







# Indobufen versus aspirin in acute ischaemic stroke (INSURE): rationale and design of a multicentre randomised trial

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## ABSTRACT

**Background** Indobufen can reversibly inhibit platelet aggregation and showed to be effective in the treatment of ischaemic heart and peripheral vascular diseases. However, it is unclear whether indobufen is an alternative antiplatelet agent for treatment of patients with ischaemic stroke.

**Aim** To test whether indobufen is non-inferior to aspirin in reducing the risk of new stroke at 3 months in patients with moderate to severe ischaemic stroke.

**Design** The Indobufen vs Aspirin in Acute Ischaemic Stroke (INSURE) is a randomised, double-blind, double-dummy, positive drug control, non-inferior multicentre clinical trial conducted in 200 hospitals in China. Participants will be randomised at a 1:1 ratio to receive either 100 mg indobufen two times daily or 100 mg aspirin once daily within 72 hours of the onset of symptoms from day 1 to 3 months.

**Study outcomes** The primary efficacy outcome is a new stroke (ischaemic or haemorrhagic) within 3 months and the primary safety outcome is a severe or moderate bleeding event within 3 months.

**Discussion** The INSURE trial will evaluate whether indobufen is non-inferior to aspirin in reducing the risk of new stroke at 3 months in patients with moderate to severe ischaemic stroke.

**Trial registration number** NCT03871517.

## INTRODUCTION AND RATIONALE

Stroke is the second leading cause of death worldwide and the leading cause of mortality and disability in China.<sup>1,2</sup> Patients with an acute ischaemic stroke have an approximately 5%–10% rate of another stroke within the first year of the initial event.<sup>3,4</sup> Dual antiplatelet therapy with clopidogrel and aspirin has been shown to be more effective than aspirin alone for reducing new stroke for patients with minor ischaemic stroke or transient ischaemic attack,<sup>5–7</sup> and was recommended as early management and secondary prevention strategy for these patients by the current guidelines.<sup>8,9</sup> However, for those with moderate to severe ischaemic stroke, aspirin

## Key messages

### What is already known on this topic

⇒ Indobufen is comparable to aspirin in the treatment of atherosclerotic ischaemic heart and peripheral vascular diseases, but the effect on stroke secondary prevention is unclear.

### What this study adds

⇒ The Indobufen vs Aspirin in Acute Ischaemic Stroke trial will test the noninferiority of indobufen to aspirin in reducing the risk of new stroke at 3 months in patients with moderate to severe ischaemic stroke.

### How this study might affect research, practice or policy

⇒ The result of the trial may provide an alternative antiplatelet agent for stroke secondary prevention.

is still the most evidence-based antiplatelet agent and currently recommended as a first-line treatment for secondary stroke prevention.<sup>8,9</sup> However, aspirin still faces the disadvantages of aspirin intolerance and potential adverse events of gastrointestinal stimulation and bleeding.<sup>10</sup> Besides aspirin desensitisation,<sup>11,12</sup> alternative antiplatelet therapies may be considered for these patients.

Indobufen is another cyclooxygenase inhibitor, which can prevent thrombosis rapidly and effectively by reversibly and selectively inhibiting platelet aggregation by reversibly inhibiting the platelet cyclooxygenase enzyme, thereby suppressing thromboxane synthesis.<sup>13</sup> Furthermore, the platelet function is recovered within 24 hours after the withdrawal of indobufen; therefore, the risk of bleeding caused by the drug is low and easy to stop.<sup>13</sup> Previous studies have indicated that indobufen is comparable to aspirin in the treatment of atherosclerotic ischaemic heart and peripheral vascular diseases with less side effects.<sup>14,15</sup> However, it is still unclear whether

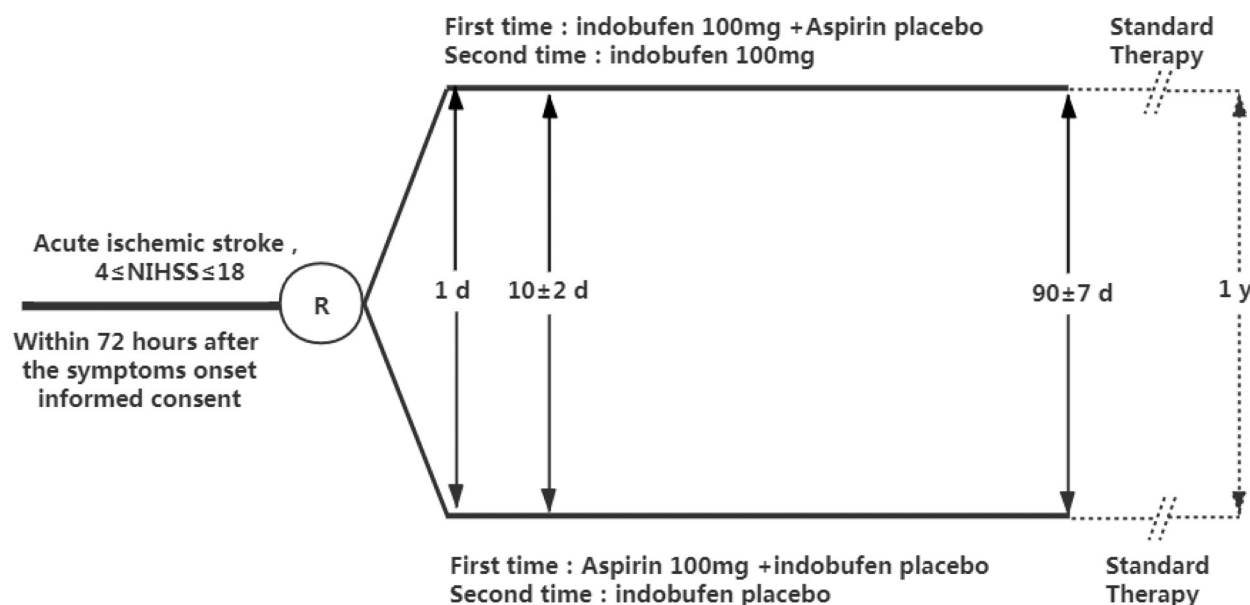


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**Figure 1** INSURE research design. INSURE, Indobufen vs Aspirin in Acute Ischaemic Stroke; NIHSS, National Institutes of Health Stroke Scale.

indobufen also has a comparable efficacy as aspirin for stroke secondary prevention and can be used as an alternative antiplatelet agent for treatment of ischaemic stroke.<sup>16</sup>

In the proposed Indobufen vs Aspirin in Acute Ischaemic Stroke (INSURE) trial, we will test the hypothesis that indobufen is non-inferior to aspirin in reducing the risk of new stroke at 3 months in patients with moderate to severe ischaemic stroke.

## METHODS

### Design

The INSURE trial is a randomised, double-blind, double-dummy, positive drug control, non-inferior multicentre clinical trial (figure 1). This trial aims to evaluate the efficacy and safety of indobufen as compared with aspirin at 3 months in patients with moderate to severe ischaemic stroke. Patients are randomised 1:1 to indobufen or aspirin within 72 hours of symptoms onset of an acute moderate to severe ischaemic stroke and followed for 3 months on study drug with an additional 9 months follow-up on standard of care.

### Patient population

In the INSURE trial, 5390 patients will be recruited from 200 participating centres in China. The inclusion and exclusion criteria are shown in box 1. Patients with acute moderate to severe ischaemic stroke, aged 18 to 80 years, with a National Institutes of Health Stroke Scale (NIHSS) score of  $\geq 4$  and  $\leq 18$ , who can be randomised within 72 hours after symptoms onset and signed informed consent will be enrolled in the trial.

### Randomisation

Participants will be randomised at a 1:1 ratio to receive either indobufen or aspirin within 72 hours of the onset of symptoms. A randomisation sequence will be generated centrally using block randomisation methods from the Statistics and Data Centre at the China National Clinical Research Centre for Neurological Diseases. For patients with randomisation qualifications, each centre will assign the random code from small to large order, and provide a treatment kit corresponding to the random code.

### Treatment

Patients meeting the criteria and offering informed consent will be assigned to one of the two arms (table 1): (1) the indobufen group will receive 100 mg indobufen twice daily plus aspirin placebo once daily from day 1 to 3 months. (2) The aspirin group will receive 100 mg aspirin once daily plus 100 mg indobufen placebo twice daily from day 1 to 3 months. After the 3-month trial period, patients were treated according to standard of care at the discretion of the local physicians.

### Study organisation

Patients will be followed up by face-to-face interviews at baseline, 10±2 days (or at the time of discharge), and 90±7 days. Medical examination including 12-lead ECG and echocardiography were performed at screening phase. Final diagnosis, classification of stroke aetiology, and relevant examination and treatment information during hospitalisation will be recorded at the time of discharge. Urine and fasting peripheral venous blood samples will be collected from all patients at baseline, 10±2 days and 90±7 days. MRI imaging were collected at baseline and 90±7 days. After 3 months, patients will be followed up by the telephone interview at 1 year. Vascular

## Box 1 Inclusion and exclusion criteria

### Inclusion criteria

- ⇒ Eighteen years to 80 years.
- ⇒ Acute moderate/severe ischaemic stroke, 4≤National Institutes of Health Stroke Scale≤18 at the time of randomisation.
- ⇒ Can be randomised within 72 hours of symptoms onset\*.
- ⇒ Informed consent signed.

\*Symptom onset is defined by the 'last see normal' principle.

### Exclusion criteria

- ⇒ History of intracerebral haemorrhagic diseases including intracerebral haemorrhage and subarachnoid haemorrhage.
- ⇒ Diagnosis of haemorrhage or other pathology, such as vascular malformation, tumour, abscess or other major non-ischaemic brain disease (eg, multiple sclerosis) on baseline head CT or MRI.
- ⇒ Moderate to severe ischaemic stroke induced by angioplasty/vascular surgery.
- ⇒ Pre-morbid modified Rankin Scale Score >2.
- ⇒ History of aneurysm (including intracranial aneurysm or peripheral aneurysms).
- ⇒ History of cardiac source of embolus, including atrial fibrillation or atrial myxoma.
- ⇒ History of haemostatic disorder, systemic bleeding, thrombocytopenia or neutropenia.
- ⇒ History of previous symptomatic non-traumatic intracerebral bleed or cerebral artery amyloidosis.
- ⇒ Gastrointestinal bleeding within the last 6 months before randomisation.
- ⇒ Major surgery within 30 days before randomisation.
- ⇒ Severe renal or hepatic insufficiency; (Severe hepatic insufficiency is defined as alanine aminotransferase (ALT) >3 times normal upper limit or aspartate aminotransferase (AST) >2 times normal upper limit. Severe renal insufficiency is defined as creatinine >2 times normal upper limit).
- ⇒ Diagnosis or suspicious diagnosis of acute coronary syndrome (ST elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina).
- ⇒ Other antithrombotic therapies are required during the study, including antiplatelet therapy (such as open-labelled aspirin, GPIIb/IIIa inhibitors, clopidogrel, ticagrelor, prasugrel, dipyridamole, ozagrel, cilostazol, etc) and anticoagulant therapy (such as warfarin, thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, heparin and low molecular heparin, etc).
- ⇒ Any venous or arterial thrombolysis within 24 hours prior to randomisation, such as mechanical bolt, snake venom, defibrase, lumbrakinase, etc. Heparin or oral anticoagulants were used within 10 days prior to randomisation.
- ⇒ Have a history of drug or food allergy and are known to be allergic to the study drug ingredients.
- ⇒ Planned or likely revascularisation (any angioplasty or vascular surgery) within the next 3 months.
- ⇒ Anticipated requirement for long-term (>7 days) non-steroidal anti-inflammatory drugs.
- ⇒ The blood pressure needs to be controlled below 90 mm Hg/60 mm Hg or beyond 220 mm Hg/120 mm Hg.
- ⇒ Suffering from serious cardiopulmonary disease, the investigators believe that it is not suitable for this study.
- ⇒ Patients with life expectancy <3 months or patients who are unable to complete the study for other reasons.

Continued

## Box 1 Continued

- ⇒ Women of childbearing age who are negative in pregnancy test but refuse to use birth control; Women who are pregnant or lactating.
- ⇒ Involving in an experimental drug or device trials within the last 30 days before randomisation.
- ⇒ Inability of the patient to understand and/or comply with study procedures and/or follow-up due to mental illness, cognitive or emotional disorders.

events, modified Rankin Scale (mRS) score and mortality will be collected at 3-month and 1-year follow-up.

### Primary outcomes

The primary efficacy outcome is a new stroke event (ischaemic or haemorrhagic) within 3 months. Definitions of stroke are provided in online supplemental table 1.

### Secondary outcomes

Secondary outcomes include the following events: (1) New stroke event within 1 year (ischaemic or haemorrhagic); (2) New vascular events including ischaemic stroke, haemorrhagic stroke, myocardial infarction and vascular death within 3 months and 1 year. At the same, independent assessment of each new vascular event; (3) New ischaemic stroke events within 3 months and 1 year; (4) early lower extremity venous thrombosis; (5) Poor functional outcome (mRS scores between 3 to 6 points) at 3 months and 1 year; (6) Neurological impairment (changes in NIHSS score at 3 months compared with baseline); (7) Quality of Life (EuroQol EQ-5dimension-5 Level scale) at 3 months and 1 year.

### Safety outcomes

The primary safety outcome is severe or moderate bleeding within 3 months defined by the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.<sup>17</sup> Severe bleeding was defined as fatal or intracranial or other haemorrhage causing substantial haemodynamic compromise that required intervention. Moderate bleeding was defined as bleeding that did not lead to

**Table 1** Treatment in the two groups

Group	Time period	Treatment
Indobufen	Day 1 to 90±7	The first time*: indobufen 100 mg+aspirin placebo The second time: indobufen 100 mg
Aspirin	Day 1 to 90±7	The first time*: aspirin 100 mg+indobufen placebo The second time: indobufen placebo

\*The interval between two administrations should be at least 8 hours.

haemodynamic compromise requiring intervention but required transfusion of blood.<sup>17</sup> Other secondary safety outcomes include the following events within a 3-month and 1-year time frame: (1) Severe or moderate bleeding within 1 year by the GUSTO criteria; (2) Any bleeding events; (3) Death; (4) Symptomatic and asymptomatic intracranial haemorrhagic events; (5) Cerebral microbleed within 3 months; (6) Adverse events or serious adverse events within 3 months, such as gastrointestinal reaction, gastrointestinal bleeding, renal impairment, etc.

### Sample size

The study hypothesised that aspirin (control group) and indobufen (treatment group) both had a primary endpoint event rate of 9%. Previous studies have shown that aspirin alone can reduce the incidence of 3 month endpoints by 50% (34%–73%) compared with placebo.<sup>18</sup> We hypothesised that one-fourth of the control event rate (equivalent to the half of the placebo risk, HR=1.25, and the treatment group had an event rate of 11.25%) as non-inferiority margin ( $\delta$ ). That is, compared with the control group, when the upper limit of the CI for the event risk in the treatment group is less than 1.25, suggesting that indobufen is not inferior to aspirin. The statistical test level  $\alpha$  is one-side 0.025, the power is 80%, and the lost to follow-up rate is 5%. The estimated total sample required is 5390 (2695 cases in each group). Power analysis was implemented in the Power Analysis and Sample Size software (NCSS, Kaysville, Utah, USA).

### Statistical analyses

Interim analyses will not be performed in this trial. However, a Data and Safety Monitoring Board is in place to ensure the safety of subjects in the study. Data will be analysed both according to intention-to-treat principle and in per-protocol set. For primary efficacy analysis, non-inferiority analysis will be performed. If the indobufen group is confirmed to be non-inferior to aspirin (control group), a superiority analysis will be further performed to analyse whether the indobufen is superior to aspirin. At the same time, Kaplan-Meier methods will be used to simulate the cumulative risk of stroke (ischaemic or haemorrhagic) at 90-day follow-up and log-rank test will be used to evaluate the treatment effect. Cox proportional hazards model with study centre set as a random effect in the model, will be used to calculate the HR and 95% CI. The influence on treatment effect by sex, different age category (<65 years vs  $\geq 65$  years), history of diabetes, history of hypertension, etiological stroke subtype, intracranial artery stenosis vs without intracranial artery stenosis, prior use of aspirin and/or other antiplatelet agents and disease severity (NIHSS 4–9 vs NIHSS 10–18) will be evaluated in subgroup analyses.

For secondary outcomes, Kaplan-Meier methods will be used to estimate the incidence of vascular events in each group and log-rank test will be used to evaluate the treatment effect. Cox proportional hazard model will be used

to calculate the HR of the two treatments and the centre effect will be set as a random effect in the model. Logistic regression will be used to analyse the difference in poor functional outcome (mRS score of 3–6 points) and lower extremity venous thrombosis between the two groups, and the OR with 95% CI will be reported. Changes of NIHSS scores between the end of study and baseline and health related quality of life will be summarised for the two treatment groups, and the treatment difference will be tested using Student's t-test or Wilcoxon rank sum test as appropriate. All statistical analyses will be performed with use of SAS software, V.9.4 (SAS Institute) and two sided with  $p < 0.05$  will be considered significant.

### DISCUSSION

The INSURE trial is a randomised clinical trial to evaluate the efficacy and safety of indobufen as compared with aspirin in stroke secondary prevention in patients with patients with moderate to severe ischaemic stroke.

With the effect of inhibition of platelet activation through reversible inhibiting platelet cyclooxygenase, indobufen has been used to prevent thromboembolism in high-risk patients, intermittent claudication, to prevent graft stenosis after coronary artery bypass grafting.<sup>14 15 19</sup> Previous studies showed that the risk of bleeding events in patients on indobufen is low.<sup>20</sup> Indobufen is considered as a major alternative antiplatelet agent for patients with aspirin intolerance undergoing coronary stent implantation,<sup>10</sup> especially when aspirin desensitisation is not feasible.<sup>21</sup> Therefore, indobufen is expected to have a comparable effect as aspirin in secondary prevention of ischaemic stroke, with lower risk of bleeding and other adverse effects. However, to date, there is no evidence from large scale clinical trials for a head-to-head comparison of treatment effect between indobufen and aspirin for stroke secondary prevention. It is still unclear whether indobufen can be used as an alternative antiplatelet agent for treatment of ischaemic stroke.

In summary, the INSURE trial is a randomised, double-blind, double-dummy, positive drug control, non-inferior multicentre clinical trial to evaluate the efficacy and safety of indobufen as compared with aspirin in stroke secondary prevention in patients with moderate to severe ischaemic stroke. Data from the INSURE trial will provide high level evidence on whether indobufen is non-inferior to aspirin in reducing the risk of new stroke at 3 months in patients with moderate to severe ischaemic stroke.

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**Contributors** YW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YP, XM, WC, HL and YW. Drafting of the manuscript: YP and YW. Critical revision of the manuscript for important intellectual content: SCJ, PMB, QD, A-DX and HL. Study supervision and organisation of the project: XM, JJ, JL, YJ and YW.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** The protocol of the INSURE trial was approved by ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2018-075-02) and all participating centres. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. Not applicable.

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## REFERENCES

- Zhou M, Wang H, Zhu J, *et al*. Cause-Specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the global burden of disease study 2013. *Lancet* 2016;387:251-72.
- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018;392:1736-88.
- Pan Y, Li Z, Li J, *et al*. Residual risk and its risk factors for ischemic stroke with adherence to Guideline-Based secondary stroke prevention. *J Stroke* 2021;23:51-60.
- Flach C, Muruet W, Wolfe CDA, *et al*. Risk and secondary prevention of stroke recurrence: a Population-Base cohort study. *Stroke* 2020;51:2435-44.
- Wang Y, Wang Y, Zhao X, *et al*. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-19.
- Johnston SC, Easton JD, Farrant M, *et al*. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018;379:215-25.
- Wang D. Precision antiplatelet therapy for the prevention of ischaemic stroke. *Stroke Vasc Neurol* 2022;7:89-91.
- Kleindorfer DO, Towfighi A, Chaturvedi S. Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart Association/American stroke association. *Stroke* 2021;2021:e364-467.
- Liu L, Chen W, Zhou H, *et al*. Chinese stroke association guidelines for clinical management of cerebrovascular disorders: Executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol* 2020;5:159-76.
- Latib A, Ielasi A, Ferri L, *et al*. Aspirin intolerance and the need for dual antiplatelet therapy after stent implantation: a proposed alternative regimen. *Int J Cardiol* 2013;165:444-7.
- Bianco M, Bernardi A, D'Ascenzo F, *et al*. Efficacy and safety of available protocols for aspirin hypersensitivity for patients undergoing percutaneous coronary intervention: a survey and systematic review. *Circ Cardiovasc Interv* 2016;9:e002896.
- Bianco M, Rossini R, Cerrato E, *et al*. Aspirin desensitization procedures in aspirin intolerant patients: a neglected topic in the ESC 2019 chronic coronary syndrome guidelines. *Eur Heart J* 2020;41:482.
- Lee J-Y, Sung K-C, Choi H-I. Comparison of aspirin and indobufen in healthy volunteers. *Platelets* 2016;27:105-9.
- Cataldo G, Heiman F, Lavezzari M, *et al*. Indobufen compared with aspirin and dipyridamole on graft patency after coronary artery bypass surgery: results of a combined analysis. *Coron Artery Dis* 1998;9:217-22.
- Belcaro G, De Simone P. Long-Term evaluation of indobufen in peripheral vascular disease. *Angiology* 1991;42:8-14.
- Bianco M, Gravinese C, Cerrato E, *et al*. Management of aspirin intolerance in patients undergoing percutaneous coronary intervention. The role of mono-antiplatelet therapy: a retrospective, multicenter, study. *Minerva Cardioangiol* 2019;67:94-101.
- GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.
- Rothwell PM, Algra A, Chen Z, *et al*. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016;388:365-75.
- Barillà F, Pulcinelli FM, Mangieri E, *et al*. Clopidogrel plus indobufen in acute coronary syndrome patients with hypersensitivity to aspirin undergoing percutaneous coronary intervention. *Platelets* 2013;24:183-8.
- Ibáñez L, Vidal X, Vendrell L, *et al*. Upper gastrointestinal bleeding associated with antiplatelet drugs. *Aliment Pharmacol Ther* 2006;23:235-42.
- Rossini R, Iorio A, Pozzi R, *et al*. Aspirin desensitization in patients with coronary artery disease: results of the multicenter adapted registry (aspirin desensitization in patients with coronary artery disease). *Circ Cardiovasc Interv* 2017;10:e004368.

## Correction: *Indobufen versus aspirin in acute ischaemic stroke (INSURE): rationale and design of a multicentre randomised trial*

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The above mentioned article is updated since it was first published. In page 458, under the title ‘Patient population’, the text ‘...aged 40 years or older...’ is changed to ‘aged 18 to 80 years...’. And in Box 1: ‘Forty years to 80 years’ under the title ‘Inclusion criteria’ is changed to ‘Eighteen years to 80 years’.

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**Supplemental Table 1. Definitions of stroke events and vascular events**

<b>Stroke</b>	Acute symptoms and signs of neurologic defect caused by sudden abnormality of the blood supply. Damage of focal or whole brain, spinal or retinal vascular damage, which is related to cerebral circulation disorder.
<b>Ischemic stroke</b>	Definitions: (1) Symptoms or imaging evidence of acute newly onset focal neurologic deficit last for more than 24 hours after excluding other non-ischemic reasons, such as brain infection, head trauma, brain tumor, epilepsy, severe metabolic diseases, degeneration diseases or adverse effect of medications; or (2) Acute brain or retinal ischemic event with focal symptoms or signs lasts for less than 24 hours after excluding other causes with imaging evidence of new infarction; or (3) Progression of original vascular ischemic stroke (NIHSS increased $\geq 4$ from baseline score after excluding hemorrhagic transformation or symptomatic intracerebral hemorrhage after cerebral infarction) lasts over 24 hours with new ischemic lesion on brain MRI or CT. Which would be classified by TOAST etiology standard.
<b>Transient ischemic attack</b>	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 24 hours, and without evidence of acute infarction, after excluding other non-ischemic reasons, such as brain infection, head trauma, brain tumor, epilepsy, severe metabolic diseases, degeneration diseases or adverse effect of medications.
<b>Hemorrhagic stroke</b>	Hemorrhagic stroke was defined as focal or whole brain or spine damage caused by non-traumatic bleeding into the brain parenchyma, intraventricular or subarachnoid.
<b>Hemorrhagic transformation after infarction</b>	<p>Any kind of non-traumatic extravascular bleeding in the area of brain tissue of existing acute/subacute infarction. Which could lead to relevant neurologic symptoms(symptomatic) or not (asymptomatic).</p> <p>1. To determine a symptomatic hemorrhagic transformation, the following two conditions must be met, (1) Image evidence of extravascular bleeding in the area of infarction on brain CT or MRI; (2) Clinical symptoms are relevant to hemorrhagic transformation. Hemorrhagic transformation can partly explain patients' neurological symptoms, for example: (a) The area and location of infarction can't explain the symptoms; (b) Clinically deterioration means NIHSS increased <math>\geq 4</math> from original ischemic event or causing death directly from hemorrhagic transformation; (c) a large space-occupying hematoma develops secondary to hemorrhagic transformation.</p> <p>2. To determine an asymptomatic hemorrhagic transformation, the following two conditions must be met, (1) Image evidence of extravascular bleeding in the area of infarction on brain CT or MRI; (2) No symptoms are caused by hemorrhagic transformation or an neurologic deterioration that lead to a less than 4</p>

	increase of NIHSS score.
<b>Myocardial infarction</b>	<p>Third universal definition of myocardial infarction (Thygesen 2012)</p> <p>The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:</p> <ol style="list-style-type: none"> <li>1、 Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: <ol style="list-style-type: none"> <li>(1) Symptoms of ischemia.</li> <li>(2) New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).</li> <li>(3) Development of pathological Q waves in the ECG.</li> <li>(4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality</li> <li>(5) Identification of an intracoronary thrombus by angiography or autopsy.</li> </ol> </li> <li>2、 Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.</li> <li>3、 Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (<math>&gt;5\times 99</math>th percentile URL) in patients with normal baseline values (<math>\leq 99</math>th percentile URL) or a rise of cTn values <math>&gt;20\%</math> if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia or (2) new ischemic ECG changes or (3) angiographic findings consistent with a procedural complication or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.</li> <li>4、 Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.</li> <li>5、 Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (<math>&gt;10\times 99</math>th percentile URL) in patients with normal baseline cTn values (<math>\leq 99</math>th percentile URL). In addition, either <ol style="list-style-type: none"> <li>(1) new pathological Q waves or new LBBB, or</li> <li>(2) angiographic documented new graft or new native coronary artery occlusion, or</li> <li>(3) imaging evidence of new loss of viable myocardium or new regional wall</li> </ol> </li> </ol>



	motion abnormality.
<b>Vascular death</b>	<p>Vascular death include death due to stroke, cardiac sudden death, death caused by acute myocardial infarction, death caused by heart failure, death caused by pulmonary embolism, death caused by cardial/cerebral interventions or operations (not caused by myocardial infarction) and death caused by other cardiovascular diseases. (Arrhythmia irrelevant to cardiac sudden death, rupture of aortic aneurysm or peripheral artery disease).</p> <p>Unexplained death happened within 30 days after stroke, myocardial infarction or cardiovascular/cerebral vascular operation will be considered as stroke, myocardial infarction and accidental death caused by operation separately.</p>