrence of END. However, tirofiban was  
31  
32 often prescribed after END in previous studies, which might cause irreversible ischemic  
33  
34 lesions and neurologic deficits[14 17]. Thus, randomised controlled trials of acute  
35  
36 BAD-related stroke are needed and have been requested by researchers[3 4]. In addition,  
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38 we speculated that tirofiban should be initiated within 48 h after onset to prevent the  
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40 occurrence of END.  
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53 The BRANT trial aims to establish the efficacy and safety of intravenous tirofiban for  
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55 improving functional outcome in patients with acute BAD-related stroke.  
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## Methods

### Design

This is a multicenter, randomized, open-label, blinded-endpoint, parallel-controlled phase III trial. The BRANT study began enrolment on November 9, 2023, and the anticipated date of study completion is October 31, 2025.

### Patient population

BRANT will enroll 516 participants with BAD-related stroke within 48 hours of onset, from 21 centers in China.

### Inclusion criteria

- Age: 18-75 years old [21 22]
- Acute ischemic stroke
- Time from onset to randomization  $\leq 48\text{h}$ ; if onset time is unknown, time from last known well to randomization  $\leq 48\text{h}$
- Meet the following BAD Diagnostic Imaging Criteria
  1. Diffusion Weighted Imaging (DWI) infarcts: single (isolated) deep (subcortical) infarcts;
  2. The culprit arteries are either lenticulostriate artery (LSA) or paramedian pontine artery (PPA), and the infarct lesion on DWI conforms to one of the following characteristics (A/B):
    - A. LSA: “Comma-like” infarct lesions with “fan-shaped” extension from bottom to top in the coronary position; or  $\geq 3$  layers (layer thickness 5–7 mm) on axial DWI brain images;



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3  
4 B. PPA: The infarct lesion extends from the deep pons to the ventral pons on  
5  
6 the axial DWI brain images;

- 7  
8  
9 ● No more than 50% stenosis on the parent artery of the criminal artery (i.e.  
10  
11 corresponding basilar or middle cerebral artery) (Confirmed by magnetic  
12  
13 resonance angiography[MRA]/ computed tomography angiography [CTA]/  
14  
15 digital subtraction angiography [DSA])  
16  
17  
18 ● Signed informed consent by the patient or legally authorized representatives.  
19  
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21

### 22 **Exclusion criteria**

- 23  
24 ● Transient ischemic attack (TIA)  
25  
26  
27 ● Intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain  
28  
29 abscesses, malignant space-occupying lesions, or other non- ischemic  
30  
31 intracranial lesions detected by baseline computed tomography(CT)/ magnetic  
32  
33 resonance imaging (MRI), or MRA/CTA/ DSA  
34  
35  
36 ● Presence of  $\geq 50\%$  stenosis in extracranial artery in tandem relationship  
37  
38 ipsilateral to the lesion  
39  
40  
41  
42 ● Cardiogenic embolism: atrial fibrillation, myocardial infarction, heart valve  
43  
44 disease, dilated cardiomyopathy, infective endocarditis, atrioventricular block  
45  
46 disease, heart rate less than 50 beats per minute  
47  
48  
49  
50 ● Have received or plan to receive endovascular therapy or thrombolysis after  
51  
52 onset  
53  
54  
55 ● Stroke of other clear causes, e.g., moyamoya disease, arterial entrapment,  
56  
57 vasculitis, etc.  
58  
59  
60

- modified Rankin Scale score  $\geq 2$  before onset
- Use of tirofiban within 1 week before or after onset
- Low platelets ( $<100 \times 10^9/L$ ), or prothrombin time  $>1.3$  times of the upper normal limit, or international normalised ratio (INR)  $>1.5$ , or other systemic hemorrhagic tendencies such as hematologic disorders
- Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 1.5 times the upper normal limit
- Glomerular filtration rate  $<60$  mL/min/1.73m<sup>2</sup>
- Known malignant tumors
- History of trauma or major surgical intervention within 6 weeks prior to onset
- History of intracranial hemorrhage
- Active or recent history (within 30 days prior to onset) of clinical bleeding (e.g., gastrointestinal bleeding)
- Malignant hypertension (systolic blood pressure  $>200$  mmHg, or diastolic blood pressure  $>120$  mmHg)
- Life expectancy  $\leq 6$  months
- Contraindications of 3 T MRI examination
- Pregnant or lactating women
- Have participated in another clinical trial within 3 months prior to the date of informed consent or are participating in another clinical trial

## Randomization

1  
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4 Participants will be randomized in a 1:1 ratio using a dynamic block randomization  
5  
6 method via an independent central website. The block sizes were set to 6, 8, and 12.  
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8  
9 The allocation sequence is stored on the central website and the participant will be  
10  
11 assigned to the intervention or control group in a 1:1 ratio according to the order of  
12  
13 enrolment.  
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15

### 16 17 18 19 **Intervention**

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22 Tirofiban group: Intravenous tirofiban will be administered immediately after  
23  
24 randomization for a total duration of 48 hours with a loading dose of 0.4µg  
25  
26 /kg/min×30min, followed by a maintenance dose of 0.1µg /kg/min×47.5h (Figure1).  
27  
28

29  
30 Control group: Standard antiplatelet therapy based on Chinese stroke guideline will be  
31  
32 initiated after randomization for a total duration of 48 hours, as the two following types:  
33  
34 (1) aspirin 150-300 mg qd, or (2) aspirin 100 mg qd plus clopidogrel 75 mg qd.[23] Its  
35  
36 initiation will be determined based on the last administration time of antithrombotic  
37  
38 drugs; however, the drug should be administered as soon as possible.  
39  
40

41  
42 After a 48-hour treatment period in both groups, the standard of care, including an  
43  
44 antithrombotic regimen, will be performed based on current guidelines and recorded in  
45  
46 detail (Figure 1).  
47  
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### 49 50 **Primary outcomes**

51  
52 The primary outcome is excellent functional outcome at 90 days, defined as modified  
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54 Rankin Scale score of 0-1[24]. Primary outcome will be measured by the qualified  
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56 evaluators who are blinded to all procedures.  
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## Secondary outcomes

Secondary efficacy outcomes include END, National Institutes of Health Stroke Scale (NIHSS) score, Barthel index score, ischemic stroke, stroke, TIA, and a composite event of new-onset stroke, myocardial infarction, and all-cause death. Excellent functional outcome at 7 days is also listed as a secondary efficacy outcome. Safety outcomes include the proportion of major bleeding as defined by the PLATO criteria, adverse events, all-cause death, and changes in bleeding-related markers[25]. The evaluators will not be aware of the treatment assignment after randomization. All the clinical and safety events will be re-examined by the independent Clinical Event Committee (CEC), who will be blinded during all procedures.

Considering the predictive value of END, we adopted the widely used and conservative definition of END for the BRANT study[26]. The presence of END is determined by an increase of  $\geq 4$  points in the NIHSS or an increase of  $\geq 2$  points in the NIHSS motor score. The NIHSS motor score refers to bilateral upper and lower extremity mobility scores. The baseline NIHSS score for the calculation of END is the first clinician evaluated and recorded NIHSS score after onset. The time frame for post-randomisation END is within 7 days of randomization.

## Study protocol and data management

A study flowchart is shown in Figure 1 and Table S1. At visit 1, trained investigators will recruit patients based on screening age, onset time, MRI, and other enrolment criteria (i.e. intracranial artery and electrocardiogram). The investigator will then

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3  
4 explain the BRANT study to the patient in detail, including the contents of each visit  
5  
6 and the interventions. After obtaining written informed consent, the participants will be  
7  
8 assigned to the tirofiban or control groups via a central website-based randomization  
9  
10 system. Patients are encouraged to undergo on-site follow-up at 90 days. Demographic,  
11  
12 clinical, radiological, laboratory, and clinical event data at each visit (Table S1) will be  
13  
14 collected and stored in an electronic case report form (CRF) via a secure website. All  
15  
16 CRFs will be checked by local investigators for completeness and correction prior to  
17  
18 data entry. The data will be checked dynamically by the principal investigator (Jun Ni)  
19  
20 with the aid of research assistants.  
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### 30 **Data Monitoring Board**

31  
32 An independent Data Security Monitoring Board (DSMB), including academic experts  
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34 and statisticians, has been established to protect the interests of the participants during  
35  
36 the study. The DSMB will review the overall implementation of the clinical study and  
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38 regularly and dynamically assess the risks and benefits, particularly unexpected adverse  
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40 events. The DSMB reports to the Executive Committee and provides professional  
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42 advice.  
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### 50 **Sample size estimates**

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52 Based on previous studies and clinical practice, we assumed the rates of the primary  
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54 outcome to be 62% and 74% in the control and tirofiban groups, respectively[2 14-16  
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4 18 27-29]. Thus, 234 participants per arm are needed for a two-sided test at alpha 0.05  
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6 and power 0.8. Considering a dropout rate of 10%, 516 patients will be required.  
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## 10 11 **Statistical analyses**

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14 According to the principle of intention-to-treat analysis, all participants who are  
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16 randomized into groups with more than one efficacy evaluation will be included in the  
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18 full analysis set. The estimation of missing values will be conducted by the carry-over  
19  
20 based on last observation carried forward (LOCF) estimation method. The proportion  
21  
22 of excellent outcomes at 90 days will be compared using the chi-square tests, and shown  
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24 as frequency (percentage). Most secondary outcome analyses will also use the primary  
25  
26 outcome analysis strategy. Survival data will be calculated using the Kaplan-Meier  
27  
28 method to estimate the survival rate in each group, and efficacy will be assessed using  
29  
30 the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CI) will be  
31  
32 calculated using the Cox proportional hazards model. Non-survival data will be  
33  
34 analysed using the chi-square test, and odds ratios and 95% CIs will be calculated.  
35  
36 Continuous variables will be compared between the two groups using the Student's t-  
37  
38 test or Wilcoxon rank-sum test. The influence of covariables will be evaluated using  
39  
40 subgroup analysis. No interim analysis is planned in this trial. All analyses will be  
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42 performed using SAS 9.4, and a two-sided  $P < 0.05$  is considered significant.  
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## 56 **Patient and public involvement statement**

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58 None.  
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7 **Ethics and dissemination:** The BRANT study was approved by the Ethics Committee  
8  
9 of Peking Union Medical College Hospital (I-23PJ1242) on July 20, 2023. Written  
10  
11 informed consent is required from all patients before enrolment. BRANT will be carried  
12  
13 out according to Good Clinical Practice and the Declaration of Helsinki. Protocol  
14  
15 amendments will be reported to the institutional ethics committee. The trial sponsor is  
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17 Peking Union Medical College Hospital. The trial results will be published in a peer-  
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19 reviewed journal.  
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## 27 **Discussion**

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29 The BRANT trial is a multicentre RCT that addresses the important treatment dilemma  
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31 of improving the functional outcomes of BAD-related stroke.  
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35 BAD was first proposed by Caplan in 1989 to be distinct from lacunar infarct[1].  
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37 However, in the past three decades, most clinical studies have classified BAD as small-  
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39 vessel occlusion or undetermined etiology based on the TOAST system[4 30]. Few  
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41 studies focused on acute BAD-related stroke, probably due to discrepant definitions[3].  
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43 Recently, an increasing number of observational studies found distinct clinical,  
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45 radiologic, and prognostic features that patients with BAD-related stroke are prone to  
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47 END and poor prognosis[2 31].  
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53 Owing to the limitations of neuroimaging techniques, the perforating artery, such as the  
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55 LSA or PPA, cannot be directly visualized. Radiological diagnosis is based on the  
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57 vascular territory, dimension, or shape of the lesion[3 32], which results in a huge  
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4 variations among BAD definitions. With the aid of neuroimaging and clinical practice,  
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6 Asian neurologists proposed radiological diagnosis criteria for BAD[33 34]. Our  
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8 previous study also found that  $\geq 4$  consecutive slices on axial view are more effective  
9  
10 than transversal diameter to differentiate atherosclerotic mechanisms of single  
11  
12 subcortical infarction in the LSA territory[35]. Considering the generalisation and  
13  
14 diagnostic accuracy of our study, we used  $\geq 3$  consecutive layers on axial DWI series  
15  
16 instead of lesion diameter to define BAD-related stroke in the LSA territory[36].  
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18 Because obtaining direct evidence of the LSA and PPA is currently not technically  
19  
20 feasible, our inclusion criteria based on MRI show considerable accuracy and  
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22 representativeness.  
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26 In addition, our study uses simplified operationalised criteria to exclude cardiogenic  
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28 embolism, and patients with these comorbidities will not be included. Some conditions  
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30 seem general, which is a limitation of our study; however, this facilitates the  
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32 researcher's ability to complete screening within a limited timeframe with low  
33  
34 inconsistency.  
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38 We set a 90-day excellent outcome instead of END or new-onset stroke as the primary  
39  
40 outcome for the following reasons: (1) historical evidence indicated that tirofiban  
41  
42 improved the functional outcome of ischemic stroke[14 17]; (2) END is an intermediate  
43  
44 indicators[7]; (3) the 90-day rate of recurrent stroke is 1.8% in our preliminary analysis  
45  
46 of a BAD-related stroke cohort and probably less than 3.8% in other cohorts[31], which  
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48 is relatively low. Thus, the BRANT study will provide direct evidence on how to reduce  
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50 disability caused by BAD, which is the major challenge in current clinical practice.  
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4 As oral mono antiplatelet therapy is unethical and against Chinese stroke guidelines for  
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6 patients with NIHSS  $\leq 3$ , there are two types of antiplatelet therapy in the control  
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8 group[23]. A double-blind design would markedly increase the complexity of the trial  
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10 procedure. Therefore, we selected a prospective randomized open blinded end-point  
11  
12 design (PROBE) for BRANT. Independent senior neurologists who will be blinded to  
13  
14 the procedure information have been trained to evaluate the primary outcome. An  
15  
16 independent CEC has been established to centrally re-examine all clinical events after  
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18 randomization. Some local investigators may know the treatment allocation; however,  
19  
20 all evaluators of the subjective indicators will be blinded to the treatment allocation.  
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30 **Contributors:** Shengde Li, and Jun Ni designed the study. Shengde Li drafted the  
31  
32 manuscript. Dingding Zhang designed the statistical method. Yuhui Sha, Lixin Zhou,  
33  
34 Yicheng Zhu, and Bin Peng critically revised the study protocol and the manuscript.  
35  
36 The entire project will be supervised by Jun Ni.  
37  
38  
39

40 **Funding:** This study is funded by the National High Level Hospital Clinical Research  
41  
42 Funding (2022-PUMCH-D-007).  
43  
44

45 **Disclaimer:** The funder has no role in this study.  
46  
47

48 **Competing interests:** None declared.  
49  
50

#### 51 **Data Availability Statement**

52  
53 The data that support the findings of this study are available from the corresponding  
54  
55 author on reasonable request.  
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**Figure I. Study Flow**

For peer review only

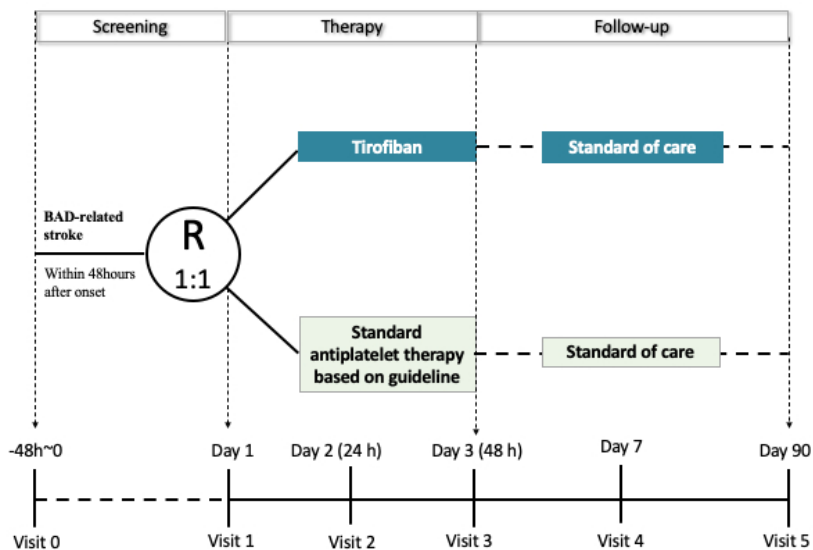


Figure 1. Study Flow

338x190mm (54 x 54 DPI)

## Supplementary materials

**Table S1. Study Procedure of BRANT trial**

Measurement	Day 1	Day 2	Day 3	Day 7	Day 90
Demographic characteristics	X				
Current medical history taking	X				
Body temperature measurement	X				
Physical examination	X			X	X
Past medical history	X				
Pre-randomization medication after onset	X				
Regular blood pressure monitoring	X	X			
NIHSS score	X			X	X
mRS score	X			X	X
Barthel index score	X				X
Magnetic resonance image	X				
Evaluation of Intracranial vessels	X				
Evaluation of extracranial vessels	X				
Laboratory tests*	X				
ECG*	X			X	
Verification of inclusion/exclusion criteria	X				
Signed informed consent	X				
Randomization	X				
Blood tests after enrollment		X	X		



Urine and fecal examination			<b>X</b>		
Compliance			<b>X</b>		
Concomitant medication				<b>X</b>	<b>X</b>
Early neurological deterioration				<b>X</b>	
Major bleeding				<b>X</b>	<b>X</b>
Adverse Events/ Serious Adverse Events				<b>X</b>	<b>X</b>
<p>*Remarks: ECG and laboratory data performed within 48 hours of onset before signing the informed consent form can be used as trial data.</p>					



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2-3
	2b	All items from the World Health Organization Trial Registration Data Set	Clinical Trials.gov
Protocol version	3	Date and version identifier	In Protocol, not shown in article
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	Clinical Trials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

**Introduction**

1				
2	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
3				
4				
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
11				
12				
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14				
15				
16	<b>Methods: Participants, interventions, and outcomes</b>			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
19				
20				
21				
22				
23	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
24				
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26				
27	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
28				
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30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	In Protocol, not shown in article
31				
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37		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	In Protocol, not shown in article
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44		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	In Protocol, not shown in article
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51	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
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2	Participant	13	Time schedule of enrolment, interventions (including any run-ins	Figure
3	timeline		and washouts), assessments, and visits for participants. A	1
4			schematic diagram is highly recommended (see Figure)	
5				
6	Sample size	14	Estimated number of participants needed to achieve study	12
7			objectives and how it was determined, including clinical and	
8			statistical assumptions supporting any sample size calculations	
9				
10	Recruitment	15	Strategies for achieving adequate participant enrolment to reach	In
11			target sample size	Protocol,
12				not
13				shown in
14				article
15				
16				
17				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21				
22	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9-10
23	generation		generated random numbers), and list of any factors for	
24			stratification. To reduce predictability of a random sequence,	
25			details of any planned restriction (eg, blocking) should be	
26			provided in a separate document that is unavailable to those who	
27			enrol participants or assign interventions	
28				
29				
30	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9-10
31	concealme		telephone; sequentially numbered, opaque, sealed envelopes),	
32	nt		describing any steps to conceal the sequence until interventions	
33	mechanism		are assigned	
34				
35	Implement	16c	Who will generate the allocation sequence, who will enrol	9-10
36	ation		participants, and who will assign participants to interventions	
37				
38	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10-11
39	(masking)		participants, care providers, outcome assessors, data analysts),	
40			and how	
41				
42				
43		17b	If blinded, circumstances under which unblinding is permissible,	NA
44			and procedure for revealing a participant's allocated intervention	
45			during the trial	
46				
47				

### Methods: Data collection, management, and analysis

49				
50	Data	18a	Plans for assessment and collection of outcome, baseline, and	11-12
51	collection		other trial data, including any related processes to promote data	
52	methods		quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known. Reference	
55			to where data collection forms can be found, if not in the protocol	
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2		18b	Plans to promote participant retention and complete follow-up, 11-12
3			including list of any outcome data to be collected for participants
4			who discontinue or deviate from intervention protocols
5			
6	Data	19	Plans for data entry, coding, security, and storage, including any 11-12
7	management		related processes to promote data quality (eg, double data entry;
8			range checks for data values). Reference to where details of data
9			management procedures can be found, if not in the protocol
10			
11			
12	Statistical	20a	Statistical methods for analysing primary and secondary 13
13	methods		outcomes. Reference to where other details of the statistical
14			analysis plan can be found, if not in the protocol
15			
16		20b	Methods for any additional analyses (eg, subgroup and adjusted 13
17			analyses)
18			
19		20c	Definition of analysis population relating to protocol non- 13
20			adherence (eg, as randomised analysis), and any statistical
21			methods to handle missing data (eg, multiple imputation)
22			
23			
24	<b>Methods: Monitoring</b>		
25			
26	Data	21a	Composition of data monitoring committee (DMC); summary of its 12
27	monitoring		role and reporting structure; statement of whether it is
28			independent from the sponsor and competing interests; and
29			reference to where further details about its charter can be found,
30			if not in the protocol. Alternatively, an explanation of why a DMC
31			is not needed
32			
33			
34		21b	Description of any interim analyses and stopping guidelines, NA
35			including who will have access to these interim results and make
36			the final decision to terminate the trial
37			
38	Harms	22	Plans for collecting, assessing, reporting, and managing solicited 12
39			and spontaneously reported adverse events and other
40			unintended effects of trial interventions or trial conduct
41			
42			
43	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and 12
44			whether the process will be independent from investigators and
45			the sponsor
46			
47			
48	<b>Ethics and dissemination</b>		
49			
50	Research	24	Plans for seeking research ethics committee/institutional review 3
51	ethics		board (REC/IRB) approval
52	approval		
53			
54	Protocol	25	Plans for communicating important protocol modifications (eg, 3
55	amendments		changes to eligibility criteria, outcomes, analyses) to relevant
56			parties (eg, investigators, REC/IRBs, trial participants, trial
57			registries, journals, regulators)
58			
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1				
2	Consent or	26a	Who will obtain informed consent or assent from potential trial	3
3	assent		participants or authorised surrogates, and how (see Item 32)	
4				
5		26b	Additional consent provisions for collection and use of participant	NA
6			data and biological specimens in ancillary studies, if applicable	
7				
8	Confidentiality	27	How personal information about potential and enrolled	In
9			participants will be collected, shared, and maintained in order to	protocol
10			protect confidentiality before, during, and after the trial	, not
11				shown in
12				article
13				
14				
15	Declaration of	28	Financial and other competing interests for principal investigators	16
16	interests		for the overall trial and each study site	
17				
18	Access to	29	Statement of who will have access to the final trial dataset, and	16
19	data		disclosure of contractual agreements that limit such access for	
20			investigators	
21				
22				
23	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	In
24	post-trial care		compensation to those who suffer harm from trial participation	protocol
25				, not
26				shown in
27				article
28				
29				
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	See
31	policy		to participants, healthcare professionals, the public, and other	consent
32			relevant groups (eg, via publication, reporting in results	from
33			databases, or other data sharing arrangements), including any	
34			publication restrictions	3
35				
36				
37		31b	Authorship eligibility guidelines and any intended use of	In
38			professional writers	protocol
39				, not
40				shown in
41				article
42				
43				
44		31c	Plans, if any, for granting public access to the full protocol,	NA
45			participant-level dataset, and statistical code	
46				
47	<b>Appendices</b>			
48				
49	Informed	32	Model consent form and other related documentation given to	We
50	consent		participants and authorised surrogates	provide
51	materials			a model
52				consent
53				from
54				
55				
56	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
57	specimens		biological specimens for genetic or molecular analysis in the	
58			current trial and for future use in ancillary studies, if applicable	
59				
60				

1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
2 Explanation & Elaboration for important clarification on the items. Amendments to the  
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
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# BMJ Open

## Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082141.R3
Article Type:	Protocol
Date Submitted by the Author:	05-Apr-2024
Complete List of Authors:	Li, Shengde; Peking Union Medical College Hospital, dingding, zhang; peking union medical college hopspital Sha, Yuhui; Peking Union Medical College, Department of Neurology yicheng, zhu; Peking Union Medical College Hospital, Neurology Zhou, Lixin; Peking Union Medical College, Department of Neurology Peng, Bin; Peking Union Medical College Hospital Ni, Jun; Peking Union Medical College Hospital Department of Neurology, Department of Neurology
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Prognosis, THERAPEUTICS

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4 **Efficacy and Safety of Tirofiban in Patients with Acute Branch Atherosclerotic**  
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6 **Disease(BAD)-Related Stroke (BRANT): Protocol for a Randomized Controlled**  
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9 **Trial**  
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56 **Total word count: 4277**  
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## Abstract

**Introduction:** Branch atheromatous disease (BAD)-related stroke is increasingly becoming a clinical entity and prone to early neurological deterioration (END) and poor prognosis. There are no effective regimens to reduce the disability caused by BAD-related stroke in acute phase. Recent studies have indicated the efficacy of tirofiban in acute ischemic stroke, however, its efficacy has not been validated in patients with BAD-related stroke. Thus, we aim to test whether intravenous tirofiban initiated within 48 hours after onset would improve the functional outcome in patients with acute BAD-related stroke, in comparison with standard antiplatelet therapy based on the current guideline.

**Methods and analysis:** BRANT is a multicenter, randomized, open-label, blinded endpoint, parallel-controlled, phase III trial conducted in 21 hospitals in China. Participants aged 18-75 years with acute BAD-related stroke within 48 h after stroke onset are randomized in a 1:1 ratio to the tirofiban or control group. The treatment period is 48 hours in both groups. The primary outcome is the excellent functional outcome (modified Rankin Scale score: 0-1) at 90 days. The secondary outcomes include END, major bleeding, stroke, death, functional status, serious adverse events, and change in bleeding-related markers. Assuming the rates of the primary outcome to be 74% in the tirofiban group and 62% in the control group, a total of 516 participants are needed for 0.8 power (two-sided 0.05 alpha).

**Ethics and dissemination:** BRANT study has been approved by the Ethics Committee of the Peking Union Medical College Hospital (I-23PJ1242). Written informed consent

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3  
4 is required for all patients before enrollment. The results of the study will be published  
5  
6 in a peer-reviewed journal.  
7

8  
9 **Trial registration number** ClinicalTrials.gov (NCT06037889)  
10

11 **Keywords:** Branch Atheromatous Disease, Acute ischemic stroke, Early neurological  
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13 deterioration, Functional outcome, Tirofiban, Treatment  
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### Strengths and limitations of this study

1. With the aid of magnetic resonance imaging, this study focuses on patients with acute BAD-related stroke, which had been inappropriately classified as small-vessel occlusion or an undetermined aetiology by the TOAST system in previous studies.
2. Intervention will be initiated within 48 hours of onset, which is more in line with the timeliness of BAD treatment.
3. Lack of double-blinded design is a limitation, but the endpoints are measured in a blinded manner.

## Introduction

Branch atheromatous disease (BAD), first described conceptually by Caplan in 1989, is being confirmed as a clinical entity with the aid of advanced neuroimaging.[1-3] BAD-related stroke, characterized by subcortical single infarcts in penetrating artery territories without severe stenosis of the large parent artery, accounts for 20.4% of all ischaemic stroke cases in Asian populations[2 4]. Differing from lacunar infarct due to lipohyalinosis, BAD-related stroke is caused by parent arterial plaque occlusion of the perforating orifice or proximal atherosclerotic occlusion of the perforating artery[1-3], which could be identified from small-vessel occlusion or stroke of undetermined source in the Trial Org 10172 in Acute Stroke Treatment (TOAST) system[5 6].

High incidence of early neurological deterioration (END) has been observed in BAD-related stroke and is strongly associated with poor prognosis[7 8]. The rate of END is higher in BAD-related stroke than lacunar infarct (26.8-37.5% vs. 6.3-18.6%), and thrombolysis itself cannot prevent the occurrence of END[7-9]. In addition, it remains unclear whether intravenous thrombolysis could improve the clinical outcome in BAD-related stroke[10]. The rate of disability can reach 61%[2]. However, there are no high-level recommendations for acute-phase treatment of BAD-related stroke, and no Randomized Controlled Trial (RCT) has examined BAD as a separate disease. Current practice—based on limited observational data and expert opinion—is heterogeneous, including anticoagulant and mono/dual antiplatelet therapy, the efficacy of which is uncertain for BAD-related stroke[11 12].

Tirofiban, a selective and reversible antagonist of glycoprotein IIb/IIIa inhibitors on

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4 platelets, might be more effective than conventional agents (such as aspirin or  
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6 clopidogrel) by blocking the final common pathway of platelet aggregation at the  
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8 pathophysiological level[13]. In clinical studies, historical evidence has also reported  
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10 that tirofiban increases the recanalization rate and improves functional prognosis in  
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12 stroke patients with endovascular therapy without increasing bleeding risk[14-16]. A  
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14 large randomized trial of patients with stroke without large or medium-sized vessel  
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16 occlusion also reported the efficacy of tirofiban[17]. However, though an  
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18 atherosclerotic mechanism is presumed to exist between BAD and large artery  
19  
20 atherosclerosis, this evidence may not be generalized to BAD-related stroke, as  
21  
22 retrospective data or small samples may introduce selection bias[14 18]. Moreover,  
23  
24 about 78.6%-90.9% of END occurs within 48 h after onset[19 20]. Our preliminary  
25  
26 results of a cohort with BAD-related stroke found that the median time from onset to  
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28 END was 38 h. We hypothesised that early tirofiban administration could improve  
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30 functional prognosis by preventing the occurrence of END. However, tirofiban was  
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32 often prescribed after END in previous studies, which might cause irreversible ischemic  
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34 lesions and neurologic deficits[14 17]. Thus, randomised controlled trials of acute  
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36 BAD-related stroke are needed and have been requested by researchers[3 4]. In addition,  
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38 we speculated that tirofiban should be initiated within 48 h after onset to prevent the  
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40 occurrence of END.  
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53 The BRANT trial aims to establish the efficacy and safety of intravenous tirofiban for  
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55 improving functional outcome in patients with acute BAD-related stroke.  
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## Methods

### Design

This is a multicenter, randomized, open-label, blinded-endpoint, parallel-controlled phase III trial. The BRANT study began enrolment on November 9, 2023, and the anticipated date of study completion is October 31, 2025.

### Patient population

BRANT will enroll 516 participants with BAD-related stroke within 48 hours of onset, from 21 centers in China.

### Inclusion criteria

- Age: 18-75 years old [21 22]
- Acute ischemic stroke
- Time from onset to randomization  $\leq 48\text{h}$ ; if onset time is unknown, time from last known well to randomization  $\leq 48\text{h}$
- Meet the following BAD Diagnostic Imaging Criteria
  1. Diffusion Weighted Imaging (DWI) infarcts: single (isolated) deep (subcortical) infarcts;
  2. The culprit arteries are either lenticulostriate artery (LSA) or paramedian pontine artery (PPA), and the infarct lesion on DWI conforms to one of the following characteristics (A/B):
    - A. LSA: “Comma-like” infarct lesions with “fan-shaped” extension from bottom to top in the coronary position; or  $\geq 3$  layers (layer thickness 5–7 mm) on axial DWI brain images;

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4 B. PPA: The infarct lesion extends from the deep pons to the ventral pons on  
5  
6 the axial DWI brain images;

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9 ● No more than 50% stenosis on the parent artery of the criminal artery (i.e.  
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11 corresponding basilar or middle cerebral artery) (Confirmed by magnetic  
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13 resonance angiography[MRA]/ computed tomography angiography [CTA]/  
14  
15 digital subtraction angiography [DSA])  
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17  
18 ● Signed informed consent by the patient or legally authorized representatives.  
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### 22 **Exclusion criteria**

- 23  
24 ● Transient ischemic attack (TIA)  
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27 ● Intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain  
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29 abscesses, malignant space-occupying lesions, or other non- ischemic  
30  
31 intracranial lesions detected by baseline computed tomography(CT)/ magnetic  
32  
33 resonance imaging (MRI), or MRA/CTA/ DSA  
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35  
36 ● Presence of  $\geq 50\%$  stenosis in extracranial artery in tandem relationship  
37  
38 ipsilateral to the lesion  
39  
40  
41  
42 ● Cardiogenic embolism: atrial fibrillation, myocardial infarction, heart valve  
43  
44 disease, dilated cardiomyopathy, infective endocarditis, atrioventricular block  
45  
46 disease, heart rate less than 50 beats per minute  
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49  
50 ● Have received or plan to receive endovascular therapy or thrombolysis after  
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52 onset  
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55 ● Stroke of other clear causes, e.g., moyamoya disease, arterial entrapment,  
56  
57 vasculitis, etc.  
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- modified Rankin Scale score  $\geq 2$  before onset
- Use of tirofiban within 1 week before or after onset
- Low platelets ( $<100 \times 10^9/L$ ), or prothrombin time  $>1.3$  times of the upper normal limit, or international normalised ratio (INR)  $>1.5$ , or other systemic hemorrhagic tendencies such as hematologic disorders
- Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 1.5 times the upper normal limit
- Glomerular filtration rate  $<60$  mL/min/1.73m<sup>2</sup>
- Known malignant tumors
- History of trauma or major surgical intervention within 6 weeks prior to onset
- History of intracranial hemorrhage
- Active or recent history (within 30 days prior to onset) of clinical bleeding (e.g., gastrointestinal bleeding)
- Malignant hypertension (systolic blood pressure  $>200$  mmHg, or diastolic blood pressure  $>120$  mmHg)
- Life expectancy  $\leq 6$  months
- Contraindications of 3 T MRI examination
- Pregnant or lactating women
- Have participated in another clinical trial within 3 months prior to the date of informed consent or are participating in another clinical trial

## Randomization

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4 Participants will be randomized in a 1:1 ratio using a dynamic block randomization  
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6 method via an independent central website. The block sizes were set to 6, 8, and 12.  
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9 The allocation sequence is stored on the central website and the participant will be  
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11 assigned to the intervention or control group in a 1:1 ratio according to the order of  
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13 enrolment.  
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### 16 17 18 19 **Intervention**

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22 Tirofiban group: Intravenous tirofiban will be administered immediately after  
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24 randomization for a total duration of 48 hours with a loading dose of 0.4µg  
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26 /kg/min×30min, followed by a maintenance dose of 0.1µg /kg/min×47.5h (Figure1).  
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30 Control group: Standard antiplatelet therapy based on Chinese stroke guideline will be  
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32 initiated after randomization for a total duration of 48 hours, as the two following types:  
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35 (1) aspirin 150-300 mg qd, or (2) aspirin 100 mg qd plus clopidogrel 75 mg qd.[23] Its  
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37 initiation will be determined based on the last administration time of antithrombotic  
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39 drugs; however, the drug should be administered as soon as possible.  
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43 After a 48-hour treatment period in both groups, the standard of care, including an  
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45 antithrombotic regimen, will be performed based on current guidelines and recorded in  
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47 detail (Figure 1).  
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### 50 51 **Primary outcomes**

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53 The primary outcome is excellent functional outcome at 90 days, defined as modified  
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55 Rankin Scale score of 0-1[24]. Primary outcome will be measured by the qualified  
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57 evaluators who are blinded to all procedures.  
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## Secondary outcomes

Secondary efficacy outcomes include END, National Institutes of Health Stroke Scale (NIHSS) score, Barthel index score, ischemic stroke, stroke, TIA, and a composite event of new-onset stroke, myocardial infarction, and all-cause death. Excellent functional outcome at 7 days is also listed as a secondary efficacy outcome. Safety outcomes include major bleeding as defined by the PLATO criteria, adverse events, all-cause death, and changes in bleeding-related markers[25]. The evaluators will not be aware of the treatment assignment after randomization. All the clinical and safety events will be re-examined by the independent Clinical Event Committee (CEC), who will be blinded during all procedures.

Considering the predictive value of END, we adopted the widely used and conservative definition of END for the BRANT study<sup>[26]</sup>. The presence of END is determined by an increase of  $\geq 4$  points in the NIHSS or an increase of  $\geq 2$  points in the NIHSS motor score. The NIHSS motor score refers to bilateral upper and lower extremity mobility scores. The baseline NIHSS score for the calculation of END is the first clinician evaluated and recorded NIHSS score after onset. The time frame for post-randomisation END is within 7 days of randomization.

## Study protocol and data management

A study flowchart is shown in Figure 1 and Table S1. At visit 1, trained investigators will recruit patients based on screening age, onset time, MRI, and other enrolment criteria (i.e. intracranial artery and electrocardiogram). The investigator will then

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4 explain the BRANT study to the patient in detail, including the contents of each visit  
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6 and the interventions. After obtaining written informed consent, the participants will be  
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8 assigned to the tirofiban or control groups via a central website-based randomization  
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10 system. Patients are encouraged to undergo on-site follow-up at 90 days. Demographic,  
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12 clinical, radiological, laboratory, and clinical event data at each visit (Table S1) will be  
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14 collected and stored in an electronic case report form (CRF) via a secure website. All  
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16 CRFs will be checked by local investigators for completeness and correction prior to  
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18 data entry. The data will be checked dynamically by the principal investigator (Jun Ni)  
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20 with the aid of research assistants.  
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### 30 **Data Monitoring Board**

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32 An independent Data Security Monitoring Board (DSMB), including academic experts  
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34 and statisticians, has been established to protect the interests of the participants during  
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36 the study. The DSMB will review the overall implementation of the clinical study and  
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38 regularly and dynamically assess the risks and benefits, particularly unexpected adverse  
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40 events. The DSMB reports to the Executive Committee and provides professional  
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42 advice.  
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### 50 **Sample size estimates**

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52 Based on previous studies and clinical practice, we assumed the rates of the primary  
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54 outcome to be 62% and 74% in the control and tirofiban groups, respectively<sup>[2 14-16 18</sup>  
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4 27-29]. Thus, 234 participants per arm are needed for a two-sided test at alpha 0.05 and  
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6 power 0.8. Considering a dropout rate of 10%, 516 patients will be required.  
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### 10 11 **Statistical analyses**

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14 According to the principle of intention-to-treat analysis, all participants who are  
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16 randomized into groups with more than one efficacy evaluation will be included in the  
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18 full analysis set. The estimation of missing values will be conducted by the carry-over  
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20 based on last observation carried forward (LOCF) estimation method. The proportion  
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22 of excellent outcomes at 90 days will be compared using the chi-square tests, and shown  
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24 as frequency (percentage). Most secondary outcome analyses will also use the primary  
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26 outcome analysis strategy. Survival data will be calculated using the Kaplan-Meier  
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28 method to estimate the survival rate in each group, and efficacy will be assessed using  
29  
30 the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CI) will be  
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32 calculated using the Cox proportional hazards model. Non-survival data will be  
33  
34 analysed using the chi-square test, and odds ratios and 95% CIs will be calculated.  
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36 Continuous variables will be compared between the two groups using the Student's t-  
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38 test or Wilcoxon rank-sum test. The influence of covariables will be evaluated using  
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40 subgroup analysis. No interim analysis is planned in this trial. All analyses will be  
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42 performed using SAS 9.4, and a two-sided  $P < 0.05$  is considered significant.  
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### 56 **Patient and public involvement statement**

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58 None.  
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7 **Ethics and dissemination:** The BRANT study was approved by the Ethics Committee  
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9 of Peking Union Medical College Hospital (I-23PJ1242) on July 20, 2023. Written  
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11 informed consent is required from all patients before enrolment. BRANT will be carried  
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13 out according to Good Clinical Practice and the Declaration of Helsinki. Protocol  
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15 amendments will be reported to the institutional ethics committee. The trial sponsor is  
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17 Peking Union Medical College Hospital. The trial results will be published in a peer-  
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19 reviewed journal.  
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## 27 **Discussion**

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29 The BRANT trial is a multicentre RCT that addresses the important treatment dilemma  
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31 of improving the functional outcomes of BAD-related stroke.  
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35 BAD was first proposed by Caplan in 1989 to be distinct from lacunar infarct[1].  
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37 However, in the past three decades, most clinical studies have classified BAD as small-  
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39 vessel occlusion or undetermined etiology based on the TOAST system<sup>[4 30]</sup>. Few  
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41 studies focused on acute BAD-related stroke, probably due to discrepant definitions[3].  
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43 Recently, an increasing number of observational studies found distinct clinical,  
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45 radiologic, and prognostic features that patients with BAD-related stroke are prone to  
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47 END and poor prognosis<sup>[2 31]</sup>.  
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53 Owing to the limitations of neuroimaging techniques, the perforating artery, such as the  
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55 LSA or PPA, cannot be directly visualized. Radiological diagnosis is based on the  
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57 vascular territory, dimension, or shape of the lesion<sup>[3 32]</sup>, which results in a huge  
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4 variations among BAD definitions. With the aid of neuroimaging and clinical practice,  
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6 Asian neurologists proposed radiological diagnosis criteria for BAD<sup>[33 34]</sup>. Our previous  
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8 study also found that  $\geq 4$  consecutive slices on axial view are more effective than  
9  
10 transversal diameter to differentiate atherosclerotic mechanisms of single subcortical  
11  
12 infarction in the LSA territory<sup>[35]</sup>. Considering the generalisation and diagnostic  
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14 accuracy of our study, we used  $\geq 3$  consecutive layers on axial DWI series instead of  
15  
16 lesion diameter to define BAD-related stroke in the LSA territory<sup>[36]</sup>. Because obtaining  
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18 direct evidence of the LSA and PPA is currently not technically feasible, our inclusion  
19  
20 criteria based on MRI show considerable accuracy and representativeness.  
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27 In addition, our study uses simplified operationalised criteria to exclude cardiogenic  
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29 embolism, and patients with these comorbidities will not be included. Some conditions  
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31 seem general, which is a limitation of our study; however, this facilitates the  
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33 researcher's ability to complete screening within a limited timeframe with low  
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35 inconsistency.  
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40 We set a 90-day excellent outcome instead of END or new-onset stroke as the primary  
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42 outcome for the following reasons: (1) historical evidence indicated that tirofiban  
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44 improved the functional outcome of ischemic stroke<sup>[14 17]</sup>; (2) END is an intermediate  
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46 indicators<sup>[7]</sup>; (3) the 90-day rate of recurrent stroke is 1.8% in our preliminary analysis  
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48 of a BAD-related stroke cohort and probably less than 3.8% in other cohorts<sup>[31]</sup>, which  
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50 is relatively low. Thus, the BRANT study will provide direct evidence on how to reduce  
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52 disability caused by BAD, which is the major challenge in current clinical practice.  
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4 As oral mono antiplatelet therapy is unethical and against Chinese stroke guidelines for  
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6 patients with NIHSS  $\leq 3$ , there are two types of antiplatelet therapy in the control  
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8 group[23]. A double-blind design would markedly increase the complexity of the trial  
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10 procedure. Therefore, we selected a prospective randomized open blinded end-point  
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12 design (PROBE) for BRANT. Independent senior neurologists who will be blinded to  
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14 the procedure information have been trained to evaluate the primary outcome. An  
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16 independent CEC has been established to centrally re-examine all clinical events after  
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18 randomization. Some local investigators may know the treatment allocation; however,  
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20 all evaluators of the subjective indicators will be blinded to the treatment allocation.  
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30 **Contributors:** Shengde Li, and Jun Ni designed the study. Shengde Li drafted the  
31  
32 manuscript. Dingding Zhang designed the statistical method. Yuhui Sha, Lixin Zhou,  
33  
34 Yicheng Zhu, and Bin Peng critically revised the study protocol and the manuscript.  
35  
36 The entire project will be supervised by Jun Ni.  
37  
38  
39

40 **Funding:** This study is funded by the National High Level Hospital Clinical Research  
41  
42 Funding (2022-PUMCH-D-007).  
43  
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45 **Disclaimer:** The funder has no role in this study.  
46  
47

48 **Competing interests:** None declared.  
49  
50

#### 51 **Data Availability Statement**

52  
53 The data that support the findings of this study are available from the corresponding  
54  
55 author on reasonable request.  
56  
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**Figure I. Study Flow**

For peer review only

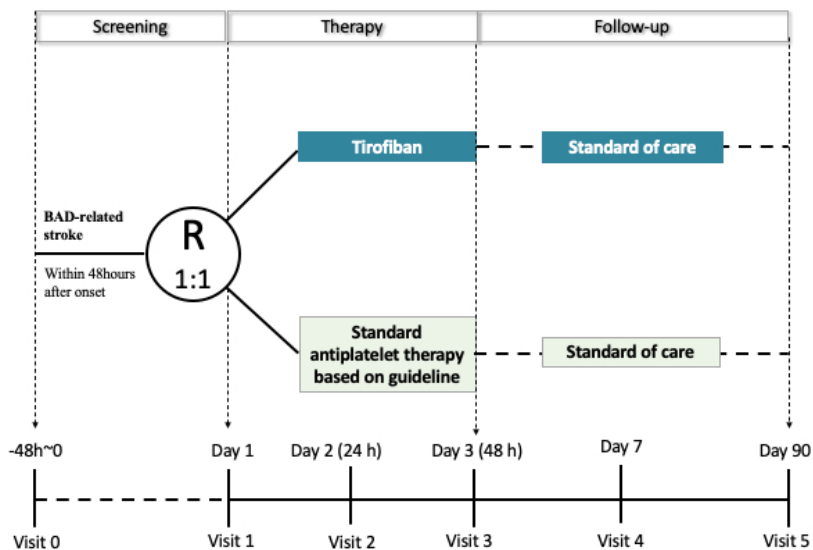


Figure 1. Study Flow

338x190mm (54 x 54 DPI)

## Supplementary materials

**Table S1. Study Procedure of BRANT trial**

Measurement	Day 1	Day 2	Day 3	Day 7	Day 90
Demographic characteristics	X				
Current medical history taking	X				
Body temperature measurement	X				
Physical examination	X			X	X
Past medical history	X				
Pre-randomization medication after onset	X				
Regular blood pressure monitoring	X	X			
NIHSS score	X			X	X
mRS score	X			X	X
Barthel index score	X				X
Magnetic resonance image	X				
Evaluation of Intracranial vessels	X				
Evaluation of extracranial vessels	X				
Laboratory tests*	X				
ECG*	X			X	
Verification of inclusion/exclusion criteria	X				
Signed informed consent	X				
Randomization	X				
Blood tests after enrollment		X	X		

Urine and fecal examination			<b>X</b>		
Compliance			<b>X</b>		
Concomitant medication				<b>X</b>	<b>X</b>
Early neurological deterioration				<b>X</b>	
Major bleeding				<b>X</b>	<b>X</b>
Adverse Events/ Serious Adverse Events				<b>X</b>	<b>X</b>
*Remarks: ECG and laboratory data performed within 48 hours of onset before signing the informed consent form can be used as trial data.					





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2-3
	2b	All items from the World Health Organization Trial Registration Data Set	Clinical Trials.gov
Protocol version	3	Date and version identifier	In Protocol, not shown in article
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	Clinical Trials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

**Introduction**

1				
2	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
3				
4				
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
11				
12				
13				
14				
15				
16	<b>Methods: Participants, interventions, and outcomes</b>			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
19				
20				
21				
22				
23	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
24				
25				
26				
27	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
28				
29				
30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	In Protocol, not shown in article
31				
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37		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	In Protocol, not shown in article
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44		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	In Protocol, not shown in article
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51	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
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2	Participant	13	Time schedule of enrolment, interventions (including any run-ins	Figure
3	timeline		and washouts), assessments, and visits for participants. A	1
4			schematic diagram is highly recommended (see Figure)	
5				
6	Sample size	14	Estimated number of participants needed to achieve study	12
7			objectives and how it was determined, including clinical and	
8			statistical assumptions supporting any sample size calculations	
9				
10	Recruitment	15	Strategies for achieving adequate participant enrolment to reach	In
11			target sample size	Protocol,
12				not
13				shown in
14				article
15				
16				
17				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21				
22	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9-10
23	generation		generated random numbers), and list of any factors for	
24			stratification. To reduce predictability of a random sequence,	
25			details of any planned restriction (eg, blocking) should be	
26			provided in a separate document that is unavailable to those who	
27			enrol participants or assign interventions	
28				
29				
30	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9-10
31	concealme		telephone; sequentially numbered, opaque, sealed envelopes),	
32	nt		describing any steps to conceal the sequence until interventions	
33	mechanism		are assigned	
34				
35	Implement	16c	Who will generate the allocation sequence, who will enrol	9-10
36	ation		participants, and who will assign participants to interventions	
37				
38	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10-11
39	(masking)		participants, care providers, outcome assessors, data analysts),	
40			and how	
41				
42				
43		17b	If blinded, circumstances under which unblinding is permissible,	NA
44			and procedure for revealing a participant's allocated intervention	
45			during the trial	
46				
47				

### Methods: Data collection, management, and analysis

49				
50	Data	18a	Plans for assessment and collection of outcome, baseline, and	11-12
51	collection		other trial data, including any related processes to promote data	
52	methods		quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known. Reference	
55			to where data collection forms can be found, if not in the protocol	
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2		18b	Plans to promote participant retention and complete follow-up, 11-12
3			including list of any outcome data to be collected for participants
4			who discontinue or deviate from intervention protocols
5			
6	Data	19	Plans for data entry, coding, security, and storage, including any 11-12
7	management		related processes to promote data quality (eg, double data entry;
8			range checks for data values). Reference to where details of data
9			management procedures can be found, if not in the protocol
10			
11			
12	Statistical	20a	Statistical methods for analysing primary and secondary 13
13	methods		outcomes. Reference to where other details of the statistical
14			analysis plan can be found, if not in the protocol
15			
16		20b	Methods for any additional analyses (eg, subgroup and adjusted 13
17			analyses)
18			
19		20c	Definition of analysis population relating to protocol non- 13
20			adherence (eg, as randomised analysis), and any statistical
21			methods to handle missing data (eg, multiple imputation)
22			
23			
24	<b>Methods: Monitoring</b>		
25			
26	Data	21a	Composition of data monitoring committee (DMC); summary of its 12
27	monitoring		role and reporting structure; statement of whether it is
28			independent from the sponsor and competing interests; and
29			reference to where further details about its charter can be found,
30			if not in the protocol. Alternatively, an explanation of why a DMC
31			is not needed
32			
33			
34		21b	Description of any interim analyses and stopping guidelines, NA
35			including who will have access to these interim results and make
36			the final decision to terminate the trial
37			
38	Harms	22	Plans for collecting, assessing, reporting, and managing solicited 12
39			and spontaneously reported adverse events and other
40			unintended effects of trial interventions or trial conduct
41			
42			
43	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and 12
44			whether the process will be independent from investigators and
45			the sponsor
46			
47			
48	<b>Ethics and dissemination</b>		
49			
50	Research	24	Plans for seeking research ethics committee/institutional review 3
51	ethics		board (REC/IRB) approval
52	approval		
53			
54	Protocol	25	Plans for communicating important protocol modifications (eg, 3
55	amendments		changes to eligibility criteria, outcomes, analyses) to relevant
56			parties (eg, investigators, REC/IRBs, trial participants, trial
57			registries, journals, regulators)
58			
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1				
2	Consent or	26a	Who will obtain informed consent or assent from potential trial	3
3	assent		participants or authorised surrogates, and how (see Item 32)	
4				
5		26b	Additional consent provisions for collection and use of participant	NA
6			data and biological specimens in ancillary studies, if applicable	
7				
8	Confidentiality	27	How personal information about potential and enrolled	In
9			participants will be collected, shared, and maintained in order to	protocol
10			protect confidentiality before, during, and after the trial	, not
11				shown in
12				article
13				
14				
15	Declaration of	28	Financial and other competing interests for principal investigators	16
16	interests		for the overall trial and each study site	
17				
18	Access to	29	Statement of who will have access to the final trial dataset, and	16
19	data		disclosure of contractual agreements that limit such access for	
20			investigators	
21				
22				
23	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	In
24	post-trial care		compensation to those who suffer harm from trial participation	protocol
25				, not
26				shown in
27				article
28				
29				
30	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	See
31	policy		to participants, healthcare professionals, the public, and other	consent
32			relevant groups (eg, via publication, reporting in results	from
33			databases, or other data sharing arrangements), including any	
34			publication restrictions	3
35				
36				
37		31b	Authorship eligibility guidelines and any intended use of	In
38			professional writers	protocol
39				, not
40				shown in
41				article
42				
43				
44		31c	Plans, if any, for granting public access to the full protocol,	NA
45			participant-level dataset, and statistical code	
46				
47	<b>Appendices</b>			
48				
49	Informed	32	Model consent form and other related documentation given to	We
50	consent		participants and authorised surrogates	provide
51	materials			a model
52				consent
53				from
54				
55				
56	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
57	specimens		biological specimens for genetic or molecular analysis in the	
58			current trial and for future use in ancillary studies, if applicable	
59				
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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
2 Explanation & Elaboration for important clarification on the items. Amendments to the  
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
4 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"  
5 license.  
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