# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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

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## Supplemental Table S1. Major intracranial and extracranial arteries in the INSPIRES trial

| Contents | Intracranial arteries | Extracranial arteries |
|---|---|---|
| **Components** | The intracranial portion of internal carotid arteries, middle cerebral arteries (M1/M2), anterior cerebral arteries (A1/A2), posterior cerebral arteries (P1/P2), intracranial portion of vertebral arteries, and the basilar artery. | The extracranial portion of carotid arteries and vertebral arteries. |
| **Methods** | MRA, CTA, DSA | CE-MRA, CTA, DSA, carotid duplex ultrasound |
| **Criteria for artery stenosis** | Criteria from the WASID study | Criteria from the NASCET study |

MRA indicates magnetic resonance angiography; CTA, computerized tomography angiography; DSA, digital substraction angiography; WASID, Warfarin–Aspirin Symptomatic Intracranial Disease; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

## Supplemental Table S2. Identity of study medication

| Groups | Date after Randomization | Dosage | | |
|---|---|---|---|---|
| | | Clopidogrel | Aspirin | Atorvastatin |
| **Intensive Antiplatelet Therapy + Immediate Intensive Statin Therapy** | Day1 | 300mg/d | 100-300mg/d* | 80mg/d |
| | Day2~Day3 | 75mg/d | 100mg/d | 80mg/d |
| | Day4~Day21±2 | 75mg/d | 100mg/d | 80mg/d |
| | Day22±2~Day90 | 75mg/d | Placebo | 40mg/d |
| **Intensive Antiplatelet Therapy + Delayed Intensive Statin Therapy** | Day1 | 300mg/d | 100-300mg/d* | Placebo |
| | Day2~Day3 | 75mg/d | 100mg/d | Placebo |
| | Day4~Day21±2 | 75mg/d | 100mg/d | 40mg/d+Placebo |
| | Day22±2~Day90 | 75mg/d | Placebo | 40mg/d |
| **Standard Antiplatelet Therapy + Immediate Intensive Statin Therapy** | Day1 | Placebo | 100-300mg/d* | 80mg/d |
| | Day2~Day3 | Placebo | 100mg/d | 80mg/d |
| | Day4~Day21±2 | Placebo | 100mg/d | 80mg/d |
| | Day22±2~Day90 | Placebo | 100mg/d | 40mg/d |
| **Standard Antiplatelet Therapy + Delayed Intensive Statin Therapy** | Day1 | Placebo | 100-300mg/d* | Placebo |
| | Day2~Day3 | Placebo | 100mg/d | Placebo |
| | Day4~Day21±2 | Placebo | 100mg/d | 40mg/d+Placebo |
| | Day22±2~Day90 | Placebo | 100mg/d | 40mg/d |

*Patients in all 4 groups will receive an open-label dose of 100-300mg of the aspirin on day1 after randomization.

## Supplemental Table S3. Definitions of cardiac-cerebral vascular events

| Event | Definition |
|---|---|
| **Stroke** | A sudden onset of focal or global brain, spinal cord or retinal vascular damage, resulting in symptoms and signs of acute nervous system defects, which is associated with cerebral circulation disorders. |
| **Ischemic Stroke** | Acute focal cerebral or retinal infarction meeting any of the following conditions:<br>(1) Clinical signs or radiological evidence of acute onset of new focal neurological damage lasting longer than 24 hours, excluding other non-ischemic etiologies (such as brain infections, brain injuries, brain tumors, seizures, severe metabolic diseases, degenerative diseases of the nervous system and side effects of drugs);<br>(2) Acute cerebral or retinal ischemic events, excluding other non-ischemic etiologies, focal symptoms or signs sustaining less than 24 hours, but with radiological evidence of new infarction;<br>(3) The worsening of pre-existing symptoms of vascular origin ischemic stroke (i.e. NIHSS increased $\geq 4$ based on primary ischemic stroke, excluding the haemorrhagic transformation after infarction or symptomatic intracranial haemorrhage) persisting for more than 24 hours, with or without deterioration of ischemic lesions on MRI or CT. Etiologic typing is based on the TOAST criteria. |
| **Transient Ischemic Attack** | Neurologic deficit caused by sudden focal brain or retinal ischemia that can fully recover, lasting less than 24 hours, with no evidence of new cerebral infarction on imaging (CT or MR). Other non-ischemic causes (such as brain infections, brain injuries, brain tumors, epilepsy, severe metabolic diseases, or degenerative neurological diseases) are excluded. |
| **Haemorrhagic Stroke** | Haemorrhagic stroke is defined as acute neurological dysfunction of the focal or whole brain or spinal cord caused by non-traumatic brain parenchymal, intraventricular, and subarachnoid haemorrhage. |

| | |
|---|---|
| **Haemorrhagic Transformation after Cerebral Infraction** | Any non-traumatic extravascular haemorrhage in acute / subacute infarcts, which could cause related neurological symptoms (symptomatic) or non-neurological symptoms (asymptomatic). Among them:<br><br>(1) <u>Ischemic stroke transformed into symptomatic haemorrhagic stroke:</u> The following two conditions must be met at the same time:<br>a. Imaging evidence (CT or MRI) of extravascular haemorrhage in the infarct area;<br>b. Symptoms are related to haemorrhagic transformation. The haemorrhagic transformation must be able to partially explain the clinical manifestations of the patient's neurological performance, such as:<br>i). Symptoms cannot be fully explained by infarct size and location<br>ii). Clinical deterioration referring to an increase of 4 points or more in NIHSS score after the initial ischemic event, or death, which is caused by haemorrhagic transformation;<br>iii). Clinical symptoms caused by volume effect secondary to haemorrhagic transformation;<br><br>(2) <u>Ischemic stroke transformed into asymptomatic haemorrhagic stroke:</u> The following two conditions must be met at the same time:<br>a. Imaging evidence (CT or MRI) of extravascular haemorrhage in the infarct area;<br>b. Haemorrhagic transformation does not cause symptoms, or cause symptoms with an increase of less than 4 points in NIHSS score after the initial ischemic event. |
| **Myocardial Infraction** | Acute myocardial infarction diagnosed by the third universal definition (Thygesen, 2012) |

If there is clinical evidence of myocardial necrosis consistent with acute myocardial ischemia (MI), acute MI should be diagnosed. It can be diagnosed if it meets any of the following criteria:

(1) A rise and/ or fall of cardiac biomarkers (preferably troponin [cTn]) values with at least one value above the 99th percentile URL, and any of the followings is required:

a. Clinical symptoms of myocardial ischemia;

b. New myocardial ischemic changes in the ECG, including new ST-segment changes or left bundle branch block (LBBB) [According to whether there is ST-segment elevation in the ECG, it is classified as acute ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI)];

c. Pathological Q wave detected in ECG;

d. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality;

e. Coronary thrombosis confirmed by angiography or autopsy.

(2) Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before cardiac biomarkers could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

(3) Myocardial infarction related to percutaneous coronary intervention (PCI) is arbitrarily defined by elevation of cTn values >5×99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, any of the followings is required:

a. Symptoms suggestive of myocardial ischemia;

b. New ischemic ECG changes or new LBBB;

c. Angiographic loss of patency of a major coronary artery or a side

branch or persistent slow- or no-flow or embolization;

d. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

(4) Myocardial infarction related to stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

(5) Myocardial infarction related to coronary artery bypass grafting (CABG) is arbitrarily defined by elevation of cardiac biomarker values＞10×99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, any of the followings is required:

a. new pathological Q waves or new LBBB;

b. angiographic documented new graft or new native coronary artery occlusion;

c. imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Vascular Death**

Vascular death includes sudden cardiac death, death due to stroke, acute myocardial infarction, heart failure, pulmonary embolism, cardiac/cerebrovascular intervention or surgery (unrelated to acute MI) and other cardiovascular causes [e.g. arrhythmia irrelevant with sudden cardiac death, aortic aneurysm rupture, or peripheral artery disease].

Any death of unknown/unclear cause within 30 d after stroke, myocardial infarction, or cardio-cerebrovascular operation/surgery will be regarded as death due to stroke, myocardial infarction, or cardio-cerebrovascular operation/surgery, respectively.

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CT indicates computed tomography; ECG, electrocardiograph; LBBB, left bundle branch block; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National

Institute of Health Stroke Scale ; TOAST, Trial of Org 10172 in Acute Stroke Treatment; URL, upper reference limit.

## Supplemental Table S4. Study Procedure of INSPIRES trial

| Measures | Screening and randomization (1st visit) | Treatment period | | Observation period | |
|---|---|---|---|---|---|
| | | Day7 (2nd visit) | Day 14 or Hospital discharge (3rd visit) | Day 90±7 (4th visit) | 12 months ± 14 days (5th visit) |
| Inclusion/Exclusion criteria | √ | | | | |
| Informed consent | √ | | | | |
| Onset | √ | | | | |
| First blood pressure and auxiliary examination | √ | | | | |
| Basic information | √ | | | | |
| Past medical history | √ | | | | |
| Personal/family history | √ | | | | |
| Medication history before randomization | √ | | | | |
| Physical examination | √ | | | | |
| $ABCD^2$ for TIA only | √ | | | | |
| NIHSS | √ | √ | √ | √ | |
| mRS | √ | | | √ | √ |
| EQ-5D scale | √ | | | √ | √ |
| Imaging assessment for enrollment | √* | | | | |
| Laboratory test | √† | √‡ | | √‡ | |
| ECG | √ | √ | | | |

| | | | | | |
|---|---|---|---|---|---|
| Randomization | √ | | | | |
| First medication time after randomization | √ | | | | |
| Primary diagnosis | √ | | | | |
| Final diagnosis | | | √ | | |
| Drug dispense/Retrieve | √ | | | √ | |
| Blood specimen (fasting) | √§ | | | √§ | |
| Endpoints | | √ | √ | √ | √ |
| AEs/SAEs | | √ | √ | √ | √ |
| Drug compliance | | √ | √ | √ | |
| Combined medication | | √ | √ | √ | √ |

AE indicates adverse event; ECG, electrocardiograph; EQ-5D, EuroQol-5D; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SAE, Serious adverse event; TIA, Transient Ischemic Attack.

* Imaging assessments include brain histology and assessments of intracranial and extracranial arteries. Brain histological examination includes head MRI or CT scan for diagnosis of TIA and cerebral infarction, and mode assessment for cerebral infarction (single infarction or multiple infarctions). If MRI cannot be completed before randomization, it must be done within 7 days after randomization. The brain MRI must include the T1+T2+FLAIR+DWI/ADC+MRA sequences. GRE-T2* or SWI shall be done according to the conditions of each sub-centre. If head MRI is completed, head CT is not required. Intracranial and extracranial artery assessments are used for screening. Intracranial artery assessment examinations include any test of MRA、CTA、DSA. Extracranial artery assessment examinations include any test of neck vascular ultrasound, CEMRA, CTA on the aortic arch, DSA. **Note**: If a patient applying only one assessment for intracranial or extracranial artery is found to meet the inclusion criteria, he or she can be included without

performing both intracranial and extracranial artery assessment. For example, if a TIA patient has only finished a neck vascular ultrasound, and finds out the responsibility artery stenosis >≥50% and is in accord with the standard set of circumstances, the patient can be recruited without assessment of intracranial arteries. All the above assessments need to be completed within 72 hours after randomization and needs no repetition if they are completed before randomization. The cervical vascular ultrasound should be uploaded in original photo, other image data should be uploaded to XXX Hospital with DICOM format.

†. Emergency laboratory assessment should be finished at screening, including emergency blood routine, emergency liver function (serum transaminases), emergency renal function (creatinine, urea nitrogen) and emergency blood clotting. The fasting laboratory tests (including biochemical kits, glycosylated haemoglobin, homocysteine, etc.) should be completed in the early morning of the second day after randomization. If not, 72 hours after randomization is the final deadline.

‡. Routine blood counts, biochemical panel(including alanine transaminase, aspartate aminotransferase, alkaline phosphatase, creatine kinase, creatine kinase-MB) and coagulation function should be performed on d 7. (If the test had been completed within 24 hours of screening or randomization and the results indicated no abnormality, there was no requirement to review it.) Routine blood counts and biochemical panels (including alanine transaminase, aspartate aminotransferase, alkaline phosphatase, creatine kinase, creatine kinase-MB, low-density lipoprotein cholesterol, high-density lipoproteincholesterol, total cholesterol, triglyceride) should be performed on day 90±7 after randomization to monitor hepatotoxicity and muscle toxicity of statin.

§. Fasting venous blood should be collected within 24 hours of randomization (if not, 72 hours after randomization is the final deadline) and 90±7 days after randomization.

## Supplemental Table S5. Inclusion and exclusion criteria of INSPIRES trial (Version 1.0)

| **Inclusion criteria** |
|---|
| 1. Age 35-80 years; |
| 2. Less than 72 hours from the onset |
| 3. At least one of the followings (a-c)<br>a) High-risk TIA ($ABCD^2 \geq 4$) with ≥50% stenosis of a major intracranial or extracranial artery that likely accounts for clinical presentation.<br>b) Acute single cerebral infarction (NIHSS≤5) with ≥50% stenosis of a major intracranial or extracranial artery that likely accounts for the infarction and clinical presentation.<br>c) Acute multiple cerebral infarction (NIHSS≤5) with stenosis of extracranial or intracranial arteries (stenosis degree unlimited) that likely accounts for the presentation. |
| 4. Written informed consent. |
| **Exclusion criteria** |
| 1. Presumed cardioembolic stroke or TIA (e.g. atrial fibrillation, heart valve prosthesis, atrial myxoma, endocarditis, etc.) |
| 2. Other determined etiology of stroke or TIA (e.g. aortic dissection, vasculitis，vascular malformation, etc.) |
| 3. Non-vascular neurological diseases (e.g. intracranial tumor, multiple sclerosis, etc.) |
| 4. Index infarction affects >50% of a cerebral lobe (e.g. parietal, frontal, occipital); |
| 5. Haemorrhagic transformation after onset; |
| 6. Contraindications to clopidogrel, aspirin or atorvastatin:<br>a. History of hypersensitivity<br>b. Severe heart failure (NYHA classification: III- IV) or asthma<br>c. Coagulation disorder or systemic bleeding<br>d. History of drug-induced hematologic or hepatic abnormalities |

e. Leukopenia (< $2\times10^9$/L) or thrombocytopenia (<$100\times10^9$/L)

f. Active liver disease

g. Pregnancy or lactation period

7. Pre-existing disability with mRS >2；
8. Intra-arterial thrombolysis, intravenous thrombolysis or endovascular therapy after onset;
9. Defibrinogen therapy (e.g. defibrase and lumbrokinase) after onset;
10. Creatine kinase > 5 times the upper limit of normal value after onset;
11. Drug use related to statin metabolism within 14 ds before randomization (e.g. immune-suppressive drugs, antifungal agents, fibrates);
12. Severe hepatic insufficiency (ALT or AST > 2 times the upper limit of normal value) or renal insufficiency (creatinine > 1.5 times the upper limit of normal value or GFR < 40 ml/min/1.73 $m^2$);
13. Dual antiplatelet therapy with Aspirin and Clopidogrel within 14 ds before randomization*;
14. High-intensity statin therapy within 14 d before randomization (e.g. atorvastatin ≥ 40mg/d, rosuvastatin ≥ 20mg/d);
15. History of intracranial haemorrhage (e.g. intracerebral haemorrhage, subarachnoid haemorrhage);
16. Gastrointestinal bleeding or major surgery within 90 ds;
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 revascularization that may need to stop taking the study drugs within the next 90 ds;
20. Anticipated life expectancy < 90 days;
21. Pregnant women, or patients of child-bearing potential with neither using birth control nor pregnancy test records;
22. Currently participating or has participated in any other investigational drug or device

study;

23. Unable to complete the follow-up (e.g. dementia, alcoholism, substance abuse, severe mental disease).

ALT indicates alkaline phosphatase; AST, aspartate aminotransferase; CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NYHA, New York Heart Association; TIA, Transient Ischemic Attack.

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