

Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial



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Summary

Background There are few proven treatments for acute spontaneous intracerebral haemorrhage, and they all target reducing expansion of the haematoma. The traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao) in an oral solution is comprised of several Chinese herbs that are widely used to treat patients with intracerebral haemorrhage in China on the understanding that they enhance resorption of the haematoma and reduce neuroinflammation. We aimed to provide a reliable assessment of the safety and efficacy of FYTF-919 in patients with moderate to severe acute intracerebral haemorrhage.

Methods We did a pragmatic, multicentre, randomised, double-blind, placebo-controlled trial at 26 hospitals in China. We enrolled adults (age ≥18 years) with a diagnosis of symptomatic spontaneous intracerebral haemorrhage (confirmed by brain imaging) within 48 h after the onset of symptoms (or last seen well), which resulted in moderate to severe neurological impairment defined by scores of at least 8 on the National Institute of Health Stroke Scale or between 7 and 14 inclusive on the Glasgow Coma Scale. Randomisation (1:1) was via a central internet-based system with a block grouping method stratified by provincial location of the hospital, severity of neurological impairment, and site of the haematoma in the brain. FYTF-919 and the placebo were masked through consistency in appearance, smell, taste, and other aspects. Participants were allocated to receive 33 mL (or 25 mL via a nasogastric tube if a participant's swallowing was impaired) of either oral liquid FYTF-919 or matching placebo administered at least 30 min after a meal every 8 h (or 6 h via nasogastric tube) over 24 h for 28 days. The primary efficacy outcome was the utility weighted modified Rankin Scale (a seven-level ordinal scale that ranges from 0 [no symptoms] to 6 [death], in which the utility weights of 0·97, 0·88, 0·74, 0·55, 0·20, −0·19, and 0·00 were assigned to the seven levels respectively, with higher scores indicating a better outcome according to the participants' perspective) at 90 days analysed in a general linear model with adjustment for baseline factors. We did several adjusted and sensitivity analyses. Primary analyses were assessed in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT05066620 and is complete.

Findings Between Nov 24, 2021, and Dec 28, 2023, of 9000 patients screened, 1648 were randomly assigned to treatment, 817 to the FYTF-919 group and 831 to the placebo group. Before receiving any treatment two patients in the FYTF-919 group and five patients in the placebo group immediately withdrew their consent leaving 1641 participants with available primary outcome data in the intention-to-treat population, 815 in the FYTF-919 group and 826 in the placebo group. 1242 (75·7%) participants consumed 80% or more of the study medication and 994 (60·6%) consumed all of it within 28 days. Mean utility weighted modified Rankin Scale scores at 90 days were 0·44 in the FYTF-919 group and 0·44 in the placebo group (difference 0·01, 95% CI −0·02 to 0·04; p=0·63). The neutral result was consistent in adjusted and sensitivity analyses. There was no significant difference in serious adverse events.

Interpretation This large, randomised, placebo-controlled, double-blind, clinical trial showed no effect of the traditional Chinese medicine herbal compound FYTF-919 on functional recovery, survival, and health-related quality of life in patients with moderate to severe intracerebral haemorrhage. The results reaffirm the need for methodologically rigorous, randomised controlled trials to evaluate the effectiveness of existing therapies, including traditional Chinese medicines that are already in widespread use throughout the world.

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Research in context

Evidence before this study

We searched PubMed (from 1970), Web of Science (from 1970), and Embase (from 1947), and the Chinese National Knowledge Infrastructure, WanFang database, VIP Chinese SciTech Periodical Database and China Biological Medicine Database on July 1, 2024, for publications with relevant text words in the title or abstract in English and Chinese that included "intracerebral haemorrhage", "haemorrhagic stroke", or "cerebral haemorrhage" and "traditional Chinese medicine" or "herbal medicine". Studies were eligible for inclusion if they were randomised and assessed the effect of traditional Chinese medicine on a clinical outcome. We identified only three randomised trials, including two small single-centre and one multicentre trial, published in English, which reported uncertain effects of traditional Chinese medicine on mortality and functional outcome. Only one other ongoing trial (ChiCTR2100043796) besides the CHAIN study was identified through a search of registered trials at ClinicalTrials.gov and the Chinese Trial Clinical Registry. There were hundreds of randomised trials published in Chinese, but most of them were single centre, had a small sample size (including less than 100 patients), and were of poor quality.

After adding the terms "Zhongfeng Xingnao" or "FYTF-919" to the above search, we identified nine randomised trials published in Chinese involving a total of 1448 participants. Two of these trials were double-blind, placebo-controlled trials. We did a systematic review and meta-analysis on the basis of these nine trials. The results showed that compared with conventional medicine alone, FYTF-919 as an adjunct treatment could reduce mortality (relative risk 0.54, 95% CI 0.40–0.74) in patients with intracerebral haemorrhage.

However, the evidence was considered weak because of small sample sizes, single-centre designs, and methodological limitations (such as the use of surrogate or non-standard outcome measures).

Added value of this study

The CHAIN study is one of the largest randomised controlled trial to date of a traditional Chinese medicine in any type of acute stroke. The primary result did not show a significant difference in mean utility weighted modified Rankin Scale scores at 90 days in the FYTF-919 group compared with the placebo group. The neutral results were consistent in sensitivity analyses of the primary outcome and across all secondary clinical outcomes. There was significant heterogeneity of the effect in the predefined subgroups of patients by size and location of the haematoma but this may be due to chance through small numbers and multiple testing. FYTF-919 is deemed safe as there was no significant difference in serious adverse events between the two groups.

Implications of all the available evidence

These results provide conclusive evidence of the lack of effect of FYTF-919, a traditional Chinese medicine which hitherto has been used throughout China for the treatment of acute intracerebral haemorrhage on the basis of weak evidence of it reducing mortality. The study has shown that it is feasible to do a large, methodologically rigorous, randomised controlled trial to evaluate a traditional Chinese medicine that is already in widespread use in China. It can serve as a paradigm for further evaluations of these medicines which are increasingly used throughout the world.

Introduction

Despite substantial recent advances in the medical and surgical management of acute intracerebral haemorrhage,¹ this condition remains the most serious and least treatable form of stroke, causing considerable global disease burden.² Intracerebral haemorrhage accounts for approximately 10% of strokes in high-income countries but rates are much higher in low-income and middle-income countries where populations have a high prevalence of hypertension. Sex-related biological and social factors may also influence the pathophysiology, response to treatments, and prognosis for recovery from intracerebral haemorrhage.^{3–5} Most interventions for intracerebral haemorrhage target reducing the size of the haematoma through the early control of elevated blood pressure, surgical decompression, and reversal of anticoagulation therapy.¹ However, these interventions need to be administered early after the onset of symptoms and may not directly modify the neuro-inflammatory response to haemoglobin breakdown products (iron and thrombin) in the brain, which manifests as perihæmatoma oedema on brain imaging.^{6–9}

Herbs have long been used in contemporary health care in China to remove so-called blood stasis in patients with intracerebral haemorrhage.¹⁰ There is now a considerable body of animal and early phase clinical data to support the use of various Chinese herbs to promote reabsorption of the haematoma, reduce perihæmatoma oedema, and enhance the immune system in intracerebral haemorrhage.^{11–14} One particular herbal compound, FYTF-919 (or Zhongfeng Xingnao oral prescription), is composed primarily of four Chinese herbs used for the treatment of intracranial haemorrhage in China. FYTF-919 has a range of potential anti-inflammatory and immunological effects,^{15–20} and as a liquid preparation for oral administration, it aligns well with how traditional Chinese medicine is commonly used and is suitable for use in patients who are disabled or unconscious. Although a systematic review and meta-analysis of nine randomised trials of 1448 participants suggests that FYTF-919 can enhance the clearance of haematoma, reduce mortality, and improve recovery after ICH, this evidence is generally of low

methodological quality, mainly in relation to deviations from the intended intervention and bias in measurement of the outcome (Xi Wu, et al, personal communication; further details are provided in the appendix pp 183–233). Moreover, a multicentre, double-blind, placebo-controlled trial involving 324 participants suggests that FYTF-919 might be harmful, when administered within 6 h after the onset of intracerebral haemorrhage.¹⁰ We therefore designed the Chinese herbal medicine in patients with acute intracerebral haemorrhage (CHAIN) study to establish the efficacy and safety of FYTF-919 in patients with acute intracerebral haemorrhage. We purposefully restricted the inclusion criteria to patients with at least a moderate degree of neurological impairment as they have the greater potential to benefit from this treatment than those with less impairment by virtue of having larger volumes of haematoma and perihæmatomal oedema.

Methods

Study design and participants

CHAIN was an investigator-initiated, pragmatic, multicentre, prospective, randomised, double-blind, placebo-controlled trial done at 27 tertiary-level hospitals with comprehensive stroke services in China (appendix pp 5–6). The aim was to assess the safety and efficacy of FYTF-919 in patients with moderate to severe acute primary intracerebral haemorrhage. The protocol and statistical analysis plan have been published elsewhere,^{21,22} and are available in the appendix (pp 234–312). A data safety and monitoring board oversaw the trial (appendix pp 31–33).

Adults (aged ≥ 18 years) were included with a diagnosis of spontaneous intracerebral haemorrhage that was confirmed by brain imaging within 48 h after the onset of symptoms or last seen well; and with a moderate to severe level of neurological impairment, defined by having a score of at least 8 on the National Institutes of Health Stroke Scale (NIHSS range 0–42, with higher scores indicating greater severity) or 7–14 inclusive on the Glasgow Coma Scale (range 3–5, with lower scores indicating greater loss of consciousness). Key exclusion criteria included being unlikely to benefit from the treatment (eg, advanced dementia or high likelihood of early death), as judged by the responsible treating clinician; having another medical illness that would interfere with the outcome assessments or follow-up (eg, known significant pre-stroke disability, with estimated scores 3–5 on the modified Rankin scale, advanced cancer, or use of haemodialysis); having a definite indication or contraindication to the use of FYTF-919; being a pregnant or lactating woman; or participation in another trial. Details of the inclusion and exclusion criteria are provided in the appendix (p 13).

The study complied with the Declaration of Helsinki and was approved by the ethics committee of each participating site and appropriate regulatory agencies.

All participants, or their approved surrogate for those who were too unwell, provided written informed consent. We followed the CONSORT extension reporting guidelines for Chinese herbal medicine formulations.²³ This trial is registered at ClinicalTrials.gov, NCT05066620.

Randomisation and masking

After confirmation of eligibility, patients were randomly assigned (1:1) to either FYTF-919 or matching placebo via a central internet-based system with a variable 4 by 6 block grouping method stratified by the location of the hospital (provincial region), severity of neurological impairment (scores <15 vs ≥ 15 on the NIHSS), and location of the haematoma in the brain (deep basal ganglia, thalamus) vs lobar vs infratentorial [cerebellum, brain stem, or ventricle]). Eligible patients were assigned to either FYTF-919 or matching placebo.

FYTF-919 (Zhongfeng Xingnao oral prescription) was developed by the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine in accordance with the Chinese standards for good manufacture practice of medical products, and this hospital (investi-

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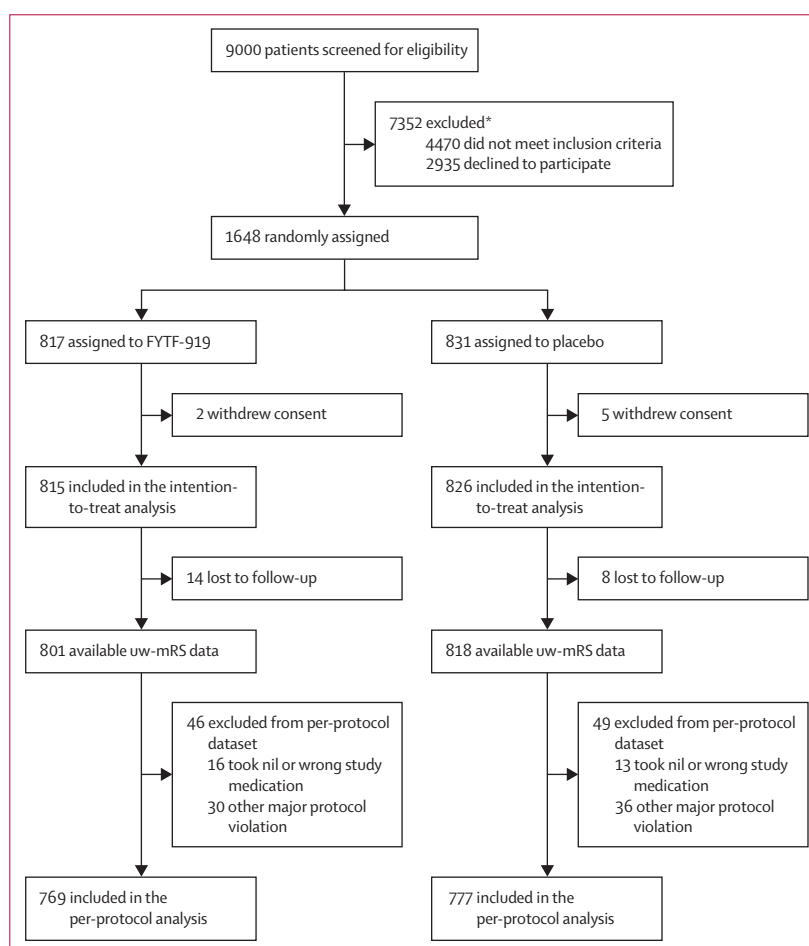


Figure 1: Trial profile over 90 days
uw-mRS=utility weighted modified Rankin Scale. *Data are not mutually exclusive.

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gator Shaohong Chen) owns the invention patent (Chinese patent ZLO 18 023262.0) from 2005. It is a plant-based compound composed mainly of renshen (*Panax ginseng*), dahuang (*Radix et Rhizoma Rhei*), Sanqi (*Radix notoginseng*), and chuanxiong (*Rhizoma Ligustici chuanxiong*), which are combined with sorbic acid and polysorbate 80 as auxiliary materials and prepared as a brown–yellow liquid in a standard 100 mL vial. The dose and method of delivery is determined by a patient's level of consciousness and ability to swallow.

The placebo was developed by Guangdong Huixiangyuan Biotechnology, as a plant-flavoured

solution without any pharmacological activity. It was composed of a soybean peptide with a black sugar syrup, combined with an edible essence and maltodextrin, and salt and monosodium glutamate, as auxiliary materials. According to the safety guarantee from the manufacturer, manual consistency testing showed that the placebo had good consistency with FYTF-919 in appearance, smell, taste, and other aspects. Our own independent designated testing also confirmed successful masking of the placebo and FYTF-919 through consistency in appearance, smell, taste, and other aspects (details are outlined in the appendix pp 14–25).

Participants who were awake and able to swallow received warm FYTF-919 (or placebo) orally, at a dose of 33 mL at least 30 min after a meal, every 8 h per day. For those with dysphagia, insufficient oral intake, unconsciousness, or who were in a critical condition, a lower dose of 25 mL was administered usually via a nasogastric tube, four times (every 6 h) per day. Treatment started immediately after randomisation and continued until 28 days. The dose regime for FYTF-919 was chosen on the basis of a systematic review showing an association with optimal efficacy (appendix pp 183–233). Participants were required to return all bottles of the study medication at the 28-day assessment visit. Full details of FYTF-919 and the placebo are outlined in appendix (pp 14–25).

Procedures

Treatment was not modified or discontinued unless a participant (or surrogate) chose to withdraw their consent to participate; a serious adverse event occurred which, in the opinion of the investigator, was related to the trial protocol; or the investigator felt it was in the participant's best interest. Cessation of treatment did not usually lead to emergency unmasking.

All participants were initially managed in a neuro-intensive care unit or similar monitored facility, and their subsequent management was in accordance with guideline recommendations. Follow-up data were collected in all participants except those who withdrew their consent for the release of such information. Follow-up evaluations were undertaken at 1, 7, 14, 28, 90, and 180 days, either by telephone or in person, by trained certified medical staff. The trial was overseen by a steering committee and all serious adverse events were reviewed with an independent data and safety monitoring board. Project management staff did the quality control activities necessary for conduct of the trial in accordance with the protocol, applicable guidelines, and regulations. A masked independent clinical events committee checked the data for completeness, accuracy, and logic, and adjudicated all serious adverse events to prespecified endpoint definitions on review of reports. Details of the assessment schedule and definitions are listed in the study protocol (appendix pp 234–70) and appendix (pp 33–34).

	FYTF-919 (n=815)	Placebo (n=826)
Mean age, years	62.2 (12.0)	61.3 (11.9)
Sex		
Male	528 (64.8%)	551 (66.7%)
Female	287 (35.2%)	275 (33.3%)
Ethnicity		
Han Chinese	790 (96.9%)	797 (96.5%)
Other	25 (3.1%)	29 (3.5%)
Medical history		
Hypertension	539/813 (66.3%)	572/823 (69.5%)
Coronary artery disease	43 (5.3%)	30 (3.6%)
Diabetes	69 (8.5%)	73 (8.8%)
Pre-stroke level of function on the modified Rankin Scale*		
0	738/814 (90.7%)	747 (90.4%)
1	47/814 (5.8%)	43 (5.2%)
2	29/814 (3.6%)	36 (4.4%)
Current smoker	211 (25.9%)	225 (27.3%)
Current alcohol consumption	206/814 (25.3%)	216/825 (26.2%)
Use of aspirin or other antiplatelet agent	35 (4.3%)	29 (3.5%)
Use of anticoagulation	1 (0.1%)	3 (0.4%)
Mean systolic blood pressure, mm Hg	172 (29)	172 (29)
Mean diastolic blood pressure, mm Hg	98 (19)	99 (20)
Median severity of neurological deficit on the NIHSS†	15 (10–21)	15 (10–20)
Median level of consciousness by scores on the Glasgow Coma Scale‡	12 (10–14)	12 (10–14)
Features of the intracerebral haemorrhage on CT imaging§		
Haematoma location		
Cerebral lobe	79/799 (9.9%)	74/810 (9.1%)
Basal ganglia or thalamus	664/799 (83.1%)	682/810 (84.2%)
Cerebellum or brainstem	56/799 (7.0%)	54/810 (6.7%)
Median haematoma volume, mL	18 (8–35)	17 (8–30)
Presence of intraventricular haemorrhage	359/809 (44.4%)	332/821 (40.4%)
Median time from the onset of symptoms to presentation, h	3.0 (2.0–5.7)	3.0 (1.9–5.2)
Median time from onset of symptoms to randomisation, h	15.1 (7.3–26.1)	15.5 (7.4–25.5)

Data are n (%), mean (SD) or median (IQR). NIHSS=National Institutes of Health Stroke Scale. *Scores on the modified Rankin Scale of functional recovery range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. The modified Rankin Scale score before stroke onset was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members. Only patients with a modified Rankin Scale score of 0 to 2 were included in the trial. †Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ‡Scores on the Glasgow Coma Scale range from 15 (normal) to 3 (deep coma). §Reported by clinician investigators. ||Includes 15 cases of isolated intraventricular haemorrhage, 10/799 (1.3%) in the FYTF-919 group and 5/810 (0.6%) in the placebo group.

Table 1: Baseline characteristics of study participants

Outcomes

The primary outcome was the utility weighted mRS score at 90 days.²⁴ The mRS is a standard global 7-level measure of disability, in which scores of 0–1 indicate a favourable outcome without or with symptoms but no disability, scores of 2–5 indicate increasing amounts of disability (and dependency), and a score of 6 indicates death. We assigned utility weights to the seven levels of 0·97, 0·88,

0·74, 0·55, 0·20, –0·19, and 0·0, respectively, with higher scores indicating a better outcome according to participants' perspective. These weights were derived from a large database of predominantly Chinese patients with intracerebral haemorrhage,²⁴ as opposed to the use of standard non-Chinese weights in trials of acute ischaemic stroke.²⁵ Secondary efficacy outcomes were utility weighted scores on the mRS at 180 days, an

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See Online for appendix

	Number of patients			Group values		Estimated mean difference or odds ratio (95% CI)	p value*
	FYTF-919	Placebo	Total	FYTF-919	Placebo		
Primary outcome—uw-mRS*							
Primary model	782	795	1577	0.44	0.44	0.01 (−0.02 to 0.04)	0.63
Sensitivity 1*	782	795	1577	0.46	0.46	0.01 (−0.03 to 0.04)	0.80
Sensitivity 2†	699	708	1397	0.56	0.56	0.01 (−0.03 to 0.04)	0.78
Sensitivity 3‡	782	795	1577	0.46	0.46	0.01 (−0.03 to 0.04)	0.80
Adjusted model§	781	795	1576	0.42	0.41	0.02 (−0.02 to 0.04)	0.33
Secondary outcome							
Ordinal mRS for poor outcome¶	782	795	1577	..	..	0.99 (0.84 to 1.18)	0.94
Death or disability (mRS 4–6)	782	795	1577	38.1	37.9	1.00 (0.80 to 1.25)	0.99
Death	795	802	1597	11.8	11.3	1.11 (0.81 to 1.52)	0.53
Disability (mRS 4–5)	782	795	1577	26.1	26.4	0.94 (0.74 to 1.19)	0.58
Barthel index	689	707	1396	71.1	69.9	1.18 (−1.58 to 3.93)	0.40
EQ-5D-5L utility score	591	607	1198	0.59	0.60	−0.76 (−2.95 to 1.43)	0.50
Pneumonia	745	755	1500	3.9	3.8	0.99 (0.58 to 1.71)	0.98
Hospital discharge by day 28	738	754	1492	81.0	81.0	..	..
Safety							
Serious adverse events**							
Number reported	507	541	..	..	..	..	0.44
Number of patients	338 (41.5%)	358 (43.3%)	..	..	..	..	..
Related to treatment††	9/507 (1.8%)	5/541 (0.9%)	..	..	..	..	..
Adverse events							
Number reported	1761	1751	..	..	..	..	0.70
Number of patients	650 (79.8%)	665 (80.5%)	..	..	..	..	..
Related to treatment††	116/1761 (6.6%)	76/1751 (4.3%)	..	..	..	..	..
Adverse events of special interest‡‡							
Number reported	116	81	..	..	..	..	0.01
Number of patients	111 (13.6%)	78 (9.4%)	..	..	..	..	..
Related to treatment††	58/116 (50.0%)	28/81 (34.6%)	..	..	..	..	..

EQ-5D-5L=5-level EuroQoL5-dimension self-report questionnaire. mRS=modified Rankin Scale. uw-mRS=utility weighted modified Rankin Scale. *uw-mRS was calculated as adding weight to mRS values for functional outcome. Scores on mRS range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. The utility weights of 0·97, 0·88, 0·74, 0·55, 0·20, –0·19, and 0·0 were assigned to each of the 7 mRS scores. †Use of scores on the EQ-5D-5L for participants at day 90 to impute utility values for participants with missing utility scores at day 90. ‡Use of available EQ-5D-5L utility scores at day 90 to derive utility weights for participants with non-missing EQ-5D-5L data. §In participants with missing EQ-5D-5L utility scores at day 90 but these were available at 180 days, the later were used to impute utility values at day 90. ¶Values are adjusted for adding the following covariates to the main linear model: age (continuous), premorbid scores on the mRS (categorical), sex (male vs female), time to randomisation (<12 h vs ≥12 h). ¶¶The common odds was estimated in an ordinal logistic regression model. The test for proportional odds across mRS scores was $p=0·38$. The distribution of mRS scores 0, 1, 2, 3, 4, 5, and 6 was 7·5%, 19·7%, 15·3%, 19·3%, 22·4%, 3·7%, and 12·0% in the FYTF-919 group and 7·4%, 19·2%, 15·5%, 20·0%, 20·9%, 5·5%, and 11·4% in the placebo group. ||The EQ-5D-5L covers 5 domains of health-related quality of life: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain has three graded levels of response: no problems, moderate problems, or extreme problems. Scores from these levels are combined to provide an overall health utility score that was calculated with population norms from the UK. **Any serious adverse event defined by standard criteria includes any of the following events that might or might not be considered related to the treatment that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in medical or surgical intervention to prevent permanent impairment to body structure or function. Refers to the number of reported serious adverse events; a patient could have more than one event. Values refer to the number of patients with a reported serious adverse event. ††Local investigator considered the event to be definitely or possibly related to the study medication. ‡‡Reported by the local investigators including haematoma enlargement (>6 mL or >33%), new intracranial haematoma, and diarrhoea.

Table 2: Primary and secondary efficacy and safety outcomes at 90 days in the intention-to-treat population

original analysis of the mRS at 28, 90, and 180 days, and dichotomous analysis of scores on the mRS at 28, 90, and 180 days: 4 to 6 (disability or death) versus 0 to 3 (independence). Other outcomes were death or neurological deterioration according to the distribution of scores on the NIHSS at 24 h and 7 days; death within 90 days; and health-related quality of life on the 5-level EuroQoL 5-dimension self-report questionnaire (EQ-5D-5L) at 28, 90, and 180 days; basic activities of daily living according to the Barthel Index at 28, 90, and 180 days; investigator-reported haematoma volumes at 24 h, 7 days, and 14 days (or hospital discharge, if sooner); hospital discharge by day 28; and stroke-associated pneumonia according to the clinical pulmonary infection score.²⁶ All serious adverse events and adverse events of special interest that were presumed to be related to FYTF-919, including diarrhoea and abnormal biochemistry, were recorded through to study completion.

Statistical analysis

We estimated that a sample of 1504 patients would provide 90% power ($\alpha=0.05$) to detect an improvement in mean utility weighted mRS scores of 20% or greater between the FYTF-919 group and placebo group (ie, 0.65 vs 0.59 , mean difference 0.06 ; $SD=0.32$), assuming equal amounts of group participation, 6% non-adherence, to the protocol (ie, drop-in-drop-out), and 10% lost to follow-up at 90 days. This calculation was based on data from the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), in which the mean utility weighted mRS score was 0.59 in the less intensive blood pressure usual care control group.²⁷

The principal analysis was done on the intention-to-treat population of all randomly assigned patients who provided consent for use of their data, regardless of whether they received the study treatment according to the protocol. The main analysis used a general linear

model with utility weighted mRS scores at day 90 as the dependent variable. Treatment allocation was included as a fixed effect along with site, baseline NIHSS scores, and haematoma location. The effect of the intervention is presented as a mean difference and 95% CI, with the placebo group as the reference. Three sensitivity analyses were done by means of different approaches to imputing utility weights in those participants with missing utility scores. A per-protocol analysis excluded participants with a major protocol violation of not meeting the inclusion or exclusion criteria, consumption of contraindicated Chinese medicines, and a deviation from the protocol for consumption of the study medication.

Adjusted analyses were also done by adding the following covariates as fixed effects to the main linear model: age (continuous), premorbid scores on the mRS (categorical), sex (male vs female), time to randomisation (<12 h vs ≥ 12 h). Sensitivity analysis of the primary and secondary outcomes at 28, 90, and 180 days was done with the primary and adjusted models. Heterogeneity of the treatment effect on the primary endpoint was assessed in the six prespecified subgroups of age (<65 vs ≥ 65 years), sex (male vs female), or time to randomisation (<12 h vs ≥ 12 h), baseline NIHSS score (<15 vs ≥ 15), baseline haematoma volume (<15 vs ≥ 15 mL), and haematoma location (cortical vs basal ganglia-thalamic vs cerebellar-brainstem-ventricular). The analysis for each subgroup was done by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the main linear model. Within each subgroup, summary measures were raw mean (SD) within each treatment group. Shift in the seven levels of the mRS was analysed by ordinal logistic regression with tests regarding whether the proportional odds assumption was violated. Secondary categorical outcomes were analysed by a logistic regression model. Analyses of the brain imaging parameters of haematoma and perihematoma oedema volumes are ongoing and will be available in a later publication. All analyses were done by use of SAS Enterprise Guide 8.3, SAS version 9.4. A data safety and monitoring board oversaw the trial (appendix pp 31–33).

Role of the funding source

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

Results

From Nov 24, 2021, to Dec 28, 2023, of 9000 patients screened, 1648 were randomly assigned at 26 tertiary-level hospitals with comprehensive stroke services in China. One activated hospital did not recruit any patients. Because seven patients withdrew their consent immediately after random assignment without receiving any study treatment, 1641 patients were included in the

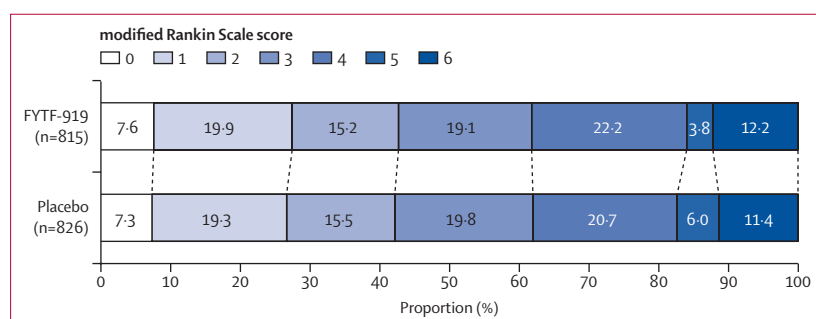


Figure 2: Raw distribution of the modified Rankin Scale scores at 90 days by treatment group in the intention-to-treat population

The figure shows the raw distribution of scores on the modified Rankin Scale at 90 days. Scores on the modified Rankin Scale range from 0 to 6. 0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death. In adjusted analysis of available data, the common odds ratio is 0.99 (95% CI 0.84 to 1.18; $p=0.94$) for poor outcome in the FYTF-919 group versus the placebo group.

modified intention-to-treat analysis: 815 were assigned to the FYTF-919 group and 826 to the placebo group (figure 1, appendix p 36). 14 participants in the FYTF-919 group and eight participants in the placebo group were lost to follow-up at 90 days, and 46 and 49 participants in each group, respectively, with prespecified protocol violations who were excluded from the per-protocol analyses of outcomes at 90 days (appendix pp 29–30, p 37). Only 1 participant was lost to follow-up in the FYTF-919 group between 90 days and 180 days (appendix p 178).

The two groups were balanced with respect to baseline demographic, clinical, and treatment characteristics, overall (table 1, and appendix 2 pp 38–39) and by age and sex (appendix pp 40–69). The mean age was 67·1 years (12·0) and 34·2% were female. The site of the haemorrhage was in the basal ganglia or thalamus in 1346 (83·7%), the median baseline NIHSS score was 15 (IQR 10–20; appendix p 179), and 30·3% had received early decompressive surgery. The median time from onset to randomisation was 15·3 h (IQR 7·4–25·8), when the mean systolic blood pressure was 172 (SD 29) mm Hg.

The median time from the onset of symptoms to receipt of the first dose of study medication was 20·0 h (IQR 11·4–30·5) and the medication was taken in nearly equal proportion orally and by nasogastric tube (appendix p 70). The median duration of medication was 29 days (27–29) and the median number of bottles completed was 28 (24–28). Overall, 1242 (75·7%) participants consumed 80% or more of the study medication (1235 [82·4%] surviving participants) and

994 (60·6%) completely adhered to the dosing schedule to consume all the study medication by 28 days (appendix p 70). There were no significant differences in the clinical management of participants over 28 days; 424 (52·0%) participants in the FYTF-919 group and 416 (50·4%) in the placebo group received neurosurgical intervention during the study period (appendix pp 71–74). Details of the clinical assessments and investigator-reported brain imaging features are outlined in the appendix (pp 75–80).

Mean utility weighted mRS scores at 90 days were 0·44 in the FYTF-919 group and 0·44 in the placebo group (difference 0·01, 95% CI, –0·02 to 0·04; $p=0·63$; table 2 and appendix pp 81–83, figure 2). The neutral result was consistent in adjusted and per-protocol analysis (table 2 and appendix pp 84–113) and in analysis of the primary outcome at 180 days (appendix pp 84–85, 114). There was significant heterogeneity in the treatment effect on the primary outcome for the prespecified subgroups of the volume and location of the haematoma (figure 3). However, apart from the location of haematoma on the treatment effect at 180 days, there was no heterogeneity of the treatment effect in post-hoc analysis using a classification of these subgroups into tertiles and in the use of surgery at 90 days and 180 days (appendix pp 180–82).

There was no significant between-group difference between the FYTF-919 group and the placebo group across any of the secondary outcomes (table 2 and appendix pp 84–85 during 90 days of follow-up). The results were consistent in per-protocol analysis (appendix pp 103–13).

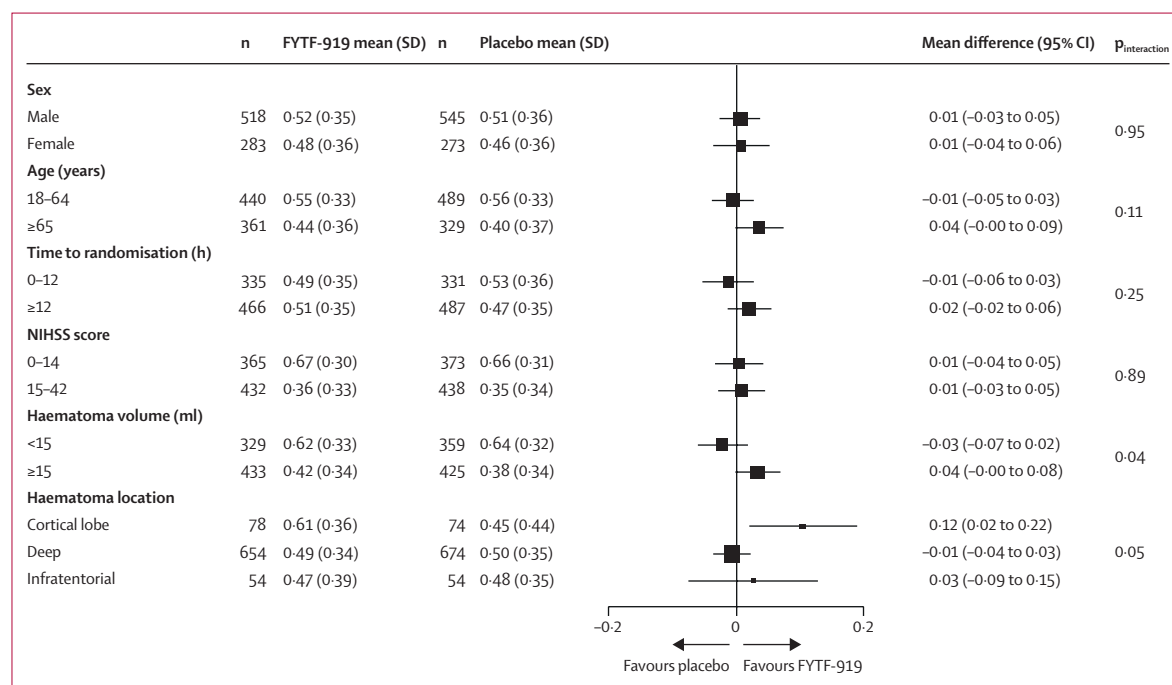


Figure 3: Functional outcomes according to utility weighted modified Rankin Scale scores at 90 days in subgroups of patients in the primary adjusted model
NIHSS=National Institutes of Health Stroke Scale.

Details regarding the causes of death are provided in the appendix (pp 115, 131–39).

Overall, there were no significant differences between the FYTF-919 group and the placebo group in adverse events (79·8% *vs* 80·5%) or serious adverse events (41·5% *vs* 43·3% during 90 days of follow-up). Among the events of special interest, diarrhoea occurred in 10·6% of the FYTF-919 group and 6·5% of the placebo group. A complete list of adverse events is provided in the appendix (pp 116–30, 140–76).

Discussion

In this multicentre, randomised, double-blind, placebo-controlled, clinical trial, the traditional Chinese medical herbal compound FYTF-919 did not affect the utility weighted mRS at 90 days in patients with moderate to severe acute intracerebral haemorrhage. In addition, there were no between-group differences in any of the secondary clinical measures (including death) or serious adverse events.

Herbal formulas have been used to treat people in China for thousands of years. Traditional Chinese medicine continues to be an integral part of mainstream health care in China, now organised alongside the conventional biomedical approaches of western medicine. Elsewhere in the world, Chinese herbal medicines are widely used as complementary or alternative medicine to maintain wellness without the need for professional advice or disclosure, and despite scarce supporting evidence of efficacy.²⁸ Despite some favourable results, the poor methodological quality of existing clinical trials has created ambiguity about the effects of traditional Chinese medicine.^{29,30} Recently, however, two large double-blind, placebo-controlled, clinical trials of traditional Chinese medicine herbal compounds have shown beneficial effects in cardiology: Tongxinluo for the treatment of 3797 patients with acute myocardial infarction³¹ and Qiliqiangxin for the treatment of 3110 patients with heart failure with reduced ejection fraction.³² Yet, even when quality control issues, such as sample size, concealment of allocation, masking, and patient selection, have been appropriately addressed, issues persist over the interpretation of results in relation to the study context and variable quality of the component ingredients.³³ A variety of Chinese herbal medicines have been tested in patients with acute ischaemic stroke, but apart from one large clinical trial of MLC601 (NeuroAiD), a combination of nine herbal and five animal components in capsule form to enhance recovery,³⁴ these have generally been small and of low quality.³⁵

We were motivated to undertake the CHAIN study because of the paucity of treatments for intracerebral haemorrhage, which causes more loss of productive life from death or disability globally than the more common ischaemic stroke.² Intracerebral haemorrhage causes the initial (primary) brain injury from mass effect and physical disruption of the haematoma.¹ The release of

iron and thrombin as haemoglobin degradation products from the haemolysis of red blood cells within the haematoma are major contributors to secondary neuronal injury after intracerebral haemorrhage.^{7–9} These products cause various processes that include apoptosis, oxidative stress, inflammation, and autophagy, which further disrupt the blood–brain barrier and lead to parenchymal cell swelling manifest on brain imaging as perihematoma oedema. Initially, these processes have the potential to increase intracranial pressure and lead to herniation and death, and later to compromise the speed and degree of recovery of physical function and wellbeing.³⁶

Our study has several strengths. It was designed with a large sample size to minimise random error and ensure we were able to establish a reliable assessment of the effects of FYTF-919 in a potential patient-responder group with a high likelihood of developing secondary neuroinflammatory injury and perihematoma oedema. The use of utility weighted mRS scores as the primary outcome measure was purposely chosen to provide efficiency gains in statistical power and as a more appropriate assessment of functional recovery in those with severe disability, many of whom would undergo neurosurgery.^{24,25} There was no systematic bias due to imbalance in the baseline characteristics of patients between the randomised groups, and no apparent unmasking of the study medication that could be recognised either through specific testing or differences in the management of participants or their adherence to procedures. Participants were managed with a high degree of background interventions and supportive care appropriate for a critical illness, and they achieved a high degree of adherence to the study medication.

The nearly two-fold increase in diarrhoea reported in the FYTF-919 group confirms that it contained active ingredients and provides some support to the hypothesis that a major therapeutic effect of traditional Chinese medicine is to improve gut microbiota and regulation of gastrointestinal hormones.³⁷ Although subgroup analysis indicates a treatment effect of FYTF-919 in participants with superficial and larger haematomas (volumes of 15 mL or greater), these findings are not reliable due to the small numbers of participants with superficial cortical haematomas and the absence of an association when haematoma volumes were reclassified into tertiles.

Our study has some limitations. Although the patients were recruited from several provinces in China and had similar characteristics to participants in the third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3), which used a stepped wedge cluster randomised design,³⁸ the generalisability of these findings outside of China is unknown. In China, patients have different demographic and clinical characteristics and patterns of intracerebral haemorrhage than patients in other high-income countries. Moreover, the high rates of active

management, including the use of neurosurgery, intensive care, and certain medical treatments, is not the usual standard of care in many countries and might have compromised the sensitivity in detecting an effect of FYTF-919. Although further data on the temporal changes in the volumes of perihematoma oedema in participants will be reported in the future, this may not be a reliable surrogate measure of neuroinflammation.⁹

In conclusion, our study has shown that in patients with primary intracerebral haemorrhage that led to a moderate to severe amount of neurological impairment within 48 h after the onset of symptoms, use of the traditional Chinese herbal compound FYTF-919 had no effect on utility weighted modified Rankin scores or any other clinical outcome. This randomised controlled trial provides a paradigm for the assessment of other traditional Chinese medical herbal compounds for the treatment of acute stroke in China, and elsewhere in the world where the use of complementary and alternative medicines are increasing.

Contributors

JG, CSA, and LS designed the study. LS, XC, YCh provided quality control oversight. XL and XR did the statistical analysis and reports. QL wrote the statistical analysis plan with input from CSA and LS. CSA wrote the first draft of the manuscript. All the other authors reviewed and commented on the final draft of the manuscript. The first authors QL, XL, and XR, and the corresponding authors had full access to verify all the study data, and they had final responsibility for the decision to submit the paper for publication. 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

JG received grants from The Department of Science and Technology of Guangdong Province, and Guangzhou Municipal Science and Technology Bureau. GJH is a member of the data safety monitoring board (DSMB) of the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT) of which CSA is the principal investigator, and is an Associate Editor of *Circulation*. CSA has received grants from the National Health and Medical Research Council (NHMRC) of Australia, the Medical Research Council and Medical Research Foundation of the UK, and Penumbra and Takeda China. He also reports receiving advisory committee fees from AstraZeneca, is President-elect of the World Stroke Organization, editor-in-chief of *Cerebrovascular Diseases*, and associate editor of the *International Journal of Stroke*. He is a member of the DSMB for the PROTECT-MT, MAGIC-MT, and DIST trials. LS has received grants from Takeda China and Unionstrong Technology, and is a member of the DSMB for the PROTECT-MT and STROKE-ICAS trials. All other authors declare no competing interests.

Data sharing

Individual de-identified participant data used in these analyses can be shared by request from any qualified investigator following approval of a protocol and signed data access agreement via a corresponding author.

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References

- Seiffge DJ, Anderson CS. Treatment for intracerebral hemorrhage in 2024: dawn of a new era. *Int J Stroke* 2024; **19**: 482–89.
- Global Burden of Disease 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; **20**: 795–98.
- Sandset EC, Wang X, Carcel C, et al. Sex differences in treatment, radiological features and outcome after intracerebral haemorrhage: pooled analysis of Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials 1 and 2. *Euro Stroke J* 2020; **5**: 345–50.
- James ML, Cox M, Xian Y S, et al. Sex and age interactions and differences in outcomes after intracerebral hemorrhage. *J Women's Health* 2017; **26**: 380–88.
- Foschi M, D'Anna L, Gabriele C, et al. Sex differences in the epidemiology of intracerebral hemorrhage over 10 years in a population-based stroke registry. *J Am Heart Assoc* 2024; **13**: e032595.
- Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematoma edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. *Stroke* 2011; **42**: 73–80.
- Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; **5**: 53–63.
- Lou M, Lieb K, Selim M. The relationship between hematoma iron content and perihematoma edema: an MRI study. *Cerebrovasc Dis* 2009; **27**: 266–71.
- Selim M, Foster LD, Moy CS, et al. Deferoxamine mesylate in patients with intracerebral haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial. *Lancet Neurol* 2019; **18**: 428–38.
- Zeng L, Tang G, Wang J, et al. Safety and efficacy of herbal medicine for acute intracerebral hemorrhage (CRRICH): a multicentre randomised controlled trial. *BMJ Open* 2019; **9**: e024932.
- Han L, Liu D, Zeng Q, et al. The neuroprotective effects and probable mechanisms of ligustilide and its degradative products on intracerebral hemorrhage in mice. *Int Immunopharmacol* 2018; **63**: 43–57.
- Zhang J, Jiang Y, Liu N, et al. A network-based method for mechanistic investigation and neuroprotective effect on post-treatment of senkyunolide-h against cerebral ischemic stroke in mouse. *Front Neurol* 2019; **10**: 1299.
- Zhao Y, Huang Y, Fang Y, et al. Chrysophanol attenuates nitrosative/oxidative stress injury in a mouse model of focal cerebral ischemia/reperfusion. *J Pharmacol Sci* 2018; **138**: 16–22.
- Zhao Y, Fang Y, Zhao H, et al. Chrysophanol inhibits endoplasmic reticulum stress in cerebral ischemia and reperfusion mice. *Eur J Pharmacol* 2018; **818**: 1–9.
- Wang HL, Zeng H, Xu MB, et al. Efficacy and safety of Chinese herbal medicine for primary intracerebral hemorrhage: a systematic review of randomized controlled trials. *Front Pharmacol* 2019; **10**: 1139.
- Song J, Lyu Y, Wang P, et al. Treatment of naoxueshu promotes improvement of hematoma absorption and neurological function in acute intracerebral hemorrhage patients. *Front Physiol* 2018; **9**: 933.
- Gao L, Zhao H, Liu Q, et al. Improvement of hematoma absorption and neurological function in patients with acute intracerebral hemorrhage treated with Xueshuantong. *J Neurol Sci* 2012; **323**: 236–40.
- Park B, Hong SC, Park SW, Yi CS, Ha YK, Choi DJ. Herbal medicine for hemorrhage-related hydrocephalus: a systematic review of randomised controlled trials. *Complement Ther Med* 2018; **39**: 146–53.
- Liu H, Yan Y, Pang P, et al. Angong niuhuang pill as adjuvant therapy for treating acute cerebral infarction and intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *J Ethnopharmacol* 2019; **237**: 307–13.
- Luo L, Li M, Wan X, Lu Y, Yu X. Meta-analysis of the efficacy of huoxue huayu method combined with conventional western medicine in the treatment of hydrocephalus after cerebral hemorrhage. *Altern Ther Health Med* 2023; **29**: 300–05.
- Zhao Y, Cui W, Xie T, et al. Efficacy and safety of Chinese Herbal medicine in patients with Acute INtracerebral hemorrhage (CHAIN): protocol for a randomized placebo-controlled double-blinded multicenter trial. *Cerebrovasc Dis* 2024; 501–07.

- 22 Li Q, Anderson CS, Al-Shahi Salman R, et al. Statistical analysis plan for the Chinese Herbal medicine in Acute INtracerebral haemorrhage (CHAIN) trial. *Cerebrovasc Dis* 2024; published online July 23. <https://doi.org/10.1159/000540444>.
- 23 Cheng C, Wu T, Shang H, et al, the CONSORT-CHM Formulas 2017 Group. CONSORT extension for Chinese herbal medicine formulas 2017: recommendations, explanation, and elaboration. *Ann Intern Med* 2017; **167**: 112–21.
- 24 Wang X, Moullaali T, Li Q, et al. Utility-weighted modified Rankin Scale scores for the assessment of stroke outcome: pooled analysis of 20 000+ patients. *Stroke* 2020; **51**: 2411–17.
- 25 Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; **378**: 11–21.
- 26 Gaudet A, Martin-Loeches I, Povoa P, et al. Accuracy of the clinical pulmonary infection score to differentiate ventilator-associated tracheobronchitis from ventilator-associated pneumonia. *Ann Intensive Care* 2020; **10**: 101.
- 27 Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; **368**: 2355–65.
- 28 Cohen M, Hunter J. Complementary medicine products: interpreting the evidence base. *Intern Med J* 2017; **47**: 992–98.
- 29 Journal of Complementary Medicine. Publishing scientifically sound papers in traditional and complementary medicine. *J Traditional Complementary Med* 2016; **6**: 1.e4.
- 30 Wu B, Liu M. How to improve the quality of a clinical trial on traditional Chinese medicine for stroke. *Stroke* 2009; **40**: e641–42.
- 31 Yang Y, Li X, Chen G, et al. Traditional Chinese medicine compound (Tongxinluo) and clinical outcomes of patients with acute myocardial infarction: the CTS-AMI randomized clinical trial. *JAMA* 2023; **330**: 1534–45.
- 32 Cheang I, Yao W, Zhou Y, et al. The traditional Chinese medicine Qiliqiangxin in heart failure with reduced ejection fraction: a randomized, double-blind, placebo-controlled trial. *Nature Med* 2024 **30**: 2295–302.
- 33 Bach RG. Traditional Chinese medicine meets evidence-based medicine in the acutely infarcted heart [editorial]. *JAMA* 2023; **330**: 1529–30.
- 34 Chen CLH, Young SHY, Gan HH, et al. Chinese medicine Neuroaid efficacy on stroke recovery: a double-blind, placebo-controlled, randomized study. *Stroke* 2013; **44**: 2093–100.
- 35 Wu B, Liu M, Liu H, et al. Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke* 2007; **38**: 1973–79.
- 36 Wan Y, Holste KG, Hua Y, Keep RF, Xi G. Brain edema formation and therapy after intracerebral hemorrhage. *Neurobiol Dis* 2023; **176**: 105948.
- 37 Zhai Z, Su PW, Ma LY, et al. Progress on traditional Chinese medicine in treatment of ischemic stroke via the gut-brain axis. *Biomed Pharmacotherapy* 2023; **157**: 114.
- 38 Ma L, Hu X, Song L, et al. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. *Lancet* 2023; **402**: 27–40.