



Indobufen versus aspirin in patients with acute ischaemic stroke in China (INSURE): a randomised, double-blind, double-dummy, active control, non-inferiority trial

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Summary

Background Aspirin is recommended for secondary stroke prevention in patients with moderate-to-severe ischaemic stroke but can lead to gastrointestinal intolerance and bleeding. Indobufen is used as an alternative antiplatelet agent in some countries, despite an absence of large-scale clinical trials for this indication. We tested the hypothesis that indobufen is non-inferior to aspirin in reducing the risk of new stroke at 90 days in patients with moderate-to-severe ischaemic stroke.

Methods We conducted a randomised, double-blind, double-dummy, active control, non-inferiority trial at 163 tertiary and district general hospitals in China. Eligible participants were aged 18–80 years with acute moderate-to-severe ischaemic stroke (National Institutes of Health Stroke Scale score 4–18). We randomly assigned (1:1) participants within 72 h of the onset of symptoms to receive either indobufen (100 mg tablet twice per day) or aspirin (100 mg tablet once per day) for 90 days. The randomisation sequence was computer generated centrally and stratified by local participating centres. Masked local investigators assigned the random code to patients in ascending order and provided a treatment kit corresponding to the random code. The primary efficacy outcome was new stroke and the primary safety outcome was severe or moderate bleeding, both within 90 days. This primary efficacy outcome was assessed in all randomly assigned and consenting patients and in a per-protocol group (ie, all patients finishing the treatment without major violation of the trial protocol). Safety analyses were done in the safety-analysis population (ie, all patients who received at least one dose of the study drug and had a safety assessment available). We assessed the non-inferiority of indobufen versus aspirin using the one-sided upper limit of the 95% CI of the hazard ratio (HR) with a prespecified non-inferiority margin of 1.25. This trial is registered with ClinicalTrials.gov (NCT03871517).

Findings This trial took place between June 2, 2019, and Nov 28, 2021. Of 84 093 patients screened, 5438 patients were randomly assigned to receive either indobufen (n=2715) or aspirin (n=2723), all of whom were included in the primary analyses. Median age was 64.2 years (IQR 56.1–70.6); 1921 (35.3%) were women and 3517 (64.7%) were men. Stroke occurred within 90 days in 213 (7.9%) patients in the indobufen group versus 175 (6.4%) in the aspirin group (HR 1.23, 95% CI 1.01–1.50; $p_{\text{non-inferiority}}=0.44$). Moderate or severe bleeding occurred in 18 (0.7%) patients in the indobufen group and in 28 (1.0%) in the aspirin group (0.63, 95% CI 0.35 to 1.15; $p=0.13$). Adverse events within 90 days occurred in 666 (24.5%) patients in the indobufen group and 679 (24.9%) patients in the aspirin group ($p=0.73$).

Interpretation In patients with acute moderate-to-severe ischaemic stroke, indobufen was not non-inferior to aspirin because the upper limit of the 95% CI was greater than 1.25. Furthermore, indobufen seemed to be inferior to aspirin in reducing the risk of recurrent stroke at 90 days because the lower limit of the 95% CI was greater than 1.00. Although moderate or severe bleeding did not differ between groups, these findings do not support the use of indobufen for secondary stroke prevention in patients with moderate-to-severe ischaemic stroke.

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Introduction

Stroke is the second leading cause of death and third leading cause of disability worldwide.^{1,2} Patients with acute ischaemic stroke have a high risk of recurrent stroke at the early stage after initial event onset (approximately 5–10% within the first year).^{3,4} Dual antiplatelet therapy with

clopidogrel and aspirin has been recommended to be administered as soon as possible for patients with minor ischaemic stroke or transient ischaemic attack to reduce the risk of new stroke.^{5–7} For those with moderate-to-severe ischaemic stroke, aspirin is the most evidence-based antiplatelet agent and is currently recommended in

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See Online for appendix 2

Research in context

Evidence before this study

We searched MEDLINE for studies published from database inception to Dec 25, 2022, using the search terms “stroke” AND “indobufen” with no language restrictions. This search yielded no randomised trials providing evidence of the effect of indobufen compared with aspirin or other antiplatelet agents for the treatment of patients with acute ischaemic stroke. Some observational and pharmacological studies have shown that indobufen can lead to initial inhibition of platelet aggregation equivalent to aspirin. Indobufen is sometimes indicated for people with aspirin intolerance. Whether indobufen would also confer a clinical benefit when used as a first-line treatment for secondary stroke prevention is unclear. The evidence had moderate-to-high risk of bias.

Added value of this study

The Indobufen versus Aspirin in Acute Ischemic Stroke (INSURE) trial assessed whether indobufen was non-inferior

to aspirin in reducing the risk of new stroke at 90 days in patients with moderate-to-severe ischaemic stroke. To our knowledge, this is the first randomised controlled trial to investigate the potential effects of indobufen compared with aspirin.

Implications of all the available evidence

The INSURE trial found that indobufen was not non-inferior to aspirin in patients with moderate-to-severe ischaemic stroke, and that it might be inferior to aspirin. The results of the INSURE trial do not support the use of indobufen for secondary stroke prevention in patients with moderate-to-severe ischaemic stroke. Administration of indobufen could be limited to patients with aspirin intolerance or a contraindication to other antiplatelet agents.

clinical guidelines.^{8,9} However, aspirin can lead to gastrointestinal intolerance and bleeding,^{10,11} therefore, alternative antiplatelet treatment is often considered for patients who have shown gastrointestinal intolerance and bleeding with aspirin.¹¹ Clopidogrel, another antiplatelet agent, is less effective for secondary stroke prevention in people who carry the *CYP2C19* loss-of-function alleles, which are present in 25% of patients who are White and 60% of patients who are Asian, than in people who do not carry these alleles.^{12,13}

Indobufen can block platelet aggregation by reversibly inhibiting the platelet cyclooxygenase enzyme, thereby suppressing thromboxane synthesis and preventing thrombosis.¹⁴ The anti-aggregation effect of indobufen subsides within 24 h after withdrawal of the drug; thus, indobufen might be associated with a lower risk of bleeding than aspirin and rapid haemostasis after withdrawal of the drug if bleeding occurs.¹⁴ Previous studies have shown that indobufen is similar to aspirin in the treatment of atherosclerotic ischaemic heart and peripheral vascular diseases in terms of vascular events, but with fewer adverse effects.^{15–17} Indobufen is also hypothesised to be useful for secondary stroke prevention, and it is used for this indication in some countries, such as China or Italy.¹⁸ However, there are no large-scale clinical trials comparing treatment between indobufen and aspirin for secondary stroke prevention. Therefore, whether indobufen can be used as an alternative antiplatelet agent for secondary stroke prevention after ischaemic stroke is still unclear.¹⁹

Because indobufen is used for stroke treatment in some European and Asian countries, we tested the hypothesis that indobufen is non-inferior to aspirin in reducing the risk of new stroke at 90 days in patients with moderate-to-severe ischaemic stroke.

Methods

Study design and patients

The Indobufen versus Aspirin in Acute Ischemic Stroke (INSURE) trial was a randomised, double-blind, double-dummy, active control, non-inferiority trial conducted at 163 tertiary and district general hospitals in China. The efficacy and safety of indobufen was compared with aspirin at 90 days in patients with moderate-to-severe ischaemic stroke. The protocol of the INSURE trial was approved by ethics committees at Beijing Tiantan Hospital, Capital Medical University (Beijing, China; KY2018-075-02) and all participating centres. All participants or their representatives provided written informed consent before enrolment.

Details of the rationale and design of this study have been described previously (appendix 2 pp 17–76).²⁰ In brief, patients with acute moderate-to-severe ischaemic stroke, aged 18–80 years, with a National Institutes of Health Stroke Scale (NIHSS) score of 4–18, who could be randomised within 72 h after symptom onset and sign an informed consent form, were eligible for enrolment and were approached in hospital. Patients with a history of intracerebral haemorrhage or cardiac source of embolus, those who required other antithrombotic therapies (eg, antiplatelet and anticoagulant therapy) during the study, and those who had planned revascularisation within the next 90 days for whom open-label antiplatelet therapy might be warranted were excluded from the trial. A full list of exclusion criteria is included in appendix 2 (pp 8–9). Sex data were self-reported by participants; the provided options were male or female.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either indobufen or aspirin within 72 h of the onset of

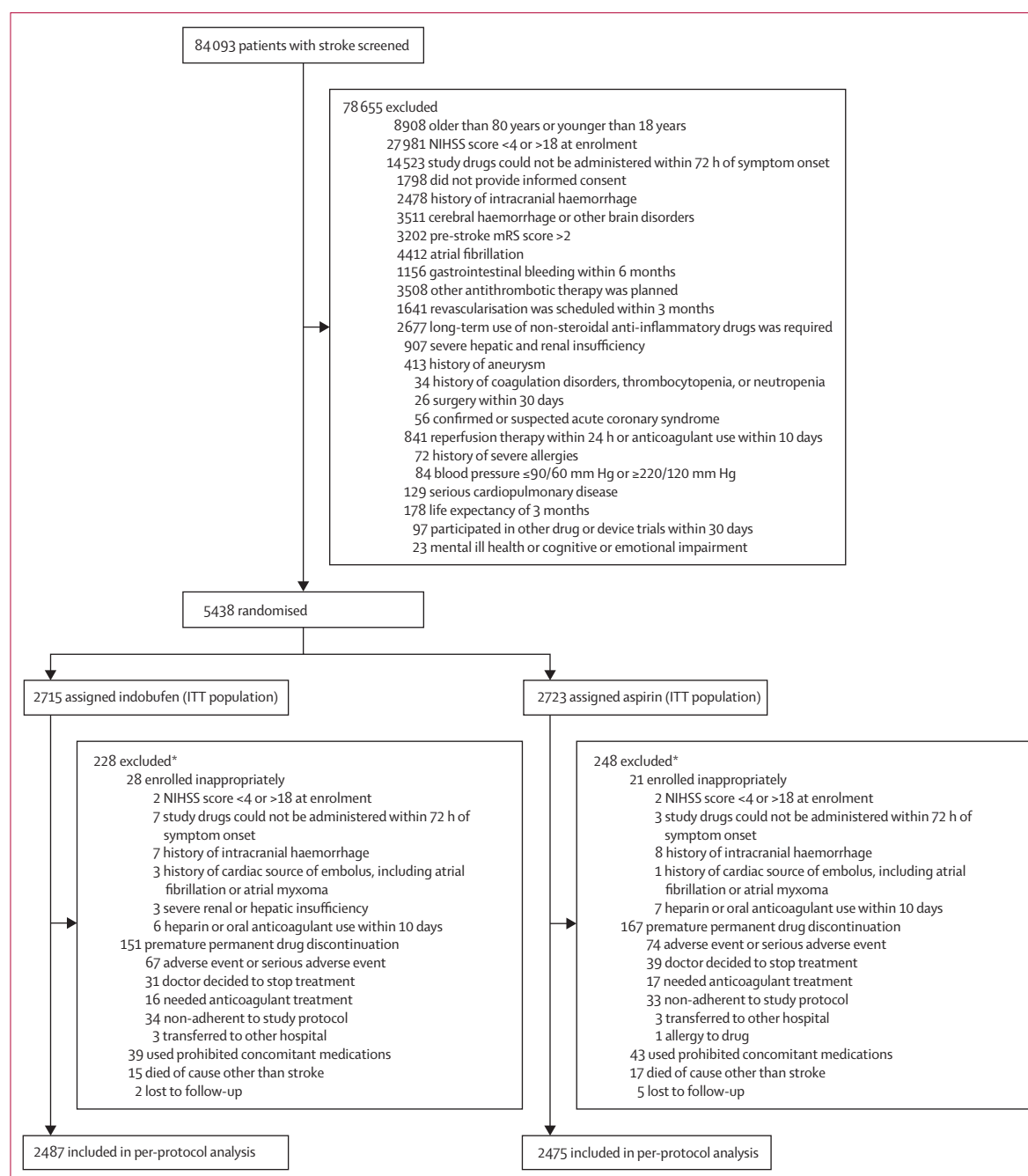


Figure 1: Trial profile

ITT=intention-to-treat. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *The total numbers of participants excluded at each stage are less than the numbers of participants for each reason because there were overlaps between different exclusion reasons.

symptoms. A randomisation sequence was computer generated centrally and stratified by participating centres via block randomisation, with a block size of six, at the Statistics and Data Centre at the China National Clinical Research Center for Neurological Diseases (Beijing, China). Local investigators enrolled participants. Once patients were deemed eligible, the local investigators in each centre who were allocating

interventions assigned the random code in ascending order and provided a treatment kit corresponding to the random code. These local investigators also allocated interventions; they knew the random code but did not know the allocation sequence, and the randomisation allocation was concealed. Participants, local investigators assigning interventions and assessing outcomes, the data manager, and statisticians were masked to

group assignments until the analyses were completed. As local investigators only saw the random code number, which corresponds to a medicine kit, and the study drugs were double-blind and double-dummy, the local investigator did not know the group assigned or the allocation sequence.

Procedures

Patients in the indobufen group received a 100 mg indobufen tablet twice per day plus an aspirin placebo that was identical in taste and appearance to aspirin once per day starting on day 1 for 90 days. Patients in the aspirin group received a 100 mg aspirin tablet once per day plus

a 100 mg indobufen placebo that was identical in taste and appearance to indobufen twice per day starting on day 1 for 90 days. After the 90-day trial period, patients were treated according to standard of care at the discretion of the local doctor (appendix 2 p 7).

Patients were assessed face-to-face at baseline, 10 days (range 8–12) or time of discharge, and 90 days (range 83–97). Medical examination, including 12-lead electrocardiogram and echocardiography, was done at the screening phase. Final diagnosis, classification of stroke aetiology, and relevant examination and treatment information during treatment in hospital were recorded at time of discharge. Lower-extremity venous ultrasound was done at the 10-day visit (or at discharge). Patients were followed up by in-person interview at 90 days and by telephone interview at 1 year. Vascular events, modified Rankin Scale (mRS) score, and mortality data were collected at 90-day and 1-year follow-up.

Outcomes

The primary efficacy outcome was a new stroke (ischaemic or haemorrhagic) within 90 days (appendix 2 pp 10–11). The primary outcome was assessed by an independent clinical-event adjudication committee. Secondary outcomes were new stroke within 1 year; new vascular events as a composite of ischaemic stroke, haemorrhagic stroke, myocardial infarction, and vascular death within 90 days and within 1 year; the components of the composite outcome; new ischaemic stroke events within 90 days and within 1 year; early lower-extremity venous thrombosis reported by lower-extremity venous ultrasound at 10-day visit (or at discharge); poor functional outcome (ie, mRS score 3–6) at 90 days and at 1 year; change in NIHSS score between admission and 90 days; and quality of life measured with EuroQol EQ-5D scale at 90 days and at 1 year.

The primary safety outcome was severe or moderate bleeding within 90 days defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for

	Indobufen group (n=2715)	Aspirin group (n=2723)
Age, years	64.7 (56.3–70.9)	63.8 (56.0–70.3)
Sex		
Male	1751 (64.5%)	1766 (64.9%)
Female	964 (35.5%)	957 (35.2%)
Ethnicity		
Han Chinese	2581 (95.1%)	2573 (94.5%)
Other	134 (4.9%)	150 (5.5%)
Medical history		
Hypertension	1703 (62.7%)	1700 (62.4%)
Diabetes	735 (27.1%)	717 (26.3%)
Dyslipidaemia	87 (3.2%)	98 (3.6%)
Stroke	555 (20.4%)	535 (19.7%)
Transient ischaemic attack	24 (0.9%)	44 (1.6%)
Myocardial infarction	28 (1.0%)	31 (1.1%)
Peripheral arterial disease	6 (0.2%)	2 (<0.1%)
Previous or current smoking	1092 (40.2%)	1140 (41.9%)
Previous or current drinking*	584 (21.5%)	570 (20.9%)
Previous antiplatelet therapy†	211 (7.8%)	200 (7.3%)
Time from onset to randomisation	46.1 (31.0–57.3)	46.9 (31.5–58.5)
<24 h	368 (13.6%)	323 (11.9%)
24–48 h	1075 (39.6%)	1102 (40.5%)
>48 h	1272 (46.9%)	1298 (47.7%)
NIHSS score	5 (4–7)	5 (4–7)
<10	2457 (90.5%)	2466 (90.6%)
≥10	258 (9.5%)	257 (9.4%)
Symptomatic intracranial artery stenosis	687/2553 (26.9%)	706/2563 (27.5%)
Aetiological stroke subtype		
Large-artery atherosclerosis	711/2564 (27.7%)	742/2592 (28.6%)
Small-artery occlusion	986/2564 (38.5%)	965/2592 (37.2%)
Undetermined pathogenesis	666/2564 (26.0%)	698/2592 (26.9%)
Other	201/2564 (7.8%)	187/2592 (7.2%)

Data are n (%), n/N (%), or median (IQR). NIHSS=National Institutes of Health Stroke Scale. *Current drinking was defined as alcohol use at least once per week in the past year. Previous drinking was defined as previous alcohol use at least once per week for a period of 1 year but have stopped alcohol use for more than 1 year. †Medication within 1 month before symptom onset.

Table 1: Baseline characteristics of the intention-to-treat population

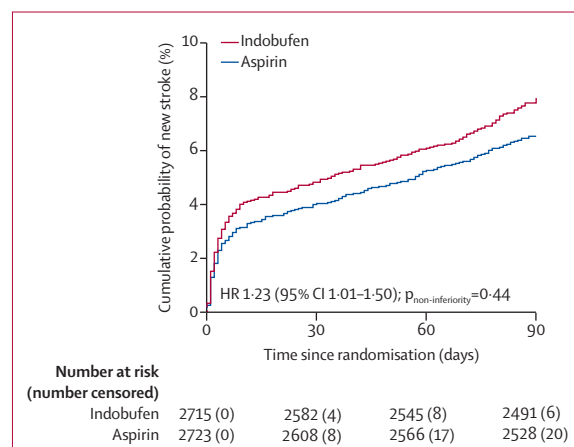


Figure 2: Kaplan-Meier plot for risk of new stroke within 90 days
HR=hazard ratio.

Occluded Coronary Arteries (GUSTO) criteria.²¹ 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 haemodynamic compromise requiring intervention but required transfusion of blood.²¹ Other secondary safety outcomes were severe or moderate bleeding defined by GUSTO criteria within 1 year, any bleeding events, death, symptomatic and asymptomatic intracranial haemorrhagic events within 90 days and within 1 year, and adverse events or serious adverse events within 90 days.

Statistical analysis

The INSURE trial investigators hypothesised that indobufen (the investigational drug) and aspirin (the active comparator) would both have a primary endpoint event rate of 9%.²² Previous studies have shown that aspirin alone can reduce the incidence of 90-day new stroke by 50% compared with placebo.²³ With the recommendation of clinical experts after discussion with statisticians, we set the non-inferiority margin (δ) at a quarter of the control event rate, preserving three-quarters of the treatment effect of aspirin (hazard ratio [HR] 1.25, corresponding to 2.25% absolute risk difference). Compared with the aspirin group, when the upper limit of the 95% CI for the event risk in the treatment group was less than 1.25, indobufen would be considered non-inferior to aspirin. A one-sided test for non-inferiority with a margin of HR 1.25, one-sided $\alpha=0.025$, and 10% attrition rate showed that 5390 patients (2695 in each group) provided a power of 80%.

For the primary efficacy analysis, data were analysed both according to the intention-to-treat (ITT) principle, including all randomised and consenting patients (ie, the full analysis set), and in a per-protocol group, defined as all patients finishing the treatment without major violation of the trial protocol. At the same time, Kaplan-Meier methods were used to simulate the cumulative risk of new stroke at 90-day follow-up. A Cox proportional hazards model with pooled study site (≥ 20 patients) set as a random effect in the model was used to calculate the HR and 95% CI. Patients were censored at their last follow-up assessment when experiencing a clinical event, at the end of the trial, or at the time of withdrawal from the trial. If there were multiple events of the same type, the time to the first event was used in the model. The influence on treatment effect by sex, age, history of diabetes, history of hypertension, aetiological stroke subtype, intracranial artery stenosis, previous antiplatelet therapy, disease severity (NIHSS score 4–9 vs NIHSS score 10–18), and time from onset to randomisation were evaluated in subgroup analyses.

For secondary outcomes, Kaplan-Meier methods were used to estimate the incidence of vascular events in each

	Indobufen group (n=2715)	Aspirin group (n=2723)	HR (95% CI) or OR (95% CI)*	p value
Primary outcome				
New stroke within 90 days in the ITT population	213 (7.9%, 6.9–8.9)	175 (6.4%, 5.6–7.4)	1.23 (1.01–1.50) [†]	..
New stroke within 90 days in the per-protocol population	181/2487 (7.3%, 6.3–8.4)	138/2475 (5.6%, 4.7–6.6)	1.32 (1.06–1.65) [†]	..
Secondary outcomes in the ITT population				
New stroke within 1 year	279 (10.4%, 9.3–11.6)	242 (9.0%, 8.0–10.1)	1.17 (0.98–1.39)	0.08
Composite vascular events within 90 days‡	214 (7.9%, 6.9–9.0)	181 (6.7%, 5.8–7.7)	1.19 (0.98–1.46)	0.08
Ischaemic stroke	200 (7.4%, 6.5–8.4)	156 (5.7%, 4.9–6.7)	1.30 (1.05–1.60)	0.01
Myocardial infarction	1 (<0.1%, <0.1–0.3)	3 (0.1%, <0.1–0.3)	0.33 (0.03–3.17)	0.34
Composite vascular events within 1 year‡	287 (10.7%, 9.5–11.9)	257 (9.5%, 8.5–10.7)	1.13 (0.96–1.34)	0.16
Ischaemic stroke	256 (9.5%, 8.4–10.7)	215 (8.0%, 7.0–9.1)	1.21 (1.01–1.45)	0.04
Myocardial infarction	5 (0.2%, <0.1–0.5)	9 (0.3%, 0.2–0.6)	0.53 (0.18–1.59)	0.26
Lower-extremity venous thrombosis§	111 (4.1%)	104 (3.8%)	1.07 (0.82–1.41)	0.61
mRS score 3–6 at 90 days¶	369 (13.6%)	364 (13.4%)	1.02 (0.87–1.19)	0.82
mRS score 3–6 at 1 year¶	320 (11.8%)	324 (11.9%)	0.99 (0.84–1.17)	0.89
Change in NIHSS between admission and 90 days¶	4 (3–5)	4 (3–5)	..	0.92
EuroQol EQ-5D at 90 days¶	85 (75–93)	87 (75–95)	..	0.90
EuroQol EQ-5D at 1 year¶	90 (80–95)	90 (80–95)	..	0.53

Data are n (%), n/N (%), or n (%; 95% CI). EuroQol EQ-5D=European quality-of-life visual analogue scale.

HR=hazard ratio. ITT=intention-to-treat. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio. *Event rates for lower-extremity venous thrombosis and mRS score 3–6 are raw estimates and ORs were estimated, whereas event rates for other outcomes are Kaplan-Meier estimates of the percentage of patients with events and HRs were estimated. 95% CIs for all Kaplan-Meier percentages in this table are provided. [†]The upper limit of 95% CI was greater than the non-inferiority margin of 1.25; thus, non-inferiority cannot be claimed. The lower limit of 95% CI was greater than 1.00, indicating that indobufen might be inferior to aspirin. [‡]Composite vascular events include ischaemic stroke, haemorrhagic stroke, myocardial infarction, and vascular death. From the clinical perspective, the components of ischaemic stroke and myocardial infarction were more of interest to doctors as haemorrhagic stroke and vascular death were rare. [§]Early lower-extremity venous thrombosis reported by lower-extremity venous ultrasound at 10-day visit (or at discharge). [¶]Three missing values for the indobufen group and five missing values for the aspirin group for mRS score 3–6 at 90 days. Three missing values for the indobufen group and six missing values for the aspirin group for mRS score 3–6 at 1 year. 27 missing values for the indobufen group and 26 missing values for the aspirin group for NIHSS score at 90 days. 31 missing values for the indobufen group and 26 missing values for the aspirin group for the EuroQol EQ-5D at 90 days. 65 missing values for the indobufen group and 65 missing values for the aspirin group for the EuroQol EQ-5D at 1 year.

Table 2: Efficacy outcomes

group and a log-rank test was used to evaluate the treatment effect. A Cox proportional hazard model with pooled study site set as a random effect in the model was used to calculate the HR of the two treatments. Logistic regression was used to analyse the difference in poor functional outcome (mRS score 3–6) and lower-extremity venous thrombosis between the two groups, and the odds ratio (OR) with 95% CI was reported. The *t* test or Wilcoxon rank sum test was used to analyse the difference in neurological impairment and quality of life, as appropriate.

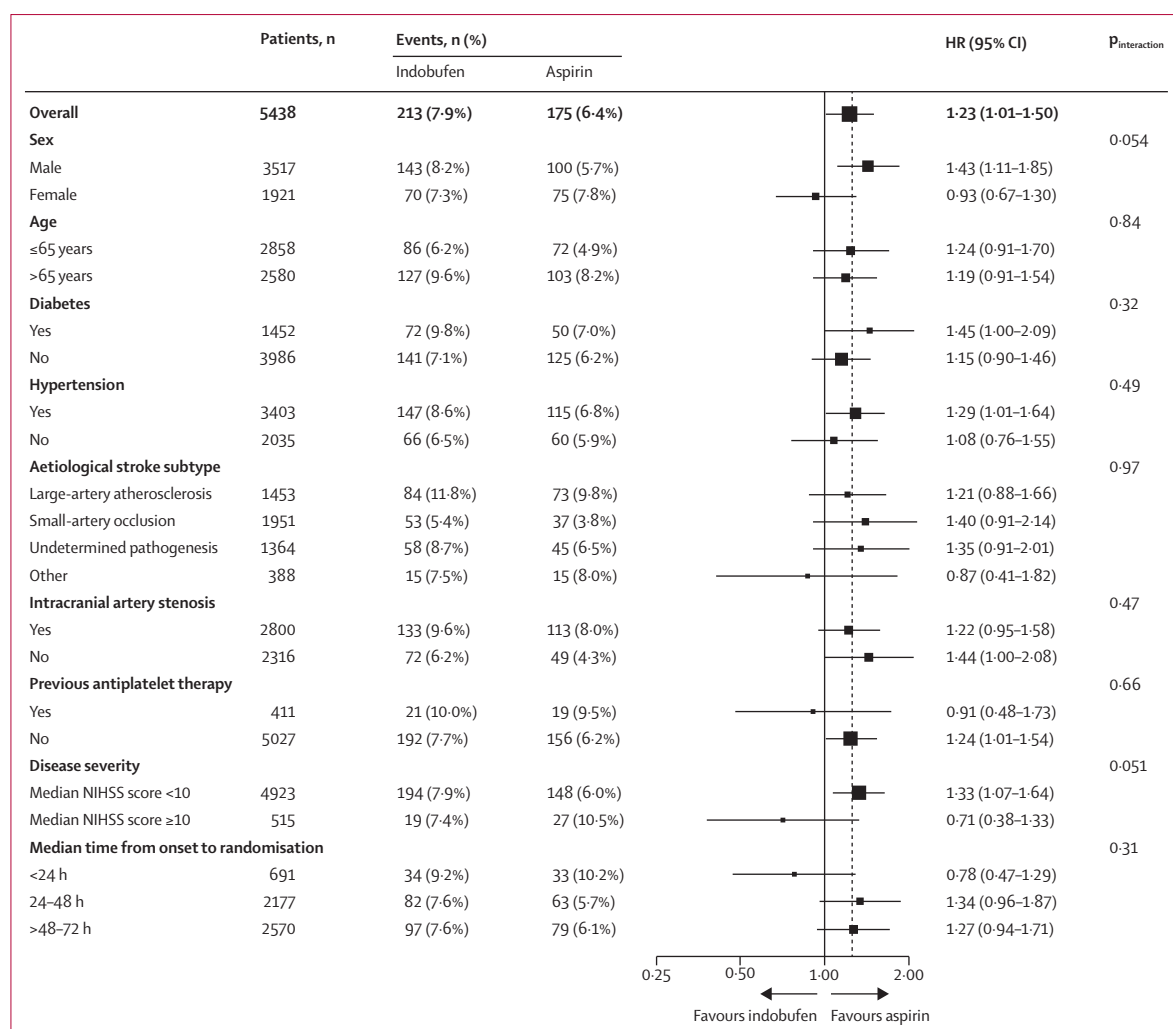


Figure 3: Hazard ratio for new stroke within 90 days according to prespecified subgroups

The dashed vertical line indicates the non-inferiority limit of 1.25. HR=hazard ratio. NIHSS=National Institutes of Health Stroke Scale. *Event rates are Kaplan-Meier estimates of the percentage of patients with stroke at 90 days.

Safety analyses were done in the safety-analysis population, defined as all patients who received at least one dose of the study drug according to the study protocol and had a safety assessment available. A Cox proportional hazards model with pooled study site set as a random effect in the model was used to calculate the HR and 95% CI. For comparison of adverse events and serious adverse events, a χ^2 test or Fisher's exact test was done, as appropriate.

No interim analyses were planned. A Data and Safety Monitoring Board ensured the safety of patients in the study. The board could halt the study because of any safety concerns. All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA). A one-sided test with $p < 0.025$ was considered significant for non-inferiority of the primary outcome and all other statistical tests were done at the two-sided 0.05 significance level. The INSURE trial is registered with ClinicalTrials.gov (NCT03871517).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 2, 2019, and Nov 28, 2021, a total of 84093 patients with moderate-to-severe ischaemic stroke were screened at 163 participating sites, of whom 5438 (6.5%) were enrolled. 2715 were randomly assigned to the indobufen group and 2723 to the aspirin group. Overall, 318 (5.8%) of 5438 patients had premature permanent drug discontinuation, 82 (1.5%) used prohibited concomitant medications, 32 (0.6%) died of causes other than stroke, and seven (0.1%) were lost to follow-up at 90 days (figure 1).

Baseline characteristics were similar between the two treatment groups (table 1). The median age of

	Indobufen group (n=2715)*	Aspirin group (n=2723)*	HR (95% CI)	p value
Primary safety outcome				
Severe or moderate bleeding within 90 days†	18 (0.7%, 0.4–1.1)	28 (1.0%, 0.7–1.5)	0.63 (0.35–1.15)	0.13
Fatal bleeding	1 (<0.1%, <0.1–0.3)	1 (<0.1%, <0.1–0.3)	0.96 (0.06–15.42)	0.98
Intracranial haemorrhage	14 (0.5%, 0.3–0.9)	19 (0.7%, 0.4–1.1)	0.74 (0.37–1.47)	0.39
Secondary safety outcomes				
Severe or moderate bleeding within 1 year†	32 (1.2%, 0.9–1.7)	39 (1.4%, 1.1–2.0)	0.82 (0.51–1.30)	0.40
Fatal bleeding	3 (0.1%, <0.1–0.3)	1 (<0.1%, <0.1–0.3)	2.91 (0.30–28.02)	0.35
Intracranial haemorrhage	25 (1.0%, 0.6–1.4)	27 (1.0%, 0.7–1.5)	0.93 (0.54–1.60)	0.79
Any bleeding within 90 days	65 (2.4%, 1.9–3.1)	70 (2.6%, 2.0–3.3)	0.93 (0.66–1.30)	0.67
Mild bleeding†	48 (1.8%, 1.3–2.3)	45 (1.7%, 1.2–2.2)	1.07 (0.72–1.61)	0.73
Any bleeding within 1 year	81 (3.0%, 2.4–3.7)	83 (3.1%, 2.5–3.8)	0.98 (0.72–1.33)	0.89
Mild bleeding†	63 (2.4%, 1.8–3.0)	58 (2.1%, 1.7–2.8)	1.09 (0.77–1.56)	0.62
Mortality within 90 days	40 (1.5%, 1.1–2.0)	39 (1.4%, 1.0–2.0)	1.03 (0.66–1.59)	0.91
Mortality within 1 year	76 (2.8%, 2.2–3.5)	85 (3.1%, 2.6–3.9)	0.89 (0.66–1.22)	0.47
Adverse events within 90 days	666 (24.5%)	679 (24.9%)	..	0.73
Serious adverse events within 90 days	85 (3.1%)	88 (3.2%)	..	0.83

Data are n (%) or n (% 95% CI). HR=hazard ratio. *Event rates for adverse events and serious adverse events are raw estimates, whereas event rates for other outcomes are Kaplan-Meier estimates of the percentage of patients with events at 90 days. †Severe or moderate bleeding and mild bleeding were defined according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.²³

Table 3: Safety outcomes

patients was 64.2 years (IQR 56.1–70.6); 1921 (35.3%) were women and 3517 (64.7%) were men. Median time from symptom onset to randomisation was 46.5 h (IQR 31.3–58.0). Concomitant treatments and prohibited medications taken during the treatment period are reported in the appendix 2 (pp 12–13).

New ischaemic or haemorrhagic stroke within 90 days (ie, the primary outcome) occurred in 213 (7.9%) of 2715 patients in the indobufen group and 175 (6.4%) of 2723 patients in the aspirin group (HR 1.23, 95% CI 1.01–1.50; $p_{\text{non-inferiority}}=0.44$; the lower limit of the 95% CI was greater than 1.00 and the upper limit of the 95% CI crossed the non-inferiority margin of 1.25; absolute risk difference 1.42, 95% CI 0.12–2.72; figure 2; table 2). Therefore, indobufen was not non-inferior to aspirin and appeared to be inferior to aspirin.

New ischaemic or haemorrhagic stroke within 1 year (ie, the secondary outcome) occurred in 279 (10.3%) of 2715 patients in the indobufen group and in 242 (8.9%) of 2723 patients in the aspirin group. Composite vascular events within 90 days occurred in 214 (7.9%) patients in the indobufen group and 181 (6.7%) in the aspirin group. New ischaemic stroke within 90 days occurred in 200 (7.4%) patients in the indobufen group and in 156 (5.7%) in the aspirin group. Other secondary outcomes are presented in table 2. Similar efficacy was observed across different predefined subgroups (all upper limits of 95% CIs crossed the non-inferiority margin of 1.25; figure 3). The results of the per-protocol analysis of efficacy were consistent with the results of the ITT analysis (appendix 2 p 14).

Moderate or severe bleeding defined by the GUSTO criteria within 90 days (ie, the primary safety outcome)

	Indobufen group (n=2715)	Aspirin group (n=2723)	p value
Overall	85 (3.1%)	88 (3.2%)	0.83
Blood and lymphatic system disorders	2 (<0.1%)	0	0.25
Cardiac disorders	7 (0.3%)	6 (0.2%)	0.78
Ear and labyrinth disorders	0	0	..
Endocrine disorders	0	1 (<0.1%)	>0.99
Eye disorders	1 (<0.1%)	1 (<0.1%)	>0.99
Gastrointestinal disorders	9 (0.3%)	9 (0.3%)	>0.99
General disorders and administration site conditions	15 (0.6%)	14 (0.5%)	0.85
Hepatobiliary disorders	0	0	..
Immune system disorders	0	0	..
Infections and infestations	0	2 (<0.1%)	0.50
Injury, poisoning, and procedural complications	7 (0.3%)	4 (0.2%)	0.36
Investigations	0	0	..
Metabolism and nutrition disorders	1 (<0.1%)	0	0.50
Musculoskeletal and connective tissue disorders	1 (<0.1%)	0	0.50
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	1 (<0.1%)	3 (0.1%)	0.62
Nervous system disorders	33 (1.2%)	41 (1.5%)	0.36
Psychiatric disorders	3 (0.1%)	1 (<0.1%)	0.37
Renal and urinary disorders	2 (<0.1%)	1 (<0.1%)	0.62
Reproductive system and breast disorders	0	0	..
Respiratory, thoracic, and mediastinal disorders	4 (0.2%)	7 (0.3%)	0.37
Skin and subcutaneous tissue disorders	0	1 (<0.1%)	>0.99
Surgical and medical procedures	0	0	..
Vascular disorders	7 (0.3%)	3 (0.1%)	0.23

Data are n (%). Patients with multiple events of one type were counted once, including serious adverse events with an onset date on or after the date of first dose of study medication and up to the date of last dose of study medication.

Table 4: Serious adverse events up to 90-day visit, by system organ class

occurred in 18 (0.7%) of 2715 patients in the indobufen group and in 28 (1.0%) of 2723 patients in the aspirin group (absolute risk difference -0.37 , 95% CI -0.88 to 0.15 ; table 3). Intracranial haemorrhage within 90 days occurred in 14 (0.5%) patients in the indobufen group and 19 (0.7%) patients in the aspirin group. Fatal bleeding within 90 days occurred in one patient ($<0.1\%$) in the indobufen group and one patient ($<0.1\%$) in the aspirin group. The rate of any bleeding event within 90 days was 2.4% in the indobufen group and 2.6% in the aspirin group (table 3). Adverse events within 90 days occurred in 666 (24.5%) patients in the indobufen group and 679 (24.9%) patients in the aspirin group. Bleeding events and gastrointestinal disorders were similar between the two treatment groups (appendix 2 p 15). Serious adverse events within 90 days occurred in 85 (3.1%) patients in the indobufen group and in 88 (3.2%) patients in the aspirin group (table 4). Adverse events or serious adverse events leading to discontinuation of trial treatment are presented in the appendix 2 (p 16).

Discussion

To our knowledge, INSURE is the first randomised controlled trial with a large sample size to compare the efficacy and safety of indobufen and aspirin for secondary stroke prevention in patients with acute ischaemic stroke.

In this study, conducted almost exclusively in patients who are Han Chinese, indobufen was not non-inferior to aspirin and appeared to be inferior to aspirin in reducing the risk of new stroke at 90 days in patients with acute moderate-to-severe ischaemic stroke. There was no statistically significant difference in adverse events, particularly bleeding events and gastrointestinal events, between the indobufen and aspirin treatment groups.

With the effect of inhibiting platelet aggregation by reversibly inhibiting platelet cyclooxygenase enzyme,²⁴ indobufen has been used to prevent intermittent claudication and graft stenosis after coronary artery bypass grafting.^{15,16,25} In particular, indobufen is considered an alternative antiplatelet agent for patients with aspirin intolerance having coronary stent implantation,¹⁰ especially when aspirin desensitisation is not feasible.²⁶ Previous studies have shown that patients taking indobufen had a low risk of bleeding events and gastrointestinal effects, and the anti-aggregation effect diminished faster than the anti-aggregation effect after aspirin.^{27,28} In the 2023 Indobufen or Aspirin on Top of Clopidogrel after Coronary Drug-eluting Stent Implantation (OPTION) trial,¹⁷ indobufen plus clopidogrel compared with aspirin plus clopidogrel significantly reduced the risk of 1-year net clinical outcomes in patients with negative cardiac troponin having coronary drug-eluting stent implantation, which was mainly driven by a reduction in bleeding events without an increase in ischaemic events. However, data are scarce for the comparison of indobufen and aspirin for secondary stroke prevention. This INSURE trial, with a large sample size, found that indobufen was not

non-inferior to aspirin. The observed event rate in the aspirin group was lower than the hypothesised rate (6.4% vs 9%), which corresponded to an HR threshold of 1.35 with 2.25% absolute risk difference. However, non-inferiority would still not have been reached if the non-inferiority margin was HR 1.35. Furthermore, there is no evidence from this trial that suggests indobufen might be non-inferior to aspirin in a specific subgroup. A similar safety profile for adverse events with numerically fewer moderate or severe bleeding was seen for indobufen treatment compared with aspirin.

The INSURE study has limitations. First, important subpopulations of patients with ischaemic stroke, such as those with cardioembolic stroke, less severe stroke (eg, NIHSS score <4), or receiving thrombectomy, were excluded. Second, the trial was conducted almost exclusively among patients who are Han Chinese, in whom there is a high proportion of intracranial artery stenosis and a specific genetic background.^{13,29} Therefore, the results might not directly be generalisable to other populations.

Future research could focus on evaluating the efficacy and safety of indobufen in patients with aspirin intolerance or a contraindication to use of other antiplatelet agents.

Contributors

YP prepared the first draft of the report. YoW, SCJ, HaoL, PMB, QD, and AX conceptualised the study design and provided critical comments for the manuscript. YoW was the principal study investigator. AJ developed the statistical plan and did the statistical analysis. YP and YoW directly accessed and verified the underlying data. All other authors were local investigators or co-investigators and recruited patients, collected data, revised the final version of the manuscript, critically reviewed the report, and approved the final version before submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PMB is a Stroke Association Professor of Stroke Medicine and an Emeritus National Institute for Health and Care Research Senior Investigator. He has received honoraria from CoMind, DiaMedica, Moleac, Phagenesis, and Roche for advisory boards. SCJ has received grants from AstraZeneca and Johnson & Johnson. He has received honoraria and support for attending meetings from Johnson & Johnson and has participated in an advisory board for AstraZeneca. All other authors declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, can be made available on reasonable request and after signing appropriate data sharing agreements. Please send data access requests to the corresponding author. Such requests must be approved by the appropriate ethics boards and data custodians. The study protocol is available in appendix 2. The statistical analysis plan will also be made available. The data and related documents will be available on publication.

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