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

Yuesong Pan PhD[1,2*], Xia Meng MD[1,2*], Baoshi Yuan MD[1,2], Prof S Claiborne Johnston MD[3], Hao Li PhD[1,2], Prof Philip M Bath MD[4], Prof Qiang Dong MD[5], Prof Anding Xu MD[6], Jing Jing MD[1,2], Jinxi Lin MD[1,2], Yong Jiang PhD[1,2], Xuewei Xie MD[1,2], Aoming Jin PhD[1,2], Yue Suo MD[1,2], Hongqin Yang MD[7], Yefang Feng MD[8], Prof Yanhua Zhou MD[9], Qing Liu MD[10], Prof Xueli Li MD[11], Prof Bin Liu MD[12], Prof Hui Zhu MD[13], Jinguo Zhao MD[14], Prof Xuerong Huang MD[15], Haitao Li MD[16], Yunyun Xiong MD[1,2], Prof Zixiao Li MD[1,2], Prof Yilong Wang MD[1,2], Prof Xingquan Zhao MD[1,2], Prof Liping Liu MD[1,2], Prof Yongjun Wang MD[1,2], for the INSURE Investigators

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

[2] China National Clinical Research Center for Neurological Diseases, Beijing, China

[3] Dell Medical School, University of Texas at Austin, Austin, TX, USA

[4] Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

[5] Department of Neurology, Huashan Hospital, State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China

[6] Department of Neurology & Stroke Center, The First Affiliated Hospital of Jinan University, Guangzhou, China

[7] Department of Neurology, Jiyuan Hospital of Traditional Chinese Medicine, Jiyuan, China

[8] Department of Neurology, The Second People's Hospital of Huludao, Huludao, China

[9] Department of Neurology, Panjin Central Hospital, Panjin, China

[10] Ward 1, Department of Neurology, The Second People's Hospital of Guiyang, Guiyang, China

[11] Department of Neurology, Liaocheng Hospital Affiliated to Shandong First Medical University, Liaocheng, China

[12] Department of Neurology, Affiliated Hospital of North China University of Science and Technology, Tangshan, China

[13] Department of Neurology, Lequn Branch, The First Hospital of Jilin University, Changchun, China

[14] Department of Neurology, Weihai Wendeng District People's Hospital, Weihai, China

[15] Department of Neurology, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[16] Department of Neurology, Qihe County People's Hospital, Dezhou, China

* Yuesong Pan and Xia Meng contributed equally to the manuscript.

Corresponding author: Yongjun Wang

Address: No.119, South 4th Ring West Road, Fengtai District, Beijing, China, 100070

Tel: 0086-010-59975807 **Fax:** 0086-010-59975807

E-mail: yongjunwang@ncrcnd.org.cn

Key Words: Transient Ischaemic Attack, Minor Stroke, Ticagrelor, Clopidogrel, Randomised Control Trial

This paper includes 130 characters in the title, 383 words in abstract, 2894 words in text, 29 references, 4 tables, 3 figures, 5 supplemental tables.

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 absence of a large-scale clinical trial for this indication. We designed INSURE to assess 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.

Methods

We did 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 to 80 years with acute moderate-to-severe ischaemic stroke (NIHSS score 4-18). We randomly assigned (1:1) participants within 72 h of the onset of symptoms to receive either indobufen (100 mg twice daily) or aspirin (100 mg once daily) for 3 months. The randomisation sequence was computer-generated and stratified by participating centres. The blinded local investigators assigned the random code in 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 3 months. We assessed the non-inferiority of indobufen versus aspirin in all randomly assigned and consenting patients using the one-sided upper limit of the confidence interval of hazard ratio, with a prespecified non-inferiority margin of 1·25. This trial is registered at clinicaltrials.gov (NCT03871517).

Findings

Between June 2, 2019, and November 28, 2021, 5438 patients were randomised: 2715 to indobufen and 2723 to aspirin, all of whom were analysed. The median age was 64·2 years and 35·3% were women. Stroke occurred within 90 days in 213 (7·9%) in the indobufen group versus 175 (6·4%) in the aspirin group (hazard ratio 1·23; 95% CI 1·01 to 1·50). Moderate or severe bleeding occurred in 18 patients (0·7%) in the indobufen group and in 28 patients (1·0%) in the aspirin group (p=0·13).

Interpretation

In patients with acute moderate to severe ischaemic stroke, there was insufficient evidence to show that indobufen was non-inferior to aspirin, and in fact indobufen seemed to be inferior to aspirin, in reducing the risk of recurrent stroke at 90 days. Although moderate or severe bleeding did not differ between groups, these findings do not support the use of indobufen for stroke prevention in patients with moderate-to-severe ischaemic stroke.

Funding

Hangzhou Zhongmei Huadong Pharmaceutical Co Ltd; Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029).

Research in context

Evidence before this study

We searched MEDLINE for studies published from its inception to Dec 25, 2022, using the following search terms with no language restrictions: “stroke” AND “indobufen”. This search yielded no randomised trial providing evidence of the effect of indobufen in comparison to aspirin or other antiplatelet agents for treatment of patients with acute ischaemic stroke. Some observational and pharmacological studies have shown that indobufen causes initial inhibition of platelet aggregation equivalent to aspirin. Indobufen is sometimes used for those with aspirin intolerance. It is unclear whether indobufen would also confer a clinical benefit when used as first line for secondary stroke prevention.

Added value of this study

The INSURE trial tested whether indobufen was non-inferior to aspirin in reducing the risk of new stroke at 3 months in patients with moderate-to-severe ischaemic stroke.

Implications of all the available evidence

INSURE found that indobufen was not non-inferior to aspirin in patients with moderate-to-severe ischaemic stroke and might be inferior to aspirin. The best available evidence does not support use of indobufen for stroke prevention in patients with moderate-to-severe ischaemic stroke.

Introduction

Stroke is the second leading cause of death and third leading cause of disability worldwide.[1, 2] Patients with an acute ischaemic stroke have a high risk of recurrent stroke at the early stage after initial event onset (approximately 5 to 10% within the first year).[3, 4] Dual antiplatelet therapy with clopidogrel and aspirin has been recommended to be administrated as soon as possible for patients with minor ischaemic stroke or transient ischaemic attack to reduce new stroke.[5-7] For those with moderate-to-severe ischaemic stroke, aspirin is the most evidence-based antiplatelet agent and currently recommended in clinical guidelines.[8, 9] However, aspirin may lead to gastrointestinal intolerance and bleeding.[10, 11] Alternative antiplatelet treatment is often considered for these patients.[11] Clopidogrel, another antiplatelet agent, is less effective for stroke secondary prevention in carriers of the *CYP2C19* loss-of-function alleles, which are present in 25% of White and 60% of Asian patients.[12, 13]

Indobufen, another cyclooxygenase inhibiter, can inhibit 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 hours after the withdrawal of the drug; thus, indobufen may cause a lower risk of bleeding and rapid haemostasis after withdrawal of the drug if bleeding occurred.[14] Previous studies demonstrated that indobufen is comparable to aspirin in the treatment of atherosclerotic ischaemic heart and peripheral vascular diseases but with less adverse effects.[15-17] It is hypothesised that indobufen may also be useful for secondary stroke prevention, and it is used for this indication at some sites.[18] However, there are no large-scale clinical trial comparing treatment between indobufen and aspirin for stroke secondary prevention. Thus, it is still unclear whether indobufen can be used as an alternative antiplatelet agent for secondary stroke prevention after ischaemic stroke.[19]

Given the fact that 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 3 months in patients with moderate-to-severe ischaemic stroke in the Indobufen versus Aspirin in Acute Ischemic Stroke (INSURE) trial.

Methods

Study design and participants

We performed a randomised, double-blind, double-dummy, active control, non-inferiority trial at 163 tertiary and district general hospitals in China, in which the efficacy and safety of indobufen was compared with aspirin at 3 months in patients with moderate to severe ischaemic stroke. 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. All participants or their representatives provided written informed consent before enrolment.

Details of the rationale and design of this study have been described previously[20] and the protocol was attached in the supplement. In brief, patients with acute moderate to severe ischaemic stroke, aged 18 to 80 years, with a National Institutes of Health Stroke Scale (NIHSS) score of 4-18, who could be randomised within 72 hours after symptoms onset (the time last seen normal) and sign informed consent were eligible for enrolment into the trial. Patients with a history of intracerebral haemorrhage or cardiac source of embolus, those who required other antithrombotic therapies (antiplatelet and anticoagulant therapy) during the study, and those who had planned revascularisation within the next 3 months for whom open-label antiplatelet therapy may be warranted were excluded from the trial. A full list of exclusion criteria are included in the appendix (pp 8-9).

Randomisation and masking

Participants were randomised 1:1 to receive either indobufen or aspirin within 72 h of the onset of symptoms. A randomisation sequence was computer-generated centrally and stratified by participating centres using block randomisation methods with the block length of 6 from the Statistics and Data Centre at the China National Clinical Research Centre for Neurological Diseases. The local investigators enrolled the participants. Once eligible, the local investigators in each centre who giving interventions assigned the random code in lowest to highest order and provided a treatment kit corresponding to the random code. The researcher only knew the random code but didn't know the allocation sequence, and the randomisation allocation was concealed. The participants, local investigators giving interventions and assessing outcomes, data manager and statisticians were blinded to the group assignment until the analyses were completed.

Procedures

Patients were assigned to one of the two arms: 1) patients in the indobufen group received 100 mg indobufen tablet twice daily plus aspirin placebo which was not identical in taste and appearance to aspirin once daily from day 1 to 3 months. 2) those in the aspirin group received 100 mg aspirin tablet once daily plus 100 mg indobufen placebo which was not identical in taste and appearance to indobufen 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 physician.

Patients were assessed face-to-face at baseline, 10±2 days (or at the time of discharge), and 90±7 days. Medical examination, including 12-lead electrocardiogram and echocardiography, was performed at the screening phase. Final diagnosis, classification of stroke aetiology, and relevant examination and treatment information during hospitalisation was recorded at the time of discharge. Lower extremity venous ultrasound was performed at 10-day (or at discharge) visit.

After 3 months, patients were followed-up by telephone interview at 1 year. Vascular events, modified Rankin Scale (mRS) score and mortality were collected at 3-month and 1-year follow-up.

Outcomes

The primary efficacy outcome was a new stroke (ischaemic or haemorrhagic) within 3 months (appendix pp 10-11). Secondary outcomes included new stroke within 1 year; new vascular events as the composite of ischaemic stroke, haemorrhagic stroke, myocardial infarction and vascular death within 3 months and 1 year; the components of the composite outcome; new ischaemic stroke events within 3 months and 1 year; early lower extremity venous thrombosis reported by lower extremity venous ultrasound at 10-day (or at discharge) visit; poor functional outcome (mRS scores of 3 to 6 points) at 3 months and 1 year; change in NIHSS between admission and 3 months; and quality of life measured using EuroQol EQ-5D scale at 3 months and 1 year.

The primary safety outcome was severe or moderate bleeding within 3 months defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for 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 included severe or moderate bleeding by GUSTO criteria within 1 year, any bleeding events, death, symptomatic and asymptomatic intracranial haemorrhagic events within 3 months and 1 year, adverse events or serious adverse events within 3 months.

Statistical analyses

The study hypothesised that indobufen (the investigational drug) and aspirin (the active comparator) would both have a primary endpoint event rate of 9%.[5, 22] Previous studies have shown that aspirin alone can reduce the incidence of 3-month new stroke by 50% compared to placebo.[23] With the recommendation of clinical experts after discussion with statisticians, we set the non-inferiority margin (δ) at 1/4 of the control event rate, i.e. preserving three quarters of the treatment effect of aspirin (hazard ratio [HR]= 1·25; corresponding to 2.25% absolute risk difference). That is, compared to the control group, when the upper limit of the confidence interval for the event risk in the treatment group is less than 1·25, indobufen would be considered non-inferior to aspirin. A one-sided test for non-inferiority with a margin of 1·25 for HR, one-side α=0·025 and 10% attrition rate showed that 5390 patients (2695 in each group) provided a power of 80%.

Data were analysed both according to the intention-to-treat principle including all randomly assigned and consenting patients (the full analysis set) and in a per protocol set defined as all patients finishing the treatment without major violation of the trial protocol. For the primary efficacy analysis, non-inferiority analysis was performed. At the same time, Kaplan-Meier methods were used to simulate the cumulative risk of new stroke at 3-month 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% confidence interval (CI). Participants were censored at their last follow-up assessment when experiencing a clinical event, at the end of trial, or at the time of withdrawal from the trial. When there were multiple events of the same type, the time to the first event was used in the model. We assessed the non-inferiority of indobufen versus aspirin using the one-sided upper limit of the 95% CI of HR, with a prespecified non-inferiority margin of 1·25. The influence on treatment effect by sex, age category, history of

diabetes, history of hypertension, aetiological stroke subtype, intracranial artery stenosis, previous antiplatelet therapy, disease severity (NIHSS 4-9 vs NIHSS10-18) 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 group and the 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 of 3-6 points) and lower extremity venous thrombosis between the two groups, and the odds ratio (OR) with 95% CI was reported. T tests and Wilcoxon rank sum tests were used to analyse the difference in neurological impairment and quality of life, as appropriate.

Safety analyses were performed in the safety analysis population defined as all patients who received at least a 1-time of 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, Chi-squared test or Fisher's exact test were performed, as appropriate.

Additional details of statistical analyses are in the statistical analysis plan attached in the supplement. No interim analyses were planned. A Data and Safety Monitoring Board (DSMB) ensured the safety of participants in the study. The board could halt the study because of any safety concerns. All statistical analyses were performed using SAS software, version 9·4 (SAS Institute Inc., 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 at clinicaltrials.gov (registration number: NCT03871517).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 2, 2019, and November 28, 2021, a total of 84,093 patients with moderate-to-severe ischaemic stroke were screened at 163 participating sites, of whom 5,438 patients (6·5%) were enrolled, with 2,715 randomly assigned to the indobufen group and 2,723 to the aspirin group. Overall, 321 patients had premature permanent drug discontinuation, 82 patients used prohibited concomitant medications, 32 patients died of causes other than stroke and 7 patients were lost to follow up at 3 months (figure 1). Baseline characteristics were similar between the two treatment groups (table 1). The median age of participants was 64·2 years, and 35·3% were women. The median time from symptom onset to randomisation was 46·5 hours. Concomitant treatment and prohibited medications taken during the treatment period are reported in table S1 and S2 in appendix pp 12-13.

A primary-outcome event, new ischemic or haemorrhagic stroke within 90 days, occurred in 213 of the 2,715 patients (7·9%) in the indobufen group and in 175 of the 2,723 patients (6·4%) in the aspirin group (HR,1·23; 95% CI, 1·01 to 1·50; the lower limit of confidence interval greater than 1 and the upper limit of confidence interval crossing the non-inferiority margin of 1·25) (absolute risk difference, 1·42; 95% CI, 0·12 to 2·72) (figure 2 and table 2). Hence, indobufen was not non-inferior to and appeared to be inferior to aspirin. The secondary outcome

of new ischemic or haemorrhagic stroke within 1 year, occurred in 279 of the 2,715 patients (10·4%) in the indobufen group and in 242 of the 2,723 patients (9·0%) in the aspirin group (HR,1·17; 95% CI, 0·98 to 1·39). Composite vascular event within 90 days occurred in 214 patients (7·9%) in the indobufen group and in 181 (6·7%) in the aspirin group (HR, 1·19; 95% CI, 0·98 to 1·46). Ischaemic stroke within 90 days occurred in 200 patients (7·4%) in the indobufen group and in 156 (5·8%) in the aspirin group (p=0·01). Other secondary end points are presented in table 2. Predefined subgroup analyses for the primary outcome are shown in figure 3. Similar efficacy was observed across different predefined subgroups (all upper limit of confidence interval crossed the non-inferiority margin of 1·25) (figure 3). The results of the per-protocol analysis of efficacy were consistent with those of the intention-to-treat analysis (table 2 and table S3 in the appendix pp 14).

A primary safety outcome, moderate or severe bleeding defined by the GUSTO criteria during 90 days, occurred in 18 patients (0·7%) in the indobufen group and in 28 patients (1·0%) in the aspirin group (HR, 0·63; 95% CI, 0·35 to 1·15; P=0·13; absolute risk difference, -0·37; 95% CI, -0·88 to 0·15) (table 3). Intracranial haemorrhage within 90 days occurred in 14 patients (0·5%) in the indobufen group and in 19 patients (0·7%) in the aspirin group. Fatal bleeding within 90 days occurred in 1 patient (0·04%) both in the indobufen group and 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 patients (24·5%) in the indobufen group, similar to that in the aspirin group (24·9%; P=0·73). Bleeding events and gastrointestinal disorders were similar between the two treatment groups (table S4 in the appendix pp 15). Serious adverse events within 90 days occurred in 85 patients (3·1%) in the indobufen group and in 88 patients (3·2%) in the aspirin group (P=0·83; table 4). Adverse events

or serious adverse events leading to discontinuation of a trial treatment are presented in table S5 in the appendix pp 16.

Discussion

In this study conducted almost exclusively in Han Chinese participants, indobufen was not non-inferior to and appeared to be inferior to aspirin in reducing the risk of 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 reversible 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 as an alternative antiplatelet agent for patients with aspirin intolerance undergoing coronary stent implantation,[10] especially when aspirin desensitisation is not feasible.[26] Previous studies showed that patients on indobufen had a low risk of bleeding events and gastrointestinal effects, and the anti-aggregation effect diminished faster than those after aspirin.[27, 28] In the recent OPTION (Indobufen or Aspirin on Top of Clopidogrel after Coronary Drug-eluting Stent Implantation) 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 undergoing coronary drug-eluting stent implantation, which was mainly driven by a reduction in bleeding events without an increase in ischaemic events. However, data are limited for the comparison of indobufen and aspirin for secondary stroke prevention. The present randomised trial with large sample size found that indobufen was not non-inferior to aspirin, with it associated with an increase in recurrent stroke compared to aspirin. It was acknowledged that the observed event

rate in the aspirin group was lower than the assumed rate (6.4% vs. 9%), which corresponded to a threshold on the HR of 1.35 with 2.25% absolute risk difference. Whereas non-inferiority still didn't reach even if non-inferiority margin was set to a HR of 1.35. Furthermore, there is no evidence from the trial that suggests indobufen may 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 as compared to aspirin.

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

In conclusion, in patients with moderate-to-severe ischaemic stroke within 72 hours after symptom onset, our trial found that indobufen treatment was not non-inferior to and might be inferior to aspirin treatment in reducing the risk of subsequent stroke. The risk of moderate or severe bleeding and other adverse events was similar between the two treatment groups.

Contributors

Yuesong Pan prepared the first draft of the report. Yongjun Wang, S. Claiborne Johnston, Hao Li, Philip M. Bath, Qiang Dong and Anding Xu conceptualised the study design and provided critical comments for the manuscript. Yongjun Wang was the study principal investigator. Aoming Jin developed the statistical plan and did the statistical analysis. Yuesong Pan and Yongjun Wang verified the underlying data. All other authors were local investigators or co-

investigators and recruited patients, collected data, and revised the final version of the manuscript, and 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 Stroke Association Professor of Stroke Medicine and Emeritus NIHR Senior Investigator; he has received honoraria from CoMind, DiaMedica Inc, Moleac, Phagenesis Ltd and Roche for advisory boards. SCJ has received grants from AstraZeneca and Johnson & Johnson; he has received honoraria and support for attending meeting from Johnson & Johnson, participating on an advisory board for AstraZeneca.

Data sharing

The data that support the findings of this study are available from the corresponding author on reasonable request. The study protocol will be available in the appendix.

Acknowledgments

The trial was investigator-initiated and managed and was funded by Hangzhou Zhongmei Huadong Pharmaceutical Co Ltd; the company also provided the drugs (research drugs and placebos). The trial operations were executed, and the data were acquired, stored, monitored, and interpreted by the research team at Beijing Tiantan Hospital, Capital Medical University (Beijing, China).

REFERENCES

1. 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**:1736-1788.
2. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1859-1922.
3. 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.
4. Flach C, Muruet W, Wolfe CDA, Bhalla A, Douiri A. Risk and Secondary Prevention of Stroke Recurrence: A Population-Base Cohort Study. *Stroke* 2020;**51**:2435-2444.
5. 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.
6. 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**:215-225.
7. Wang D. Precision antiplatelet therapy for the prevention of ischaemic stroke. *Stroke Vasc Neurol* 2022;**7**:89-91.
8. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 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;**52**:e364-e467.
9. 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**:159-176.
10. 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**:444-447.
11. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006;**367**:606-617.
12. Wang Y, Zhao X, Lin J, et al. Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *JAMA* 2016;**316**:70-78.

13. Pan Y, Chen W, Xu Y, et al. Genetic Polymorphisms and Clopidogrel Efficacy for Acute Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis. *Circulation* 2017;**135**:21-33.
14. Lee JY, Sung KC, Choi HI. Comparison of aspirin and indobufen in healthy volunteers. *Platelets* 2016;**27**:105-109.
15. Cataldo G, Heiman F, Lavezzari M, Marubini E. Indobufen compared with aspirin and dipyridamole on graft patency after coronary artery bypass surgery: Results of a combined analysis. Coron Artery Dis. 1998;9:217-222.
16. Belcaro G, De Simone P. Long-term evaluation of indobufen in peripheral vascular disease. Angiology. 1991;42:8-14.
17. Wu H, Xu L, Zhao X, et al. Indobufen or Aspirin on Top of Clopidogrel after Coronary Drug-eluting Stent Implantation (OPTION): a Randomized, Open-label, Endpoint-blinded, Non-inferiority Trial. *Circulation* 2022. doi: 10.1161/CIRCULATIONAHA.122.062762. Online ahead of print.
18. Kral M, Herzig R, Sanak D, et al. Oral antiplatelet therapy in stroke prevention. Minireview. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2010;**154**:203-210.
19. 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.
20. Pan Y, Meng X, Chen W, et al. Indobufen versus aspirin in acute ischaemic stroke (INSURE): rationale and design of a multicentre randomised trial. *Stroke Vasc Neurol* 2022;**7**:457-461.
21. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673-682.
22. Xu J, Zhang X, Jin A, et al. Trends and Risk Factors Associated With Stroke Recurrence in China, 2007-2018. *JAMA Netw Open* 2022;**5**:e2216341.
23. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. 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**:365-375.
24. Bhana N, McClellan KJ. Indobufen: an updated review of its use in the management of atherothrombosis. *Drugs Aging* 2001;**18**:369-388.

25. 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**:183-188.
26. 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.
27. Ibáñez L, Vidal X, Vendrell L, Moretti U, Laporte JR; Spanish-Italian Collaborative Group for the Epidemiology of Gastrointestinal Bleeding. Upper gastrointestinal bleeding associated with antiplatelet drugs. *Aliment Pharmacol Ther* 2006;**23**:235-242.
28. Marzo A, Crestani S, Fumagalli I, Giusti A, Lowenthal DT. Endoscopic evaluation of the effects of indobufen and aspirin in healthy volunteers. *Am J Ther* 2004;**11**:98-102.
29. Wang Y, Zhao X, Liu L, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* 2014;**45**:663-669.

FIGURE LEGENDS

Figure 1. Trial profile.

Figure 2. Kaplan-Meier curve for the primary outcome.

Figure 3. Hazard ratio for the primary outcome according to prespecified subgroups. NIHSS= National Institutes of Health Stroke Scale. The dashed vertical line indicates the non-inferiority limit of 1·25.
* Event rates are Kaplan-Meier estimates of the percentage of patients with events at 90 days.

TABLES

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

	Indobufen (n=2715)	Aspirin (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)
Others	134 (4·9)	150 (5·5)
Medical history		
Hypertension	1703 (62·7)	1700 (62·4)
Diabetes mellitus	735 (27·1)	717 (26·3)
Dyslipidaemia	87 (3·2)	98 (3·6)
Stroke	555 (20·4)	535 (19·7)
TIA	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)
Median time from onset to randomisation, hours	46·1 (31·0-57·3)	46·9 (31·5-58·5)
<24 hour	368 (13·6)	323 (11·9)
24-48 hour	1075 (39·6)	1102 (40·5)
>48 hour	1272 (46·9)	1298 (47·7)
Median NIHSS score	5 (4-7)	5 (4-7)
<10 score	2457 (90·5)	2466 (90·6)
≥10 score	258 (9·5)	257 (9·4)
Symptomatic intracranial artery stenosis	687 (26·9)	706 (27·6)
Etiological stroke subtype		

Large-artery atherosclerosis	711 (27·7)	742 (28·6)
Small-artery occlusion	986 (38·5)	965 (37·2)
Undetermined pathogenesis	666 (26·0)	698 (26·9)
Others	201 (7·8)	187 (7·2)

Data are mean (SD), n (%), or median (IQR). TIA=transient ischaemic attack; NIHSS= National Institutes of Health Stroke Scale.

* Current drinking was defined as alcohol use at least once a week in the past year. Previous drinking was defined as previous alcohol use at least once a week for a period of one year but have quitted alcohol use for more than one year.

† Medication within 1 month before symptom onset.

Table 2. Efficacy outcomes

	Indobufen (N=2715)*	Aspirin (N=2723)*	Hazard Ratio or Odds Ratio (95% CI)*	p value
Primary outcome				
Stroke within 3 months (Intention-to-treat)	213 (7·9)	175 (6·4)	1·23 (1·01 to 1·50)†	…
Stroke within 3 months (Per-Protocol)	181/2487 (7·3)	138/2475 (5·6)	1·32 (1·06 to 1·65)†	…
Secondary outcome (Intention-to-treat)				
Stroke within 1 year	279 (10.4)	242 (9.0)	1·17 (0·98 to 1·39)	0.08
Composite vascular events within 3 months‡	214 (7·9)	181 (6·7)	1·19 (0·98 to 1·46)	0·08
Ischaemic stroke	200 (7·4)	156 (5·8)	1·30 (1·05 to 1·60)	0·01
Myocardial infarction	1 (0·04)	3 (0·11)	0·33 (0·03 to 3·17)	0·34
Composite vascular events within 1 year‡	287 (10·7)	257 (9·5)	1·13 (0·96 to 1·34)	0·16
Ischaemic stroke	256 (9·5)	215 (8·0)	1·21 (1·01 to 1·45)	0·04
Myocardial infarction	5 (0·19)	9 (0·33)	0·53 (0·18 to 1·59)	0·26
Lower extremity venous thrombosis§	111 (4·1)	104 (3·8)	1·07 (0·82 to 1·41)	0·61
mRS scores of 3-6 at 3 months‖	369 (13·6)	364 (13·4)	1·02 (0·87 to 1·19)	0·82
mRS scores of 3-6 at 1 year‖	320 (11·8)	324 (11·9)	0·99 (0·84 to 1·17)	0·89
Change in NIHSS between admission and 3 months‖	4 (3 to 5)	4 (3 to 5)	…	0·92
European quality of life visual analogue scale at 3 months‖	85 (75 to 93)	87 (75 to 95)	…	0·90
European quality of life visual analogue scale at 1 year‖	90 (80 to 95)	90 (80 to 95)	…	0·53

Data are n (%). CI=confidence interval; mRS=modified Rankin Scale; NIHSS= National Institutes of Health Stroke Scale.

* Event rates for lower extremity venous thrombosis and mRS scores of 3-6 are raw estimates and odds ratios were estimated, whereas event rates for other outcomes are Kaplan-Meier estimates of the percentage of patients with events and hazard ratios were estimated.

† Upper limit of 95% CI was larger than the non-inferiority margin of 1·25; thus, non-inferiority cannot be claimed. The lower limit of 95% CI was greater than 1, indicating indobufen might to be inferior to aspirin.

‡ Composite vascular events include ischaemic stroke, haemorrhagic stroke, myocardial infarction and vascular death.

§ Early lower extremity venous thrombosis reported by lower extremity venous ultrasound at 10-day (or at discharge) visit.

‖ 3 and 5 missing values for mRS scores of 3-6 at 3 months, 3 and 6 for mRS scores of 3-6 at 1 year, 27 and 26 for NIHSS at 3 months, 31 and 26 for European quality of life visual analogue scale at 3 months, 65 and 65 for European quality of life visual analogue scale at 1 year in the indobufen and aspirin group, respectively.

Table 3. Safety outcomes

	Indobufen (N=2715)*	Aspirin (N=2723)*	Hazard Ratio (95% CI)	p value
Primary safety outcome				
Severe or moderate bleeding within 3 months†	18 (0·7)	28 (1·0)	0·63 (0·35 to 1·15)	0·13
Fatal bleeding	1 (0·04)	1 (0·04)	0·96 (0·06 to 15·42)	0·98
Intracranial haemorrhage	14 (0·5)	19 (0·7)	0·74 (0·37 to 1·47)	0·39
Secondary safety outcome				
Severe or moderate bleeding within 1 year†	32 (1·2)	39 (1·5)	0·82 (0·51 to 1·30)	0·40
Fatal bleeding	3 (0·11)	1 (0·04)	2·91 (0·30 to 28·02)	0·35
Intracranial haemorrhage	25 (1·0)	27 (1·0)	0·93 (0·54 to 1·60)	0·79
Any bleeding within 3 months	65 (2·4)	70 (2·6)	0·93 (0·66 to 1·30)	0·67
Mild bleeding†	48 (1·8)	45 (1·7)	1·07 (0·72 to 1·61)	0·73
Any bleeding within 1 year	81 (3·0)	83 (3·1)	0·98 (0·72 to 1·33)	0·89
Mild bleeding†	63 (2·4)	58 (2·2)	1·09 (0·77 to 1·56)	0·62
Mortality within 3 months	40 (1·5)	39 (1·4)	1·03 (0·66 to 1·59)	0·91
Mortality within 1 year	76 (2·8)	85 (3·2)	0·89 (0·66 to 1·22)	0·47
Adverse events within 3 months	666 (24·5)	679 (24·9)	…	0·73
Serious adverse events within 3 months	85 (3·1)	88 (3·2)	…	0·83

Data are n (%). CI=confidence interval.

* 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 GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria.

➢ **Table 4. Number of patients with serious adverse events*† (by system organ class) up to 3-month visit**

System organ class	Indobufen (N=2715)	Aspirin (N=2723)	p value
Overall	85 (3·1)	88 (3·2)	0·83
Blood and lymphatic system disorders	2 (0·1)	0 (0·0)	0·25
Cardiac disorders	7 (0·3)	6 (0·2)	0·78
Ear and labyrinth disorders	0 (0·0)	0 (0·0)	
Endocrine disorders	0 (0·0)	1 (0·04)	>0·99
Eye disorders	1 (0·04)	1 (0·04)	>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 (0·0)	0 (0·0)	
Immune system disorders	0 (0·0)	0 (0·0)	
Infections and infestations	0 (0·0)	2 (0·7)	0·50
Injury, poisoning and procedural complications	7 (0·3)	4 (0·2)	0·36
Investigations	0 (0·0)	0 (0·0)	
Metabolism and nutrition disorders	1 (0·04)	0 (0·0)	0·50
Musculoskeletal and connective tissue disorders	1 (0·04)	0 (0·0)	0·50
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0·04)	3 (0·1)	0·62
Nervous system disorders	33 (1·2)	41 (1·5)	0·36
Psychiatric disorders	3 (0·1)	1 (0·04)	0·37
Renal and urinary disorders	2 (0·1)	1 (0·04)	0·62
Reproductive system and breast disorders	0 (0·0)	0 (0·0)	
Respiratory, thoracic and mediastinal disorders	4 (0·2)	7 (0·3)	0·37
Skin and subcutaneous tissue disorders	0 (0·0)	1 (0·04)	>0·99
Surgical and medical procedures	0 (0·0)	0 (0·0)	
Vascular disorders	7 (0·3)	3 (0·1)	0·23

* Patients with multiple events of one type were counted once. This includes serious adverse events with an onset date on or after the date of first dose and up to the date of last dose of study medication.

† Patients with multiple events of one type were counted once.