

Rationale and design of a randomised double-blind 2×2 factorial trial comparing the effect of a 3-month intensive statin and antiplatelet therapy for patients with acute mild ischaemic stroke or high-risk TIA with intracranial or extracranial atherosclerosis (INSPIRES)

Ying Gao,¹ Yuesong Pan,^{1,2} Shangrong Han ,¹ Weiqi Chen ,¹ Jing Jing,^{1,2} Chunjuan Wang,^{1,2} Yingying Yang ,¹ Tingting Wang ,¹ Xia Meng ,^{1,2} Xingquan Zhao ,^{1,2} Liping Liu,^{1,2} Hao Li ,^{1,2} S Claiborne Johnston ,³ Pierre Amarenco,^{4,5} Philip M Bath ,⁶ Yongjun Wang ,^{1,2,7,8,9} Yilong Wang ,^{1,2,7,8,10} For the INSPIRES Investigators

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For numbered affiliations see end of article.

Correspondence to

Dr Yilong Wang;
yilong528@aliyun.com

Dr Yongjun Wang;
yongjunwang@ncrcnd.org.cn

ABSTRACT

Background It remains unclear if intensive antiplatelet and statin treatments begun within 24–72 hours of cerebral ischaemic events from intracranial or extracranial atherosclerosis is effective or safe.

Methods The Intensive Statin and Antiplatelet Therapy for High-risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial is a randomised, double-blind, placebo-controlled, multicentre and 2×2 factorial trial. 6100 individuals between the ages of 35 and 80 who have experienced a mild ischaemic stroke or high-risk transient ischaemic attack (TIA) within the previous 72 hours that is attributed to ≥50% atherosclerotic stenosis of a major intracranial or extracranial artery or multiple infarctions of atherosclerotic origin will be enrolled in the trial. Eligible subjects will be randomised 1:1:1:1 to one of four groups: (1) intensive antiplatelet therapy (combined clopidogrel and aspirin for days 1–21, then aspirin placebo and clopidogrel for days 22–90) plus immediate intensive statin therapy (atorvastatin at a dose of 80 mg daily for the first 21 days, then 40 mg daily for days 22–90); (2) intensive antiplatelet therapy plus delayed intensive statin therapy (atorvastatin placebo for days 1–3, followed by 40 mg per day of atorvastatin for days 4–90); (3) standard antiplatelet therapy (combination of clopidogrel placebo with aspirin for 90 days) plus immediate intensive statin therapy and (4) standard antiplatelet therapy plus delayed intensive statin therapy. The primary efficacy endpoint is any new stroke (ischaemic or haemorrhagic) within 90 days after randomisation. The primary safety endpoint is moderate to severe bleeding at 90 days.

Conclusion The INSPIRES trial will assess the efficacy and safety of intensive antiplatelet therapy and immediate statin therapy begun within 72 hours of onset in

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ According to current guidelines, subjects with minor ischaemic stroke or high-risk transient ischaemic attack (TIA) during the last 24 hours are advised to receive dual antiplatelet therapy (DAPT). Subgroup analyses show that DAPT offers the best protection in patients whose events are related to large artery atherosclerosis. However, the risk of recurrent stroke remains high (5.3%–7.6% at 30 days, 10.1%–11.3% at 90 days and 12.5% at 1 year) despite DAPT, evidenced by the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis trial and subgroup analyses of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events and Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death trials.
- ⇒ Regarding the therapeutic time window, studies have shown that delaying DAPT for 3 days after the acute ischaemic event might still result in a net benefit.
- ⇒ Current guidelines recommend intensive statin therapy for secondary stroke prevention. Nevertheless, there are limited evidence for the efficacy of starting statins within 72 hours of an ischaemic stroke or TIA in reducing new stroke and improving function outcomes, as well as decreasing the bleeding risk of intensive statin combined with DAPT.

decreasing the recurrent stroke at 90 days in patients with acute mild ischaemic stroke or high-risk TIA of intracranial or extracranial atherosclerosis origin.

Trial registration number NCT03635749.

WHAT THIS STUDY ADDS

- ⇒ It is a double-blind randomised controlled trial to assess the efficacy and safety of intensive antiplatelet therapy and immediate intensive statin begun within 72 hours in patients with mild ischaemic stroke or high-risk TIA of atherosclerotic origin (large artery atherosclerotic stenosis and multiple infarctions from artery-to-artery embolism).
- ⇒ Both clopidogrel and atorvastatin require hepatic activation through cytochrome P450 system. The trial will determine whether this interaction has any impact on clinical outcomes in patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The trial prospectively explores whether delaying the initiation of DAPT until 72 hours after mild ischaemic stroke/high-risk TIA is still safe and effective, and thus clarify whether more patients could benefit from DAPT.
- ⇒ This study prospectively explores whether high-dose statin therapy is safe and effective when initiated immediately for patients with acute (within 72 hours) mild ischaemic stroke/high-risk TIA to reduce recurrent and progressive stroke.
- ⇒ The planned intensive medical treatment is hypothesised to decrease the risk of new stroke by approximately 35% during 90 days compared with standard treatment.

INTRODUCTION

The high risk of stroke recurrence within 90 days was reported in patients with acute mild ischaemic stroke or transient ischaemic attack (TIA). According to current guidelines, dual antiplatelet therapy (DAPT) is supposed to be initiated within 24 hours in individuals with a minor stroke (National Institutes of Health Stroke Scale (NIHSS) score ≤ 3) or high-risk TIA. This evidence was provided by the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial and the Platelet Oriented Inhibition in New TIA and Minor Ischaemic Stroke trial.¹

Additionally, the Acute Stroke or TIA Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) trial found that patients with ischaemic stroke (NIHSS score 4–5) may also benefit from DAPT started within 24 hours of ictus.^{2,3} Meta-analyses and exploratory analyses indicated that starting DAPT within 3 days of onset may still be beneficial.^{4,5} These studies suggested that DAPT may be effective for individuals with mild ischaemic stroke (NIHSS score ≤ 5) if treatment began in the first 72 hours after onset, but high-quality evidence is lacking. However, the additional benefit of DAPT relative to aspirin alone decreases with delayed initiation.⁵ Moreover, DAPT has limited efficacy in some of patients who had a ischaemic stroke, so we hope to find the most beneficial population within 72 hours of onset. Subgroup analyses of the CHANCE and THALES trials indicated that patients with large artery atherosclerosis or multiple infarctions from artery-to-artery embolism might be at highest risk of recurrence and benefit the most from DAPT.

Besides antiplatelet therapy, lipid-lowering therapy may benefit patients who had a stroke with atherosclerosis. Intensive statins are recommended to reach a target

low-density lipoprotein cholesterol (LDL-C) level of lower than 70 mg/dL for secondary prevention in individuals with ischaemic stroke of atherosclerotic origin in current guidelines.⁶ While, statins were also reported to have neuroprotective effects, such as antioxidant, anti-inflammatory, antithrombotic, vasodilator and promoting angiogenesis and synaptogenesis effects, some of which may be independent of lipid-lowering effect.^{7,8} Results of animal experiments suggested that administering statin immediately after ischaemic stroke effectively decreased infarct size and improving neurological deficit scores.^{9,10}

The result of the North Dublin Population Stroke Study indicated that statin therapy initiated within 72 hours of stroke is significantly related to a decrease in mortality after ischaemic stroke.¹¹ Statin withdrawal after admission for the first 3 days was reported to induce an increase of risk of death or dependence compared with immediate statin administration in a randomised controlled trial (RCT).¹² Nevertheless, some other randomised trials showed no superiority of moderate-to-high intensity statin treatment began acutely after ischaemic stroke in reducing dependency, the result of which may be limited by small sample sizes, causes of stroke and inadequate doses of statins.^{13–15}

Therefore, it remains unclear whether applying statin immediately after ischaemic stroke could decrease the risk of recurrent and progressive stroke.

The Intensive Statin and Antiplatelet Therapy for High-risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial hypothesised that intensive antiplatelet and statin therapies initiated within 72 hours after onset would reduce the risk of new stroke in mild ischaemic stroke or high-risk TIA patients attributed to intracranial or extracranial large artery atherosclerosis within 90 days, compared with standard antiplatelet and delayed intensive statin therapy.

METHODS

Study design

INSPIRES (ClinicalTrials.gov NCT03635749) is a randomised, double-blind, placebo-controlled, multi-centre 2×2 factorial trial. It will assess whether intensive antiplatelet therapy and/or statin therapy, initiated within 72 hours after ischaemic stroke or high-risk TIA of atherosclerotic origin, will decrease the risk of stroke recurrence within 90 days. There will be enrolment of patients from 222 hospitals in China.

Patient selection

Patients aged 35–80 years with mild ischaemic stroke (NIHSS score ≤ 5) or high-risk TIA (ABCD² score ≥ 4) between 24 and 72 hours after onset, or ischaemic stroke (NIHSS score 4–5) within 24 hours of ictus who satisfy at least one of the requirements will be considered for inclusion: (A) >50% stenosis of a major intracranial or extracranial artery confirmed by carotid duplex ultrasound or vascular imaging that likely accounts for the clinical presentation and infarction and (B) acute multiple

Box 1 Inclusion and exclusion criteria of INSPIRES trial

Inclusion criteria

1. Age 35–80 years.
2. At least one of the followings (a–b):
 - a. Mild ischaemic stroke (NIHSS score 4–5) within 24 hours after onset and either of the following imaging characteristics:
 1. Acute single infarction with $\geq 50\%$ stenosis of a major intracranial or extracranial artery that likely accounts for the infarction and clinical presentation.
 2. Acute multiple infarctions documented by head CT or MRI, attributed to large-artery atherosclerosis, including non-stenotic vulnerable plaques.
 - b. Mild ischaemic stroke (NIHSS score ≤ 5) or high-risk TIA (ABCD² score ≥ 4) within 24–72 hours after onset and meet any of the following imaging characteristics:
 1. TIA with $\geq 50\%$ stenosis of a major intracranial or extracranial artery that likely accounts for the clinical presentation.
 2. Acute single infarction with $\geq 50\%$ stenosis of a major intracranial or extracranial artery that likely accounts for the infarction and clinical presentation.
 3. Acute multiple infarctions documented by head CT or MRI, attributed to large-artery atherosclerosis, including non-stenotic vulnerable plaques.
3. Written informed consent.

Exclusion criteria

1. Presumed cardioembolic stroke or TIA (eg, atrial fibrillation, heart valve prosthesis, atrial myxoma, endocarditis);
2. Other determined aetiology of stroke or TIA (eg, aortic dissection, cervicocerebral artery dissection, vasculitis, vascular malformation, moyamoya disease/syndrome, fibromuscular dysplasia).
3. Non-vascular neurological diseases (eg, intracranial tumour, multiple sclerosis).
4. Index infarction affects $>50\%$ of a cerebral lobe (eg, parietal, frontal, occipital).
5. Haemorrhagic transformation after onset.
6. Contraindications to clopidogrel, aspirin or atorvastatin: (A) history of hypersensitivity; (B) severe heart failure (New York Heart Association classification: III–IV) or asthma; (C) coagulation disorder or systemic bleeding; (D) history of drug-induced haematological or hepatic abnormalities; (E) leucopenia ($<2 \times 10^9/L$) or thrombocytopenia ($<100 \times 10^9/L$); (F) active liver disease and (G) pregnancy or lactation period.
7. Pre-existing disability with modified Rankin Scale score >2 .
8. Intra-arterial or intravenous thrombolysis, or endovascular therapy after onset.
9. Defibrinogen therapy (eg, defibrase and lumbrokinase), anticoagulation therapy (eg, argatroban) or antiplatelet therapy (eg, ticagrelor, tirofiban) except for clopidogrel and aspirin after onset.
10. Creatine kinase >5 times the upper limit of normal value of onset.
11. Drug use related to statin metabolism within 14 days before randomisation (eg, immune-suppressive drugs, antifungal agents, fibrates).
12. Severe hepatic insufficiency (alanine transaminase or aspartate transaminase >2 times the upper limit of normal value) or renal insufficiency (creatinine >1.5 times the upper limit of normal value or glomerular filtration rate <40 mL/min/1.73 m²).
13. Dual antiplatelet therapy with aspirin and clopidogrel within 14 days before randomisation*.
14. High-intensity statin therapy within 14 days before randomisation (eg, atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day).
15. History of intracranial haemorrhage (eg, intracerebral or subarachnoid haemorrhage).
16. Gastrointestinal bleeding or major surgery within 90 days.
17. History of intracranial or extracranial angioplasty.
18. Planned long-term use of antiplatelet drugs or non-steroidal anti-inflammatory drugs except for study drugs.
19. Planned surgery or revascularisation that may need to stop taking the study drugs within the next 90 days.
20. Anticipated life expectancy <90 days.
21. Pregnant women, or patients of childbearing potential with neither using birth control nor pregnancy test records.
22. Currently participating in any other investigational drug or device study.
23. Unable to complete the follow-up (eg, dementia, alcoholism, substance abuse, severe mental disease).

*Patients who started aspirin plus clopidogrel without loading dose (300 mg) of clopidogrel after onset are not excluded from the trial.

INSPIRES, Intensive Statin and Antiplatelet Therapy for High-risk Intracranial or Extracranial Atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

infarctions documented by head CT or MRI of large-artery atherosclerosis origin, including with non-stenotic unstable plaque. The detailed criteria for inclusion and exclusion are shown in [box 1](#).

As shown in online supplemental table S1, the stenosis of intracranial artery is defined on MR angiography (MRA), CT angiography (CTA) or digital subtraction angiography (DSA) by criteria from the Warfarin–Aspirin Symptomatic Intracranial Disease study¹⁶ and assessments of extracranial arteries stenosis degree are based on carotid duplex ultrasound, CTA, CE-MRA or DSA by standards

from the North American Symptomatic Carotid Endarterectomy Trial.¹⁷ More than one lesion appearing in different locations (separated in space or non-continuous on contiguous slices) on diffusion-weighted imaging/apparent diffusion coefficient imaging is defined as acute multiple infarctions.^{18 19}

Key exclusion criteria included presumed cardioembolic TIA or ischaemic stroke, other determined aetiology of ischaemic stroke or TIA, modified Rankin Scale (mRS) score >2 , intravenous thrombolysis or endovascular therapy after onset, defibrinogen therapy, anticoagulation

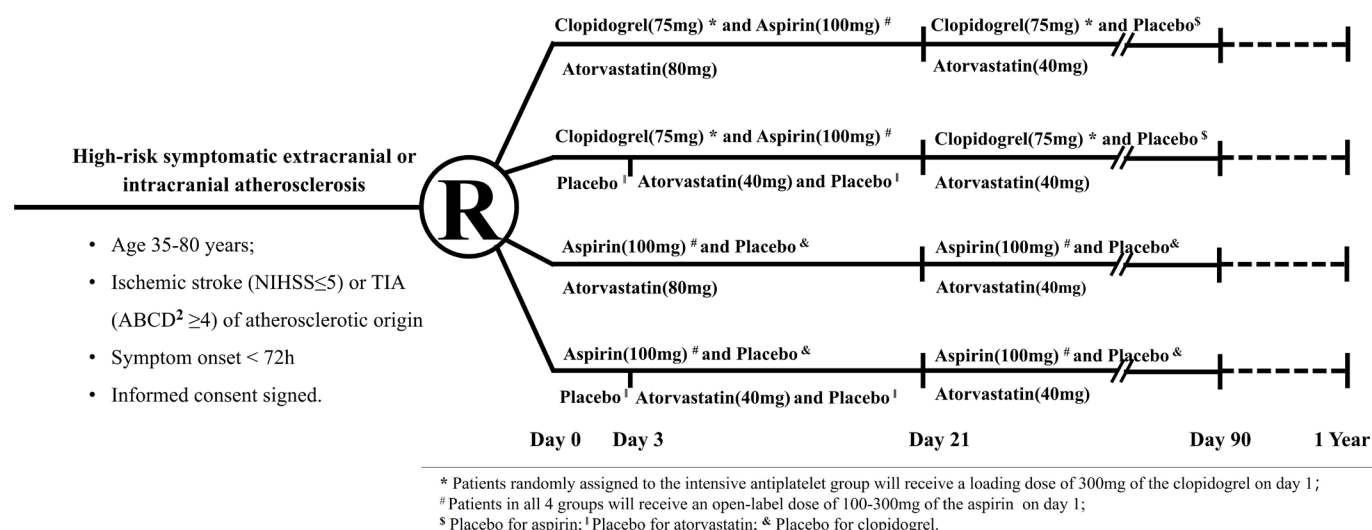


Figure 1 Flow chart of the INSPIRES trial. INSPIRES, Intensive Statin and Antiplatelet Therapy for High-risk Intracranial or Extracranial Atherosclerosis; NIHSS, National Institutes of Health Stroke Scale.

therapy, antiplatelet therapy except for clopidogrel and aspirin after onset, either DAPT with aspirin and clopidogrel or intensive statin therapy within 2 weeks prior to randomisation and severe hepatic or renal dysfunction.

Randomisation and treatment intervention

This trial has a 2×2 factorial design, with separate randomisations for antiplatelet therapy and statin therapy. Randomisation assignments are centrally generated using a block design. Subjects are given a random number that corresponds to a drug package that will be administered to the patient. Eligible individuals will be randomly divided in a 1:1:1:1 ratio into four sets as follows: (1) intensive antiplatelet therapy (clopidogrel at a loading dose of 300 mg on day 1, then 75 mg daily for days 2–90, combined with aspirin at a dosage of 100–300 mg on day 1, then 100 mg daily for days 2–21) plus immediate intensive statin therapy (atorvastatin at a dose of 80 mg daily for days –21, then 40 mg daily for days 22–90); (2) intensive antiplatelet therapy plus delayed intensive statin therapy (atorvastatin placebo for days 1–3, followed by atorvastatin at a dose of 40 mg daily for days 4–90); (3) standard antiplatelet therapy (clopidogrel placebo combined with aspirin at a dose of 100–300 mg on day 1, then 100 mg daily for days 2–90) plus immediate intensive statin therapy and (4) standard antiplatelet therapy plus delayed intensive statin therapy (online supplemental table S2). The flow chart of INSPIRES trial is shown in figure 1.

All subjects should take the initial dose of study drugs as soon as feasible within 1 hour after being randomly assigned. After the 90-day study therapy, patients will get standard care in accordance with the latest guidelines at investigators' discretion and be followed up for an additional 9 months.

Study endpoints

The primary efficacy endpoint is any new stroke (ischaemic or haemorrhagic) within 90 days.²⁰ Haemorrhagic stroke

refers to acute neurological dysfunction of the focal or whole brain or spinal cord caused by non-traumatic brain parenchymal, intraventricular and subarachnoid haemorrhage. Ischaemic stroke refers to an acute focal cerebral or retinal infarction excluding other non-ischaemic causes meeting any of the following conditions: (1) with clinical signs or radiological evidence of acute new focal neurological damage exceeding 24 hours in duration, (2) with focal symptoms or signs sustaining shorter than 24 hours, but with radiological evidence of new infarction, (3) the worsening of pre-existing symptoms of vascular origin ischaemic stroke (ie, NIHSS increased $\geq$ 4 based on primary ischaemic stroke, excluding the haemorrhagic transformation after infarction or symptomatic intracranial haemorrhage) persisting for more than 24 hours, with or without deterioration of ischaemic lesions on MRI or CT (online supplemental table S3). Secondary efficacy endpoints include a composite vascular event (stroke, myocardial infarction (MI) or vascular death), ischaemic stroke, TIA, MI, vascular death, all-cause death, poor functional outcome (mRS 2–6) and poor quality of life (EuroQoL-5 Dimensions index score $\leq$ 0.5) within 90 days, increase in NIHSS score at 7 days, as well as any new stroke (ischaemic or haemorrhagic), all-cause death and poor functional outcome (mRS 2–6) within 1 year. The new stroke or TIA is classified on a six-level ordered category scale combined vascular events with mRS score at 90 days or at 1 year, respectively: fatal stroke (stroke with subsequent death), severe stroke (stroke followed by mRS of 4–5), moderate stroke (stroke followed by mRS of 2–3), mild stroke (stroke followed by mRS of 0–1), TIA and no stroke/TIA.²¹ Definitions of vascular events are shown in online supplemental table S3.

The primary safety endpoint is moderate to severe bleeding at 90 days determined by standards from the Global Utilisation of Streptokinase and tissue-type plasminogen activator for Occluded Coronary Arteries trial.

Severe bleeding refers to fatal or intracranial haemorrhage or bleeding resulting in haemodynamic changes requiring blood or fluid transfusions, cardiac stress therapy, ventricular assist devices, surgery or cardiopulmonary resuscitation. Moderate bleeding refers to bleeding requiring transfusion therapy but not resulting in haemodynamic changes that require intervention.²²

Other safety outcomes include intracranial haemorrhage, hepatotoxicity (alkaline phosphatase or aspartate aminotransferase >3 times the upper limit of normal value), muscle toxicity (creatinine kinase >10 times the upper limit of normal value, or presence of muscle pain, myopathy or rhabdomyolysis), death, other adverse or severe adverse events within 90 days.

Visits and data collection

Each subject will be seen in person on the day of randomisation, day 7, day 14 or discharge day, and day 90 with 1-year follow-up by a telephone visit. Fasting venous blood samples will be collected from all subjects at baseline as well as day 90 for genetic analyses and measurement of biomarkers. For a detailed study plan, see online supplemental table S4.

Neurological assessments including NIHSS, ABCD² and mRS scores are performed by local investigators. All local investigators received standardised training in order to ensure the accuracy and consistency of assessments. Eligibility on brain imaging including the diagnosis of stroke or TIA, the degree of arterial stenosis and the infarction pattern will be first determined by local investigators.

Study organisation

The steering committee will provide scientific and strategic recommendations, and ensure the quality of the study. The executive committee will collect blinded data according to the study protocol, and conduct appropriate guidance based on the progress of the study. An independent clinical research organisation will review the execution process of the trial as well as all data collected. The data safety and monitoring board, consisting of independent academic members and statisticians who are not involved in the study, will monitor the trial's progress on a regular basis to guarantee that the trial is conducted according to the highest ethics and patient safety standards. The Clinical Event Adjudication Committee, composed of independent experts with extensive clinical experience, will review all clinical outcome events (including stroke, MI, death and moderate to severe bleeding) and safety outcome events and make the final adjudications.

Sample size calculation

We make the following primary null hypotheses: in patients with high-risk symptomatic intracranial or extracranial atherosclerosis treated within 72 hours of ictus, there is no difference in the risk of a new stroke within 90 days: (1) between subjects with intensive antiplatelet therapy and those with standard antiplatelet therapy; (2)

between subjects with immediate intensive statin therapy and those with delayed intensive statin therapy and (3) between subjects with intensive antiplatelet and immediate intensive statin therapy and those with standard antiplatelet and delayed intensive statin therapy.

The minimal sample size for the trial is determined by the necessity that a clinically meaningful difference in effectiveness between treatment and control groups has to be detected. Based on previous studies, the risk of new stroke during 90 days is presumed to be 11.5% in the group with standard antiplatelet therapy (with half delayed intensive statin therapy and half early high-intensity statin therapy) and 11.5% in the delayed intensive statin therapy group (with half standard antiplatelet therapy and half DAPT) and 13% in the group with standard antiplatelet therapy plus delayed intensive statin therapy, intensive antiplatelet therapy and immediate intensive statin therapy can reduce this risk by 22%, and the effects of intensive antiplatelet and lipid-lowering therapy will be similar and additive.^{19 20 23–25} With a sample size of 6100 subjects, a two-sided α of 0.05 and 5% lost to follow-up, we will have 97% power to detect that the risk is decreased by 35% in the group with DAPT plus immediate intensive statin therapy compared with standard antiplatelet therapy plus delayed intensive therapy, and 80% power to detect that the risk is reduced by 20% by intensive antiplatelet therapy compared with standard antiplatelet therapy, and immediate intensive statin compared with delayed intensive statin therapy, respectively.

Statistical analyses

In this trial, we will use intention-to-treat analysis as the primary analysis. Kaplan-Meier analyses will be used to estimate survival curves for stroke events over a 90-day period, and the therapy effect will be assessed through log-rank test. HRs and related 95% CIs will be evaluated through Cox proportional hazards methods. Comparisons in each arm, between intensive and standard antiplatelet therapy, and between immediate and delayed intensive statin therapy will be performed. We will evaluate the interaction between the two treatment arms for the primary outcome. We will use cox proportional hazards regression to analyse the differences in the risks of the composite vascular event, ischaemic stroke, TIA, MI, cardiovascular death, all-cause death, moderate to severe bleeding and intracranial haemorrhage. While, the outcomes of poor functional outcome and quality of life will be evaluated via logistic regression analysis. Sensitivity analysis will also be undertaken in the population with exclusion of those with minor stroke (NIHSS $\leq$ 3) or TIA (ABCD² score $\geq$ 4) within 24 hours of ictus that recruited before protocol revision. SAS software V.9.4 (SAS Institute) will be used for all analyses.

Subgroup analyses

Several subgroup analyses for the primary outcome are planned:

- Subjects aged >65 years vs those aged $\leq$ 65 years.

Table 1 Some randomised controlled trials (RCTs) of dual antiplatelet therapy for patients who had a ischaemic stroke

RCT	CARESS	CLAIR	FASTER	CHANCE	POINT	PRINCE	THALES	CHANCE-2	INSPIRES
Population									
Age, years	> 18	≥18	≥40	≥40	≥18	40–80	≥40	≥40	35–80
NIHSS (stroke)	–	<8	≤3	≤3	≤3	≤3	≤5	≤3	≤5
ABCD ² (TIA)	–	–	–	≥4	≥4	≥4	≥6	≥4	≥4
Stenosis	≥50%(symptomatic carotid)	≥50% (symptomatic internal carotid or middle cerebral)	–	–	–	≥50%(symptomatic cervical or intracranial)	≥50%(symptomatic intra-/extracranial)	–	≥50%(symptomatic intracranial/extracranial) or multiple infarctions of atherosclerotic origin
Start	≤3 months	≤7 days	≤24 hours	≤24 hours	≤12 hours	≤24 hours	≤24 hours	≤24 hours	≤72 hours
Intervention	ASA+CLOP	ASA+CLOP	ASA+CLOP (Simvastatin)	ASA+CLOP	ASA+CLOP	ASA+TICA	ASA+TICA	ASA+TICA	ASA+CLOP (atorvastatin)
Control	ASA+placebo	ASA	ASA+placebo	ASA+placebo	ASA+placebo	ASA+CLOP	ASA+placebo	ASA+CLOP	ASA+placebo
Dose	CLOP 75mg/day (first dose 600 mg) for first 7 days ASA 75mg/day	CLOP 75mg/day (first dose 600 mg) ASA 75–160 mg/day	CLOP 75mg/day (first dose 300 mg) ASA 81 mg/day (first dose 162 mg)	CLOP 75mg/day (first dose 300 mg) ASA 75mg/day (first dose 75–300 mg)	CLOP 75mg/day (first dose 600 mg) ASA 50–325 mg/day	TICA 90mg two times per day (first dose 180mg) CLOP 75mg/day (first dose 300mg) ASA 100mg/day for first 21 days	TICA 90mg two times per day (first dose 180mg) ASA 75–100mg/day (first dose 300–325mg)	TICA 90mg two times per day (first dose 180mg) CLOP 75mg/day (first dose 300mg) ASA 75mg/day for first 21 days (first dose 75–300mg)	CLOP 75mg/day (first dose 300mg) ASA 100mg/day for first 21 days (first dose 100–300mg)
Primary outcome	Proportion of MES positive patients in 1 hour on day 7	Proportion of patients detected MES on day 2	Stroke at 90 days	Stroke at 90 days	Stroke, MI, vascular death at 90 days	proportion of patients with high platelet reactivity at 90 days	Stroke/death at 30 days	Stroke at 90 days	Stroke at 90 days
N	107	100	392	5170	4881	675	11016	6396	6100
ASA, aspirin; CLOP, clopidogrel; MES, microembolic signals; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; TICA, ticagrelor.									

Table 2 Some randomised controlled trials (RCTs) of lipid-lowering therapy patients who had a stroke

RCT	EUREKA	STARS	ASSORT	SPARCL	TST	INSPIRES
Population	Ischaemic stroke	Ischaemic stroke	Ischaemic stroke	Stroke or TIA	Ischaemic stroke/TIA	Ischaemic stroke/TIA
Age, years	> 20	≥18	≥20	≥18	≥18	35–80
NIHSS	–	4–22	0–20	–	–	0–5
premorbid mRS	0–3	0–1	0–2	0–3	0–3	0–2
Blood lipid	LDL-C ≤190mg/dL TG ≤500mg/dL	–	Dyslipidaemia or LDL-C ≥100mg/dL	LDL-C 100– 190mg/dL	LDL-C ≥100mg/dL with or without statin usage	–
Start	≤48 hours	≤12 hours	≤24 hours	1–6 months	Ischaemic stroke ≤3 months TIA ≤15 days	≤72 hours
Intervention	Rosuvastatin	Simvastatin	Atorvastatin, pitavastatin, or rosuvastatin for days 1–84.	Atorvastatin	Any type of statin with or without other lipid- lowering drugs, with target LDL-C ≤70mg/ dL	Atorvastatin (80mg/ day) for the first 21 days followed by 40mg daily for days 22–90
Control	Placebo	Placebo	Atorvastatin, pitavastatin, or rosuvastatin for days 7–84.	Placebo	Any type of statin with or without other lipid-lowering drugs, with target LDL-C 90–110mg/dL	Placebo for days 1–3, followed by atorvastatin(40mg/ day) for days 4–90.
Dose	Rosuvastatin 20mg/ day	Simvastatin 40mg/ day	Atorvastatin 20mg/ day, pitavastatin 4mg/day or rosuvastatin 5mg/ day, with LDL-C maintained <1.8mmol/L	Atorvastatin 80mg/day	Any dose	–
Primary outcome	New ischaemic lesions on DWI at five or 14 days	Proportion of independent patients (mRS ≤2) at 90 days	Patient disability at 90 days	A first non-fatal or fatal stroke	Major cardiovascular events	Stroke at 90 days
Follow-up	14 days	90 days	90 days	4.9 years (median)	3.5 years (median)	90 days
N	316	104	257	4731	2860	6100
Result	No significance	No significance	No significance	Atorvastatin decreased the incidence of strokes.	The target LDL-C ≤70mg/dL reduced the incidence of cardiovascular events.	–

DWI, diffusion-weighted imaging; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TST, treat Stroke to target.

- ▶ Female versus male patients.
 - ▶ Those with NIHSS score 4–5 vs those with NIHSS score ≤3 at admission.
 - ▶ Those randomised within 24 hours of onset versus those randomised between 24 and 72 hours since onset.
 - ▶ Those with ischaemic stroke/TIA related to extracranial artery atherosclerosis versus those related to intracranial artery atherosclerosis.
 - ▶ Those with intracranial stenosis versus those without intracranial stenosis.
 - ▶ Those with extracranial stenosis versus those without extracranial stenosis.
 - ▶ Those with multiple infarctions versus those with single infarction versus those without infarction.
 - ▶ Those with severe stenosis (≥70%) versus those with moderate stenosis (50%–69%).
 - ▶ Those with hypertension versus those who are normotensive.
 - ▶ Patients with diabetes versus non-diabetics.
 - ▶ Those with dyslipidaemia versus without dyslipidaemia.
 - ▶ Those with atherogenic dyslipidaemia (high-density lipoprotein cholesterol <40mg/dL and triglycerides >200mg/dL) versus without atherogenic dyslipidaemia.
 - ▶ Those with statin therapy within 1 month before randomisation versus without statin therapy.
- In addition, relevant subgroups will be examined for genetic variability and biomarker characteristics.

DISCUSSION

Intensive medical management including antiplatelet and lipid-lowering therapies is necessary for secondary prevention of non-cardiogenic ischaemic stroke.²⁴ The INSPIRES trial explores whether delaying the initiation of DAPT until 72 hours after onset and whether immediate intensive statin administration

(within 72 hours) is safe and effective in patients with acute mild ischaemic stroke/high-risk TIA of atherosclerotic origin.

Previous antiplatelet strategies for ischaemic stroke/TIA were mostly stratified based on the symptomatology, and begun within 24 hours after ischaemic stroke or TIA (table 1). Patients with symptomatic atherosclerotic stenosis of the intracranial or extracranial large arteries or with multiple infarctions are at an increased risk of new stroke.^{19 23 26} Artery-to-artery embolism is the common pathogenesis for multiple infarctions. Atherosclerotic plaque in a large artery may dislodge and cause distal cerebral infarction. Previous researches have indicated that these patients might benefit more from DAPT compared with aspirin alone and intensive medical therapy could reduce stroke recurrence rates and mortality.^{24 27 28} In the INSPIRES trial, we excluded presumed cardioembolic stroke or TIA (eg, atrial fibrillation, heart valve prosthesis) through medical history, ECG, ultrasonic cardiogram and some other examinations as deemed necessary by investigators. Besides, for patients with multiple acute infarctions in territories of different large arteries but without stenosis, transoesophageal echocardiography is necessary. Patients with detected emboli from the aortic arch will be allowed to be included in the trial. In this trial, a more precise DAPT during the acute phase and based on the stroke aetiology would be explored first. The data will help provide evidence for a more individualised antiplatelet strategy.

The benefit and safety of aspirin combined with ticagrelor has been investigated in the THALES and CHANCE-2 trials, especially for patients of atherosclerotic origin.^{2 3 29 30} However, enrolment in INSPIRES had already begun before the results of these two studies were published, such that aspirin combined with ticagrelor was not available as DAPT in INSPIRES.

In the original version of the study protocol, subjects with minor ischaemic stroke (NIHSS score ≤ 3) or TIA (ABCD² score ≥ 4) within 24 hours of ictus were included. After the American Heart Association and the American Stroke Association new recommendations of DAPT initiated within 24 hours of onset of ischaemic stroke (NIHSS score ≤ 3) from non-cardioembolic causes in 2019, we revised the protocol and no longer enrolled patients in this time window. A sensitivity analysis will be performed in this population. Online supplemental table S5 shows the initial inclusion criteria and exclusion criteria before revisions.

Evidence on the role of neuroprotection of statins in patients administered immediately after ischaemic stroke remains unclear (table 2). The current guidelines recommend high-intensity statin and ezetimibe as one of the secondary prevention treatments to lowering LDL-C in patients who had a ischaemic stroke evidenced by the SPARCL and Treat Stroke to

Target trials, which did not focus on patients in the hyperacute phase (within 72 hours).^{1 31 32} In the past decade, some registry studies have revealed that statin pretreatment and acute poststroke statin therapy may both improve functional outcomes and decrease the risk for mortality in patients who had a ischaemic stroke.^{33 34} While, the results from several small sample RCTs on the immediate initiation or withdrawal of statins in the acute phase were inconsistent.^{12–15} The INSPIRES trial also explores whether intensive statin therapy administered immediately was more effective in improving functional outcomes than intensive statin administered with a 3-day delay in acute (within 72 hours) patients who had a ischaemic stroke.

As well known, the effect of atorvastatin on LDL-lowering is similar at a dose of 40 mg and 80 mg per day, especially in the Asian population.³⁵ While, we found that higher dose of atorvastatin may be related with a higher risk of bleeding and myopathy in Chinese patients. Similar results were reported in several small sample studies in Asians.³⁶ The risk of major bleeding may be increased when intensive statin, especially at the higher doses, is used with DAPT in acute stage of ischaemic stroke. We would like to explore the safety of a potential interaction of intensive statin with DAPT, and used a dose of 40 mg daily for days 4–21 in the delayed intensive statin group.

In recent years, some trials have reported the effectiveness of ezetimibe and PSK9 inhibitors in conjunction with statin in decreasing LDL-C levels.^{32 37 38} In the future, there may be more trials exploring their effects in acute ischaemic stroke.

Author affiliations

¹Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

²China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

³Dean's Office, Dell Medical School, University of Texas at Austin, Austin, Texas, USA

⁴Department of Neurology and Stroke Center, Assistance Publique-Hôpitaux de Paris (APHP), Bichat Hospital, INSERM LVTS-U1148, University of Paris, Paris, France

⁵Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

⁶Stroke Trials Unit, Mental Health & Clinical Neuroscience, University of Nottingham, Nottingham, UK

⁷Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China

⁸National Center for Neurological Diseases, Beijing, China

⁹Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, China

¹⁰Chinese Institute for Brain Research, Beijing, China

Twitter Yilong Wang @yilong

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ORCID iDs

Shangrong Han <http://orcid.org/0000-0003-2608-484X>

Weiqi Chen <http://orcid.org/0000-0002-2551-9314>

Yingying Yang <http://orcid.org/0000-0001-9431-9925>

Tingting Wang <http://orcid.org/0000-0002-3809-2209>

Xia Meng <http://orcid.org/0000-0002-4918-0845>

Xingquan Zhao <http://orcid.org/0000-0001-8345-5147>

Hao Li <http://orcid.org/0000-0002-8591-4105>

S Claiborne Johnston <http://orcid.org/0000-0002-2912-0714>

Philip M Bath <http://orcid.org/0000-0003-2734-5132>

Yongjun Wang <http://orcid.org/0000-0002-9976-2341>

Yilong Wang <http://orcid.org/0000-0002-3267-0039>

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