

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial



Lu Ma*, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu Ouyang, Laurent Billot, Qiang Li, Alejandra Malavera, Xi Li, Paula Muñoz-Venturelli, Asita de Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandian, Mohammad Wasay, Octavio M Pontes-Neto, Carlos Abanto, Antonio Arauz, Haiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leibo Liu, Yuki Sakamoto, Shoujiang You, Qiao Han, Bernard Crutzen, Emily Cheung, Yunke Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jianguo Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators†



Summary

Background Early control of elevated blood pressure is the most promising treatment for acute intracerebral haemorrhage. We aimed to establish whether implementing a goal-directed care bundle incorporating protocols for early intensive blood pressure lowering and management algorithms for hyperglycaemia, pyrexia, and abnormal anticoagulation, implemented in a hospital setting, could improve outcomes for patients with acute spontaneous intracerebral haemorrhage.

Methods We performed a pragmatic, international, multicentre, blinded endpoint, stepped wedge cluster randomised controlled trial at hospitals in nine low-income and middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Viet Nam) and one high-income country (Chile). Hospitals were eligible if they had no or inconsistent relevant, disease-specific protocols, and were willing to implement the care bundle to consecutive patients (aged ≥ 18 years) with imaging-confirmed spontaneous intracerebral haemorrhage presenting within 6 h of the onset of symptoms, had a local champion, and could provide the required study data. Hospitals were centrally randomly allocated using permuted blocks to three sequences of implementation, stratified by country and the projected number of patients to be recruited over the 12 months of the study period. These sequences had four periods that dictated the order in which the hospitals were to switch from the control usual care procedure to the intervention implementation of the care bundle procedure to different clusters of patients in a stepped manner. To avoid contamination, details of the intervention, sequence, and allocation periods were concealed from sites until they had completed the usual care control periods. The care bundle protocol included the early intensive lowering of systolic blood pressure (target < 140 mm Hg), strict glucose control (target 6.1–7.8 mmol/L in those without diabetes and 7.8–10.0 mmol/L in those with diabetes), antipyrexia treatment (target body temperature $\leq 37.5^\circ\text{C}$), and rapid reversal of warfarin-related anticoagulation (target international normalised ratio < 1.5) within 1 h of treatment, in patients where these variables were abnormal. Analyses were performed according to a modified intention-to-treat population with available outcome data (ie, excluding sites that withdrew during the study). The primary outcome was functional recovery, measured with the modified Rankin scale (mRS; range 0 [no symptoms] to 6 [death]) at 6 months by masked research staff, analysed using proportional ordinal logistic regression to assess the distribution in scores on the mRS, with adjustments for cluster (hospital site), group assignment of cluster per period, and time (6-month periods from Dec 12, 2017). This trial is registered at Clinicaltrials.gov (NCT03209258) and the Chinese Clinical Trial Registry (ChiCTR-IOC-17011787) and is completed.

Findings Between May 27, 2017, and July 8, 2021, 206 hospitals were assessed for eligibility, of which 144 hospitals in ten countries agreed to join and were randomly assigned in the trial, but 22 hospitals withdrew before starting to enrol patients and another hospital was withdrawn and their data on enrolled patients was deleted because regulatory approval was not obtained. Between Dec 12, 2017, and Dec 31, 2021, 10857 patients were screened but 3821 were excluded. Overall, the modified intention-to-treat population included 7036 patients enrolled at 121 hospitals, with 3221 assigned to the care bundle group and 3815 to the usual care group, with primary outcome data available in 2892 patients in the care bundle group and 3363 patients in the usual care group. The likelihood of a poor functional outcome was lower in the care bundle group (common odds ratio 0.86; 95% CI 0.76–0.97; $p=0.015$). The favourable shift in mRS scores in the care bundle group was generally consistent across a range of sensitivity analyses that included additional adjustments for country and patient variables (0.84; 0.73–0.97; $p=0.017$), and with different approaches to the use of multiple imputations for missing data. Patients in the care bundle group had fewer serious adverse events than those in the usual care group (16.0% vs 20.1%; $p=0.0098$).

Published Online

May 25, 2023

[https://doi.org/10.1016/S0140-6736\(23\)00806-1](https://doi.org/10.1016/S0140-6736(23)00806-1)

See Online/Comment

[https://doi.org/10.1016/S0140-6736\(23\)00911-X](https://doi.org/10.1016/S0140-6736(23)00911-X)

*Joint first authors

†INTERACT3 Investigators listed in the appendix (pp 4–9)

Department of Neurosurgery

(Prof L Ma MD, X Hu MD,

X Li MM, Prof H Li MD,

Prof Y Liu MD, Prof J Xu MD,

Prof C You MD,

Prof C S Anderson PhD) and

Department of Neurology

(Prof L Chen PhD, Prof B Wu MD,

Prof M Liu PhD), West China

Hospital, Sichuan University,

Chengdu, China; The George

Institute for Global Health

China, Beijing, China

(L Song PhD, M Ouyang PhD,

Y Li MD, C Chen MD, Y Zhao PhD,

Prof C S Anderson); The George

Institute for Global Health,

Faculty of Medicine, University

of New South Wales, Sydney,

NSW, Australia (L Song,

X Chen PhD, M Ouyang,

Prof L Billot MRes, Q Li MBIostat,

A Malavera MD,

Prof P Muñoz-Venturelli PhD,

L Liu MScEng, X Wang PhD,

C Chen, Prof C S Anderson);

Clinical Research Center,

Faculty of Medicina Clínica

Alemana Universidad del

Desarrollo, Santiago, Chile

(Prof P Muñoz-Venturelli,

Prof C S Anderson); Clinical Trials

Unit, Faculty of Medicine,

University of Kelaniya,

Colombo, Sri Lanka

(Prof A de Silva DPhil); Stroke

Unit, 115 Hospital,

Ho Chi Minh City, Viet Nam

(Prof N H Thang MD);

Department of Medicine,

University of Ilorin & University

of Ilorin Teaching Hospital, Ilorin, Nigeria (Prof K W Wahab MD); Neurology Department, Christian Medical College and Hospital, Ludhiana, India (Prof J D Pandian MD); Department of Medicine, The Aga Khan University, Karachi, Pakistan (Prof M Wasay MD); Department of Neurology, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil (Prof O M Pontes-Neto PhD); The Cerebrovascular Disease Research Center, National Institute of Neurological Sciences, Lima, Peru (Prof C Abanto MD); Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suarez, Mexico City, Mexico (Prof A Arauz PhD); Department of Neurosurgery, Suining Central Hospital, Suining, China (H Shi MM); Department of Neurology, Liaoning Thrombus Treatment Centre of Integrated Chinese and Western Medicine, Shenyang, China (G Tang MBBS); Department of Neurosurgery, Dazhou County People's Hospital, Dazhou, China (S Zhu MBBS); Department of Neurosurgery, Jiangsu Rudong County People's Hospital, Nantong, China (X She MM); Department of Neurology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan (Y Sakamoto MD); Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, China (S You MD); Department of Neurology, Suzhou Hospital of Traditional Chinese Medicine, Suzhou, China (Q Han MD); Department of Radiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium (B Crutzen MD); Department of Radiology, Grand Hôpital de Charleroi, Charleroi, Belgium (B Crutzen); Neurology Department, Royal Prince Alfred Hospital, Sydney, Australia (E Cheung MD, Prof C S Anderson); Department of Neurology, Shanghai East Hospital, Tongji University, Shanghai, China (C Chen, F Liu MM); Department of Nursing and Evidence-based Nursing Center, West China Hospital, Sichuan University,

Interpretation Implementation of a care bundle protocol for intensive blood pressure lowering and other management algorithms for physiological control within several hours of the onset of symptoms resulted in improved functional outcome for patients with acute intracerebral haemorrhage. Hospitals should incorporate this approach into clinical practice as part of active management for this serious condition.

Funding Joint Global Health Trials scheme from the Department of Health and Social Care, the Foreign, Commonwealth & Development Office, and the Medical Research Council and Wellcome Trust; West China Hospital; the National Health and Medical Research Council of Australia; Sichuan Credit Pharmaceutic and Takeda China.

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Intracerebral haemorrhage is the most serious and least treatable form of stroke and accounts for approximately 20% of the almost 20 million new strokes that occur globally each year.¹ Most cases of intracerebral haemorrhage occur in low-income and middle-income countries (LMICs), where there is a high prevalence of hypertension, unhealthy diets (eg, a high salt intake), and other risk factors.² Because elevated blood pressure is common after the onset of intracerebral haemorrhage and is strongly associated with a poor outcome, a central component of the management of patients is to provide treatment to lower blood pressure towards a systolic target of 140 mm Hg or less.^{3–7} However, inconsistent

results across randomised controlled trials^{8,9} and little evidence specifically in patients with a large intracerebral haemorrhage or who require neurosurgical intervention¹⁰ has restricted the uptake of this strategy in clinical practice where guidelines generally provide an intermediate strength to their recommendation.^{3–7} Moreover, the absence of a proven medical or surgical treatment for intracerebral haemorrhage has resulted in an absence of urgency to treat these patients and a low threshold for the withdrawal of active care in these patients,^{11,12} which contrasts sharply with modern systems of care for patients with acute ischaemic stroke.

Efforts to improve the success of randomised controlled trials in identifying an effective treatment for intracerebral

Research in context

Evidence before this study

We searched PubMed (from Jan 1, 1970, to Oct 30, 2022) and Embase (from Jan 1, 1947, to Oct 30, 2022), with no language or data restrictions, on Nov 24, 2022, for publications with relevant text words in the title or abstract or keywords that included: “intracerebral haemorrhage” OR “haemorrhagic stroke”, “care bundle” OR “treatment combination”, “blood pressure” OR “blood pressure lowering”, “blood glucose” OR “hyperglycaemia”, “body temperature”, and “anticoagulation reversal”. Studies were eligible for inclusion if they assessed the effectiveness of a combination of treatments on clinical outcomes. We identified only one completed cluster randomised controlled trial, done in 2011, the Quality in Acute Stroke Care trial, which showed that a combined protocol to manage fever, hyperglycaemia, and swallowing dysfunction improved the functional outcome in patients with acute stroke (both intracerebral haemorrhage and ischaemic stroke). A 2019 study in Salford, UK, showed a significant association between the implementation of a care bundle of anticoagulation reversal, blood pressure control, and rapid access to neurosurgery and improved survival after cerebral haemorrhage. The 2011 trial did not include blood pressure lowering in the protocol and there were few cases of intracerebral haemorrhage, whereas the 2019 study was limited by its before-and-after design. No ongoing trials were identified through a search of registered trials at ClinicalTrials.gov. There was no strong evidence to recommend the

implementation of an intensive care bundle in acute intracerebral haemorrhage.

Added value of this study

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial is the only randomised controlled trial involving a care bundle that included intensive blood pressure lowering treatment in acute intracerebral haemorrhage. The primary result was that the implementation of the care bundle across participating hospitals resulted in patients having a better functional outcome (measured on the modified Rankin Scale) at 6 months post-treatment compared with usual care. This result included favourable effects on survival and health-related quality of life. The results could not be explained by temporal trends in the characteristics of the patients or their management.

Implications of all the available evidence

A simple, time-sensitive, goal-directed, care bundle protocol, with a foundation strategy of early intensive blood pressure management to a systolic blood pressure target of less than 140 mm Hg, was safe and effective in improving the functional outcome of acute intracerebral haemorrhage. These results provide a clear implication for the rapid control of blood pressure and other physiological variables to be incorporated into clinical practice as a part of active management for this serious disease.

haemorrhage have included the use of clinical and imaging variables to define a potential responder group with a high likelihood of early neurological deterioration from ongoing haemorrhage or haematoma growth.^{13–15} Another effort has been to extend the assessment of functional outcome beyond the conventional 90 days, because recovery from intracerebral haemorrhage takes longer than from acute ischaemic stroke.¹⁶ Assessing combinations of interventions as part of a multifaceted care bundle might also offer advantages, as shown in an Australian cluster clinical trial where the implementation of a treatment protocol for hyperglycaemia, fever, and dysphagia improved outcome from acute stroke.¹⁷ Further support for this approach was provided by a single-site, so-called before-and-after study in the UK, where the implementation of a quality improvement protocol that included the reversal of anticoagulation, intensive blood pressure lowering, and rapid triage to neurosurgery and critical care was associated with a lower 30-day case fatality after intracerebral haemorrhage.¹⁸ A post-hoc analysis of the second phase of the international Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2)¹⁹ showed that higher scores assigned for any elevation in the baseline of systolic blood pressure, glucose, body temperature, and previous use of anticoagulants in participants independently predicted a poor functional outcome after intracerebral haemorrhage. These issues informed the design of the third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3), with the aim of establishing whether a goal-directed care bundle protocol, comprising early intensive lowering of blood pressure with other management protocols for abnormal physiological variables, improves functional outcome in a broad range of patients with acute spontaneous intracerebral haemorrhage.

Methods

Study design

INTERACT3 was an international, multicentre, prospective, stepped wedge, cluster randomised, blinded, outcome assessed, controlled trial undertaken at hospitals located in nine LMICs (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Viet Nam), and one high-income country (Chile). The trial had a hybrid discovery–implementation design, in which clusters of patients were prospectively followed up to establish their outcome as their hospitals were randomly allocated to switch from control usual care to the intervention implementation at different timepoints. The experimental approach was done to mirror the natural process of rolling out a new quality improvement policy, that of implementing a goal-directed intensive care bundle protocol involving the rapid correction of any abnormal physiological variables (hypertension, hyperglycaemia, and pyrexia) and altered coagulation profile in patients with acute intracerebral haemorrhage. The trial

followed the Consolidated Standards of Reporting Trials Extension reporting guideline for stepped wedge cluster randomised trials.²⁰ Details of the protocol and statistical analysis plan have been published elsewhere^{21,22} and are available in the appendix (pp 89–221).

The study was approved by the ethics committees at participating hospitals and appropriate regulatory authorities. A mixed consent process was applied, whereby a cluster guardian (an appropriate senior delegate [eg, chief executive officer]) provided consent for patients with acute intracerebral haemorrhage to receive the intervention as part of routine care. Participants (or an approved surrogate) provided written informed consent for the collection of sociodemographic, medical, and clinical information, and for them to be contacted to assess their outcome at 6 months. Two amendments were made to the original protocol dated July 12, 2017, to document additional sources of funding, extend the time for each intervention period to 4 months for sites in Asia to maximise the recruitment of patients, allow a transition time of 7–10 days before the sites entered the implementation period, for stratification variables to be incorporated into the randomisation programme, and to extend the study timelines (April 8, 2018); and additionally to expand the number of hospitals, further extend the study timelines, embed a process evaluation and economic evaluation within the trial, clarify the inclusion criteria for the diagnosis of intracerebral haemorrhage, include a form to document consent in patients who withdrew from the study, and clarify the patient recruitment targets within the study periods for the required sample size (Aug 12, 2019).

Clusters and participants

Hospital sites were approached through neurosurgery and neurology professional networks. To be eligible, they either had no or inconsistent protocols for managing abnormal physiological variables in patients with acute intracerebral haemorrhage and had to be willing to implement the required interventional care bundle protocol as part of routine care. Eligible sites needed to enrol consecutive adult (age ≥ 18 years) patients presenting within 6 h after the onset of acute intracerebral haemorrhage, have a local representative (known as a champion) who was willing to lead the implementation of the intervention, and be able to provide the required study data. Key patient exclusion criteria included the intracerebral haemorrhage being secondary to a structural abnormality in the brain (eg, an arteriovenous malformation, intracranial aneurysm, tumour, trauma, or previous cerebral infarction) or to reperfusion therapy (eg, intravenous thrombolysis or endovascular thrombectomy), or that a patient was unlikely to adhere to the study treatment or follow-up regimen, or both, as judged by the treating clinician. Full details of the inclusion and exclusion criteria are provided in the appendix (p 14).

Chengdu, Sichuan, China
(Prof Y Jiang PhD); Heart Health
Research Center, Beijing, China
(Prof C S Anderson)

Correspondence to:
Prof Craig S Anderson,
The George Institute for Global
Health, Faculty of Medicine,
University of New South Wales,
Sydney, NSW 2050, Australia
canderson@georgeinstitute.
org.au

or

Prof Chao You, Department of
Neurosurgery, West China
Hospital, Sichuan University,
Chengdu 610041, China
youchao@vip.126.com

See Online for appendix

Randomisation and masking

Eligible hospital sites were randomly assigned into three sequences (with four periods) by use of a computer-generated list by the trial statistician (QL) using permuted blocks, stratified by country and the projected number of patients to be recruited per site during the study period (<80, 80–160, and >160 patients). In period 1, all sites kept to their usual care and monitoring procedures for patients with intracerebral haemorrhage. Sites assigned to sequence 1 commenced the care bundle in period 2, those in sequence 2 received the intervention at period 3, and those in sequence 3 received the intervention at period 4, as outlined in the appendix (pp 26–30, 78). The criteria that triggered sites to progress to the next period were either achieving the predetermined patient enrolment target or reaching a time of 3 months (4 months in Asia where there was greater capacity for patient recruitment) from the start date for each period. To avoid contamination, details of the intervention, sequence, and allocation periods were concealed from sites until they had completed the usual care control periods. A period of 7–10 days was used to allow sites time for their staff to receive training before transitioning from usual care to the intervention period. Trained research staff masked to group allocation and patient details located in country-based central offices (in China, Chile, Brazil, and Nigeria) or at hospitals (in the other countries), undertook telephone assessments of the outcome of patients at 6 months post-randomisation.

For logistical reasons and according to available funding, sites were activated in batches beginning in China in 2017, and subsequently in the other countries in 2019 (appendix pp 26–32, 79–80). However, because of the COVID-19 pandemic, patient recruitment was suspended in Chile, Pakistan, and Peru between March 1 and Aug 31, 2020, and no new hospitals outside of China commenced the recruitment of patients until Nov 2, 2020. Because the pandemic affected patient recruitment, mainly at sites in the intervention phase, and caused an imbalance in patient numbers between the randomly assigned groups, the duration of this phase was extended to allow as many sites as possible to participate and enrol patients into the intervention group.

Procedures

Before hospitals began screening and recruiting patients, key staff from participating sites were trained in the study procedures at regional and individual hospital meetings. In the 7–10 days after sites had completed the control usual care period, these staff received online training and remote communication on the intensive care bundle protocol to be applied as a system of care for eligible patients. The components of the care bundle included: early intensive blood pressure management with the goal of achieving a target systolic blood pressure of less than 140 mm Hg within 1 h of the initiation of treatment, with a systolic blood pressure of 130 mm Hg being the

threshold for the cessation of treatment; intensive control of elevated blood glucose with the goal of achieving a glucose target of 6.1–7.8 mmol/L for patients without diabetes and 7.8–10.0 mmol/L for patients with diabetes as soon as possible after the initiation of treatment, as recommended in guidelines for minimal risk of harm from hypoglycaemia;²³ treatment of pyrexia with the goal of achieving a body temperature of less than 37.5°C within 1 h of initiation; and the reversal of abnormal anticoagulation in those taking warfarin using fresh frozen plasma or prothrombin concentrate complex with the goal of reaching an international normalised ratio of less than 1.5 within 1 h of treatment. All target concentrations within the care bundle were to be maintained in patients for 7 days (or until discharge or death, should these events occur earlier). Site-specific data uploaded to the study database on blood pressure, glucose, temperature, and international normalised ratio served as a method to check adherence to the protocol, and also allowed feedback and further training to be offered to sites by trial staff. All sites received monthly performance reports and were required to have staff attend at least two online quality improvement meetings held repeatedly during the study. A process evaluation, whereby formative stakeholder engagement interviews were conducted during the trial, allowed insight to be gained into the barriers and facilitators to change systems of care and to implement the protocol.²⁴ The information also served as a further guide to the training of site staff in their integration of the care bundle into practice. Further details of the care bundle protocol are provided in the appendix (pp 88–170).

To ensure continuous recruitment, each participating site was required to register all patients with a diagnosis of intracerebral haemorrhage into screening and enrolment logs. For enrolled patients, demographic and clinical data, including the amount of neurological impairment measured using the National Institutes of Health Stroke Scale (NIHSS; range 0–42, with higher scores indicating greater severity) were collected at the time of admission to hospital. Follow-up data were collected on clinical status, management, and outcomes at days 1 and 7 of treatment (or discharge or death if earlier) by hospital staff, and of outcomes to be ascertained at 6 months by independent staff. Brain imaging undertaken at presentation (the diagnostic scan), and at 24 h and 7 days of treatment in a subsample of 1619 patients (first seven patients in each of the usual care and intervention phases at each site) were uploaded to a secure central imaging server for analysis by trained physicians who were masked to treatment allocation. Results of the centrally adjudicated brain imaging will be presented in future publications.

Outcomes

The primary outcome was functional recovery measured at 6 months according to the modified Rankin scale (mRS) and analysed as an ordinal outcome (shift across all categories). The mRS is a standard global measure of

disability scored from 0 to 6, 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. Secondary outcomes included the dichotomous analysis of scores on the mRS at 6 months: 3–6 (disability or death) versus 0–2, and 3–5 (major disability) versus 0–2 in survivors; death at 6 months; death or neurological deterioration at 7 days according to a change in scores on the NIHSS, both as a continuous measure and categorised into seven groups (<5, 5–9, 10–14, 15–19, 20–24, ≥25, and death);²⁵ health-related quality of life measured using the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-3L); and residence (own home *vs* other) at 6 months. Time to discharge from hospital was also planned but was only recorded at day 7 to coincide with the other assessments undertaken at this time, and was therefore censored at 7 days. The safety outcomes of all-cause and cause-specific serious adverse events were recorded according to standard definitions for the duration of follow-up.

Statistical analysis

This study was designed with 90% power ($\alpha=0.05$) to detect a common odds ratio (OR) of 0.8 for worse functional outcome at 6 months using ordinal logistic regression. This design required a sample size of 8360 patients from 110 sites, on the assumption that the distribution in the scores on the mRS in the usual care group would be similar to the control group who received standard less-intensive blood pressure lowering treatment in the INTERACT2 study,²⁶ and with 5% of patients lost to follow-up. This treatment effect corresponded to a 5.6% absolute decrease in worse functional outcome (mRS scores 3–6) from receiving the care bundle, from 55.6% down to 50.0% compared with usual care. We assumed an intraclass correlation coefficient of 0.04 on the basis of the results of INTERACT2 and another international cluster randomised trial in acute stroke.²⁵ The required sample size, which corresponded to an average of 19 patients being recruited per phase at each participating hospital (ie, 110 sites \times 4 phases \times 19 patients), was calculated using PASS software 2019, by tests for two ordered categorical variables,²⁷ and by adjusting for the clusters corresponding to the stepped wedge design.²⁸

All analyses were undertaken at the patient level with adjustment for clustering. The main analyses were performed on a modified intention-to-treat basis by including all participants who provided written consent and had primary outcome data available, regardless of protocol adherence. The primary analysis was to be done using ordinal logistic regression with a random effect for cluster (hospital site), a fixed categorical effect of time (four periods), and a fixed effect indicating the group assignment of each cluster at each period. However,

upon unmasking the data, we recognised that the trial did not conform to a standard stepped wedge design in which all clusters contemporaneously switch from one period to the next,²⁹ because the period lengths were not equal and the times at which the different clusters crossed from control to intervention conditions varied widely (appendix pp 26–30, 78–79). To more appropriately account for the effect of time, we adjusted for calendar time instead of trial period by using 6-month calendar periods that corresponded to the length of follow-up for the assessment of the clinical outcomes in individual patients from the time the first patient was recruited (Dec 12, 2017) to the time the last patient was recruited (Dec 31, 2021; appendix p 32).^{30,31}

We undertook a series of preplanned sensitivity analyses with various approaches to the imputation of missing values,²² variable time effects across sites,³² and additional adjustment for the covariates of country (grouped regionally as China *vs* India, Pakistan, Sri Lanka, and Viet Nam *vs* Brazil, Peru, Chile, Mexico, and Nigeria), pre-stroke function (estimated categorical mRS scores of 0 to 5), age, sex, and baseline NIHSS score to the primary model. The NIHSS score was also analysed as a continuous variable using an unadjusted hierarchical linear regression model assuming a normal distribution and an identity link function. We also conducted post-hoc sensitivity analyses by modelling the effect of time continuously using restricted cubic splines based on 1-month and 3-month calendar time windows.

We found the proportional-odds assumption was violated but the analyses proceeded on the understanding that the treatment effect was not constant across categories of the mRS. The result was complemented by a graphical assessment of shifts across categories using bar plots as well as binary analyses. As prespecified, the six subgroups for analysis were age, sex, country, NIHSS score (<15 *vs* ≥15), and clinician-reported volume (<15 mL *vs* 15 to <30 mL *vs* ≥30 mL) and location (cortical *vs* deep *vs* brainstem, cerebellar, or primary ventricular) of the haematoma reported by investigators at baseline, with tests of interaction applied between the specific subgroup and the treatment effect on the primary outcome. A post-hoc estimation of the number needed to treat for a benefit from the treatment was made to help in the interpretation of the results.

Although two interim analyses were undertaken during the study period, given the use of a conservative Haybittle–Peto stopping rule³³ and the negligible amount of type 1 error rate spent, the significance threshold for the primary outcome, including sensitivity analyses, was still $p<0.05$. For the seven secondary clinical outcomes, we controlled the family-wise error rate by applying a sequential Holm–Sidak correction³⁴ to facilitate an interpretation of the findings.³⁵ Between-group differences in interventional physiological variables were assessed using a repeated-measure linear mixed model with adjustments for treatment, time, and

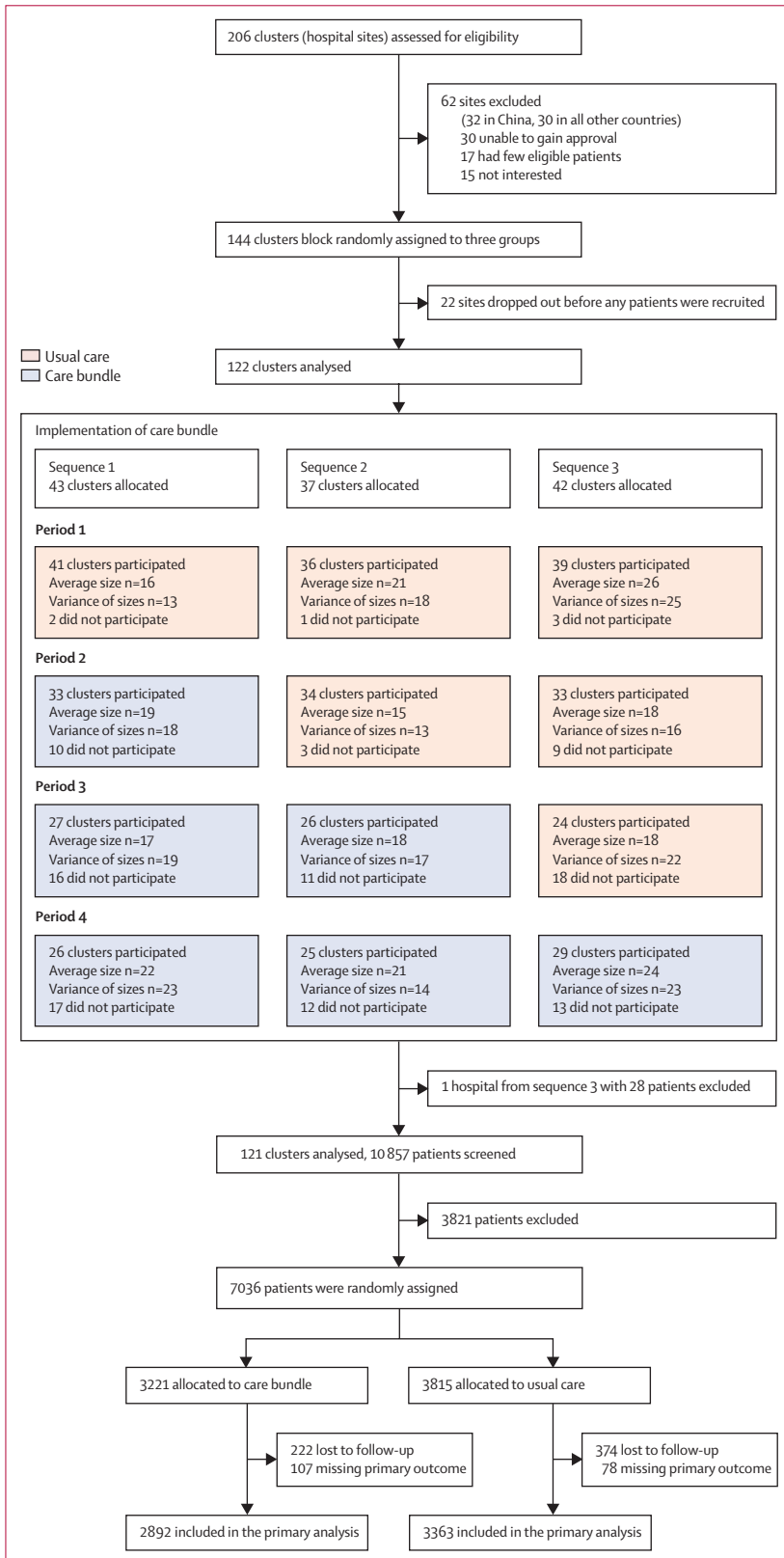


Figure 1: Flow diagram of participating hospitals and patients

treatment-by-time interactions fixed effects, site as a random effect, and with within-patient correlations modelled using a repeated patient effect assuming a compound-symmetry structure. We used SAS Enterprise Guide (version 8.2) and R (version 4.0.0 or newer) for statistical analysis. This trial is registered with ClinicalTrials.gov (NCT03209258) and the Chinese Clinical Trial Registry (ChiCTR-IOC-17011787).

Role of the funding source

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

Results

Between May 27, 2017, and July 8, 2021, 206 hospitals were assessed for eligibility, of which 144 hospitals in ten countries agreed to join and were randomly assigned in the trial, but 22 hospitals subsequently withdrew before any patients were enrolled. Of the remaining 122 hospitals, 43 hospitals were randomly assigned into sequence 1, 37 hospitals into sequence 2, and 42 hospitals into sequence 3. For logistical reasons, sites were randomly assigned in four batches. The first three batches (30 sites in each) were for sites in China, with each lasting 3–4 months; batch 1 from Nov 17, 2017, to Sept 16, 2019; batch 2 from April 20, 2018, to June 25, 2019; and batch 3 from Aug 29, 2018, to Nov 2, 2019. Random assignment of the fourth batch, which included six sites in China from April 16 to Nov 25, 2020, and all sites outside of China, occurred between March 20, 2019 and March 31, 2021. One hospital allocated to sequence 3 was later withdrawn and their data deleted after the implementation of the intervention because a necessary regulatory approval was not obtained. The continued participation of the hospitals in the trial tended to decline across the phases because of the effect of COVID-19 (32 sites), unavailability of eligible patients (17 sites), loss of interest after the champion left the hospital (11 sites), regulatory changes (two sites), and early achievement of the recruitment target (two sites; appendix pp 26–30). Even so, the number of patients enrolled was balanced across the randomised sequences and periods (figure 1; appendix p 31). Between Dec 12, 2017, and Dec 31, 2021, 10857 patients with acute intracerebral haemorrhage were screened for eligibility, with 3821 considered ineligible most often due to having a presentation longer than 6 h after the onset of symptoms. 7036 patients were randomly assigned in the trial, of whom 3815 were allocated to the usual care group and 3221 were allocated to the care bundle intervention group. The stepped wedge study timeline, number of patients recruited across sequences and periods, and reasons for excluding patients are outlined in the appendix (p 33). 374 (9.8%) patients in the usual care group and 222 (6.9%) patients in the care bundle group were lost to follow-up, and another 78 (2.0%) patients in the usual care group and

107 (3.3%) patients in the care bundle group had a missing functional status on the mRS obtained at the final visit. Thus, 3363 patients in the usual care group and 2892 patients in the care bundle group had data available on the primary outcome and were included in the primary efficacy analysis (figure 1). The proportions of participants with primary outcome data and the method of assessment were well balanced by group and period (appendix pp 31, 34–35).

Baseline demographic, medical history, and the clinical and brain imaging characteristics of patients were well balanced between the treatment groups (table 1; appendix p 36). The mean age was 62.0 (SD 12.6) years, 2533 (36.0%) of 7036 patients were female, and 6350 (90.3%) were Chinese. Median scores were 12 (IQR 9–14) on the Glasgow coma scale and 13 (IQR 7–22) on the NIHSS. The cause of the intracerebral haemorrhage was presumed to be related to hypertension in 6574 (94.3%) of 6972 patients and located deep in a cerebral hemisphere in 5638 (82.3%) of 6849 patients (appendix p 37). The median volume of haemorrhage was recorded as 15.0 mL (IQR 7.8–30.0) in 6652 patients and intraventricular haemorrhage was present in 2093 (29.8%) of 7032 patients. 5160 (73.3%) of 7035 patients were admitted directly to a neurosurgery department, and 6320 (90.4%) of 6988 patients had a blood pressure of 140 mm Hg or greater, with an overall mean systolic blood pressure of 174.5 mm Hg (SD 28.3). 2413 (36.0%) of 6711 patients had elevated blood glucose and the overall mean blood glucose concentration was 8.0 mmol/L (SD 2.9). Only 120 (1.7%) of 6930 patients had an elevated body temperature and 84 (1.2%) of 6760 patients had a higher international normalised ratio at presentation.

The proportion of patients administered any intravenous blood pressure lowering drug in the first 24 h was higher in the care bundle group (2542 of 3221 [78.9%]) than the usual care group (2703 of 3811 [70.9%]); results were similar during days 2–7 (2131 of 3188 in the care bundle group [66.8%] vs 2277 of 3775 in the usual care group [60.3%]; table 2; appendix pp 38–39). The most common intravenous agents used in the first 24 h were urapidil (3351 [61.2%]), sodium nitroprusside (1169 [21.4%]), labetalol (663 [12.1%]), nicardipine (438 [8.0%]), and nimodipine (432 [7.9%]) reported in 5473 patients who received blood pressure lowering treatment (appendix p 38). Mean systolic blood pressures were 148.4 mm Hg (SD 21.5) at 1 h and 136.1 mm Hg (16.5) at 24 h in the care bundle group, and 154.7 mm Hg (22.5) at 1 h and 139.0 mm Hg (17.2) at 24 h in the usual care group (adjusted mean difference at 24 h of –3.6 mm Hg; 95% CI –4.5 to –2.7; $p < 0.0001$; figure 2A). The systolic blood pressure target of 140 mm Hg or less was achieved more quickly in the care bundle group than in the usual care group (median, 2.3 h [IQR 0.8–8.0] vs 4.0 h [1.9–16.0]; table 2). The mean diastolic blood pressures were 86.2 mm Hg (SD 13.8) at 1 h and

	Care bundle (n=3221)	Usual care (n=3815)
Age, years	61.8 (12.6)	62.1 (12.6)
Sex		
Female	1146 (35.6%)	1387 (36.4%)
Male	2075 (64.4%)	2428 (63.6%)
Ethnicity		
Han Chinese	2807 (87.1%)	3490/3814 (91.5%)
Non-Han Chinese	19 (0.6%)	34/3814 (0.9%)
Caucasian or European	2 (0.1%)	3/3814 (0.1%)
Latin American	45 (1.4%)	45/3814 (1.2%)
Mixed	4 (0.1%)	2/3814 (0.1%)
Other Asian	92 (2.9%)	76/3814 (2.0%)
Indian subcontinent	194 (6.0%)	143/3814 (3.7%)
Other	58 (1.8%)	21/3814 (0.6%)
Main occupation*		
Unskilled	2855/3218 (88.7%)	3289/3809 (86.3%)
Skilled	363/3218 (11.3%)	520/3809 (13.7%)
BMI, kg/m ² †		
Number for which this information was collected	2713	3172
Mean	24.1 (3.7)	24.1 (3.6)
Medical history		
History of hypertension	2207 (68.5%)	2681/3814 (70.3%)
Previous intracerebral haemorrhage	247 (7.7%)	294/3814 (7.7%)
Previous ischaemic stroke	246 (7.6%)	319/3814 (8.4%)
History of coronary artery disease	70 (2.2%)	123/3814 (3.2%)
History of other heart disease	142 (4.4%)	155/3814 (4.1%)
History of atrial fibrillation	31 (1.0%)	51/3814 (1.3%)
History of diabetes	338 (10.5%)	391/3814 (10.3%)
History of hypercholesterolaemia	90 (2.8%)	117/3813 (3.1%)
Current smoker	588 (18.3%)	771/3813 (20.2%)
Current alcohol consumption	622 (19.3%)	772/3813 (20.2%)
Modified Rankin scale score before onset‡		
0	2489 (77.3%)	2894/3748 (77.2%)
1	358 (11.1%)	440/3748 (11.7%)
2	109 (3.4%)	149/3748 (4.0%)
3	89 (2.8%)	77/3748 (2.1%)
4	102 (3.2%)	108/3748 (2.9%)
5	74 (2.3%)	80/3748 (2.1%)
Medications		
Antihypertensive medication	1446 (44.9%)	1626/3813 (42.6%)
Blood glucose lowering agents	250 (7.8%)	263/3814 (6.9%)
Statin or other lipid lowering agent	89 (2.8%)	133/3814 (3.5%)
Aspirin or other antiplatelet agent	151 (4.7%)	227/3814 (6.0%)
Anticoagulation agent	28 (0.9%)	37/3814 (1.0%)
Systolic blood pressure, mm Hg		
Number for which this information was collected	3221	3813
Mean	174.6 (28.2)	174.5 (28.4)
Diastolic blood pressure, mm Hg		
Number for which this information was collected	3221	3813
Mean	99.7 (17.7)	99.0 (17.9)

(Table 1 continues on next page)

	Care bundle (n=3221)	Usual care (n=3815)
(Continued from previous page)		
Severity of neurological deficit by scores on the NIHSS‡		
Number for which this information was collected	3149	3693
Median (IQR)	13 (7–23)	13 (6–22)
Consciousness by scores on the GCS¶		
Number for which this information was collected	3219	3810
Median (IQR)	12 (9–14)	12 (9–14)
Brain imaging features		
Haematoma present on CT scan	3175 (98.6%)	3680/3814 (96.5%)
Volume of haematoma, mL		
Number for which this information was collected	3129	3523
Median (IQR)	15 (7–30)	15 (8–30)
Side of haematoma		
Left	1628/3175 (51.3%)	1775/3676 (48.3%)
Right	1410/3175 (44.4%)	1751/3676 (47.6%)
Midline	176/3175 (5.5%)	217/3676 (5.9%)
Location of the haematoma		
Cortical	299/3175 (9.4%)	329/3674 (9.0%)
Deep	2631/3175 (82.9%)	3007/3674 (81.8%)
Cerebellum	157/3175 (4.9%)	212/3674 (5.8%)
Brainstem	156/3175 (4.9%)	195/3674 (5.3%)
Intraventricular haemorrhage	863 (26.8%)	1230/3811 (32.3%)
Presumed cause		
Hypertension vasculopathy	3043/3197 (95.2%)	3531/3775 (93.5%)
Cerebral amyloid angiopathy	167/3197 (5.2%)	178/3775 (4.7%)
Abnormal physiological variables		
Systolic blood pressure ≥140 mm Hg	2905 (90.2%)	3415/3767 (90.7%)
Blood glucose >7.8 mmol/L in those without diabetes and >10.0 mmol/L in those with diabetes	1094/3175 (34.5%)	1319/3536 (37.3%)
Body temperature >37.5°C	52/3214 (1.6%)	68/3716 (1.8%)
International normalised ratio ≥1.5	25/3113 (0.8%)	59/3647 (1.6%)

Data are shown as mean (SD), n (%), median (IQR), or n/N (%). GCS=Glasgow coma scale. NIHSS=National Institutes of Health Stroke Scale. *Skilled includes professional or executive, business, sales, and service jobs; unskilled includes driver, farmer or labourer, home duties, and other jobs. †Derived from self-reported height and weight. ‡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. §Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶Scores on the GCS range from 15 (normal) to 3 (deep coma). ||Reported by clinician investigators; multiple options recorded.

Table 1: Patient characteristics at baseline

78.9 mm Hg (11.5) at 24 h in the care bundle group, and 88.3 mm Hg (14.2) at 1 h and 80.4 mm Hg (12.1) at 24 h in the usual care group (adjusted mean difference at 24 h of -2.4 mm Hg; 95% CI -3.0 to -1.8; p<0.0001; figure 2B). In the care bundle group, the proportion of patients who achieved the blood glucose target control was higher than in the usual care group (147 of 1094 [13.4%] vs 86 of 1319 [6.5%]), although there were minimal differences in adjusted mean glucose concentrations over 24 h (-0.5 mmol/L; 95% CI -0.8 to -0.2; figure 2C) and in the time to achieving the glycaemic control target

(median, 1.0 h [IQR 1.0–1.0] vs 1.0 h [1.0–1.0]). Patients in the care bundle group with pyrexia also had more frequent control of their body temperature than those in the usual care group (45 of 52 [86.5%]) at a median of 3.0 h [IQR 1.3–9.5] vs 57 of 68 [83.8%] at a median of 4.0 h [2.0–12.3]), but there was no overall adjusted mean difference over 24 h between the two groups (figure 2D). There were no clear differences in the reversal of anticoagulation (12 of 25 [48.0%] at a median of 27 h [IQR 24.0–48.0] in the care bundle group and 24 of 59 [40.7%] at a median of 25.5 h [IQR 24.0–48.0] in the usual care group). Table 3 (and appendix p 40) shows there were no major differences in other management methods over 7 days, especially in the use of decompressive surgery, endotracheal intubation, and early withdrawal of care. The distribution of the reported volumes of the haematoma and NIHSS scores over time are shown in the appendix (pp 80–81).

Patients in the care bundle group had better scores on the mRS levels compared with those allocated to the usual care group, with a common OR of 0.86 (95% CI 0.76–0.97; p=0.015) for an average effect across all mRSs violated in the proportion odds assumption test (p=0.0003; figure 3; appendix pp 41–43). The favourable shifts in mRS scores in the care bundle group were still present when the prespecified methods of imputation were used to replace missing data, except for an extreme score of 6 (death; appendix pp 44–46). These shifts were also significant after further adjustment for country and patient characteristics (table 3) and when using varying time trends (appendix p 46). Furthermore, the results were consistent with post-hoc analyses with time modelled using restricted cubic splines variables (appendix p 52). When modelling time as originally planned using study period instead of calendar time, there was no clear difference between the randomised groups in either unadjusted or adjusted analyses, and with or without varying time trends (appendix pp 52–54).

Secondary outcome results were consistent with all point estimates favouring the care bundle group including significant differences in mortality, health-related quality of life, and time to discharge (table 3; appendix pp 46–48). Compared with the usual care group, the care bundle group had lower odds of death over 6 months in the primary model (common OR 0.77; 95% CI 0.63–0.95; p=0.015; appendix p 82). The difference became non-significant after adjustment for country and patient characteristics (0.84; 0.65–1.07; p=0.16). There was no significant difference in the odds of death or disability at 90 days (mRS scores 3–6, 54% vs 57%; 0.89; 0.78–1.02; p=0.10) or death or neurological deterioration at 7 days (0.89; 0.77–1.03; p=0.12). Some differences were observed in health-related quality of life between the randomised groups, including an increase in overall utility score in the care bundle group compared with the usual care group (mean difference 0.04, 95% CI 0.02–0.07; p=0.0008; table 3),

but these differences diminished after further adjustment. The proportion of patients discharged from hospital by day 7 was significantly less in the care bundle group (OR 0.72, 95% CI 0.53–0.98; $p=0.034$) but there was no difference in the place of residence at 6 months. After controlling the family-wise error for multiple testing, only the EQ-5D-3L utility score was significantly higher in the care bundle group of the seven secondary outcomes (appendix p 54).

There was significant heterogeneity in the treatment effect on the primary outcome in the subgroups based on region and COVID-19 period (appendix pp 55–61, 83), which were related variables because all non-China sites were activated after the COVID-19 pandemic. There was no heterogeneity by COVID-19 for sites in China (appendix p 84). Between-group separations in the target systolic blood pressure being reached were greater in patients recruited in the first grouped country region of India, Pakistan, Sri Lanka, and Viet Nam compared with those in China and the other grouped country region (Brazil, Peru, Chile, Mexico, and Nigeria; appendix pp 85–87). However, no major regional differences between the randomised groups were apparent between China and each of the grouped regions regarding other aspects of management including decompressive surgery (care bundle vs usual care, 29.5% vs 28.8% in China, 2.1% vs 2.3% in India, Pakistan, Sri Lanka, and Viet Nam, and 7.2% vs 7.6% in Brazil, Peru, Chile, Mexico, and Nigeria) and intensive care (10.9% vs 8.4% in China, 9.2% vs 6.6% in India, Pakistan, Sri Lanka, and Viet Nam, and 9.3% vs 15.2% in Brazil, Peru, Chile, Mexico, and Nigeria; appendix pp 62–64).

Overall, patients in the care bundle group had significantly fewer serious adverse events than the usual care group (516/3221 [16.0%] vs 767/3815 [20.1%]; $p=0.0098$). A complete list of serious adverse events and causes of deaths is provided in the appendix (pp 65–72), as well as details regarding the causes of death (appendix pp 73–76). From the primary model, adjusted frequencies indicated 54.1% (crude number, 1553/2892 [53.7%]) of patients in the care bundle group and 56.9% (1927/3363 [57.3%]) in the usual care group were estimated with death or major disability, and 11.4% (407/2999 [13.6%]) in the care bundle group and 14.3% (571/3441 [16.6%]) in the usual care group were estimated with death alone, therefore the estimated number needed to treat for the care bundle to prevent one patient was 35 (95% CI 15 to infinity) to prevent one patient from death or major disability and 35 (17 to infinity) to prevent one patient from death.

Discussion

This pragmatic stepped wedge, cluster randomised, controlled trial conducted in various health-care settings has shown that, in patients presenting within 6 h of the onset of acute intracerebral haemorrhage, the use of a care bundle protocol incorporating the early control of

elevated blood pressure together with management algorithms for hyperglycaemia, pyrexia, and abnormal coagulation resulted in an improved functional outcome at 6 months. The positive result was consistent across a range of sensitivity analyses and secondary outcomes.

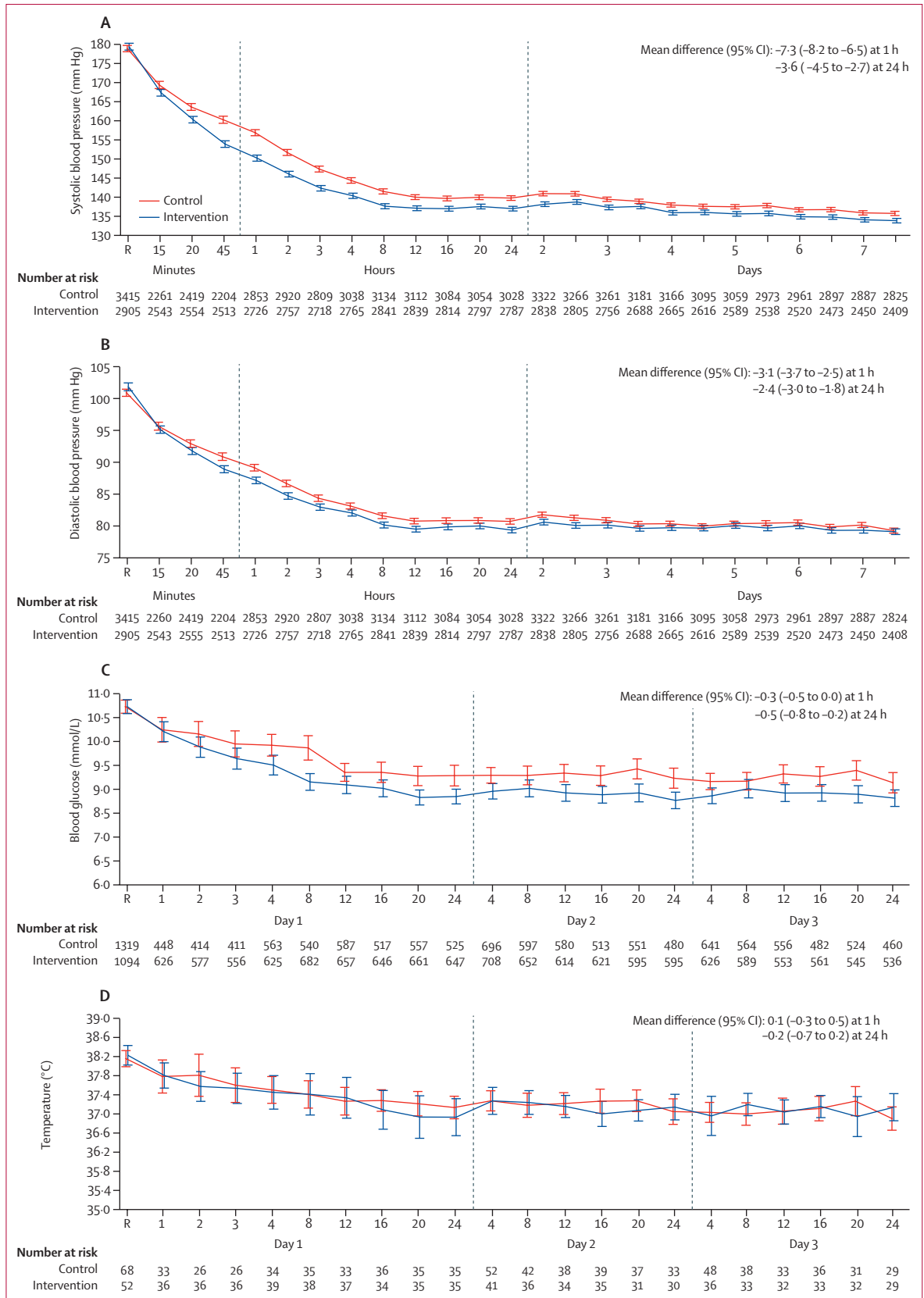
	Care bundle (n=3221)	Usual care (n=3815)
Location of patients after admission to hospital		
Neurosurgery ward	2222 (69.0%)	2938/3814 (77.0%)
Intensive care unit	463 (14.4%)	351/3814 (9.2%)
Neurology ward	255 (7.9%)	260/3814 (6.8%)
Emergency department	149 (4.6%)	163/3814 (4.3%)
Other area	132 (4.1%)	103/3814 (2.7%)
Treatment in the first 24 h		
Intravenous blood pressure lowering treatment	2542 (78.9%)	2703/3811 (70.9%)
Systolic blood pressure target <140 mm Hg reached*	2809/2905 (96.7%)	3223/3415 (94.4%)
Median time to reaching target (IQR)	2.3 (0.8 to 8.0)	4.0 (1.9 to 16.0)
Intensive treatment of blood glucose	250 (7.8%)	263/3814 (6.9%)
Type of agent used for glycaemic control		
Oral agents	205/250 (82.0%)	211/263 (80.2%)
Insulin	56/250 (22.4%)	72/263 (27.4%)
Blood glucose target of 6.1–7.8 mmol/L in patients without diabetes and 7.8–10.0 mmol/L in patients with diabetes reached*	147/1094 (13.4%)	86/1319 (6.5%)
Median time to reaching target (IQR), h	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Antipyrexia treatment	314/3219 (9.8%)	280/3809 (7.4%)
Type of antipyrexia treatment		
Paracetamol	39/314 (12.4%)	43/280 (15.4%)
Metamizole	7/314 (2.2%)	12/280 (4.3%)
Hypothermia cooling with calf packing	228/314 (72.6%)	166/280 (59.3%)
Intravenous infusion with cooled (4°C) saline	17/314 (5.4%)	35/280 (12.5%)
Other	44/314 (14.0%)	60/280 (21.4%)
Temperature target ($\leq 37.5^\circ\text{C}$) reached*	45/52 (86.5%)	57/68 (83.8%)
Time to reach target, h	3.0 (1.3 to 9.5)	4.0 (2.0 to 12.3)
Correction of abnormal coagulation		
International normalised ratio target <1.5 reached*	12/25 (48.0%)	24/59 (40.7%)
Time to achieving target, h	27.0 (24.0 to 48.0)	25.5 (24.0 to 48.0)
Other management from day 2 to day 7		
Intravenous blood pressure lowering treatment	2131/3188 (66.8%)	2277/3775 (60.3%)
Oral blood pressure lowering treatment	2267/3188 (71.1%)	2547/3775 (67.5%)
Insulin	499/3188 (15.7%)	440/3775 (11.7%)
Hypothermia treatment	669/3188 (21.0%)	751/3775 (19.9%)
Prothrombin complex concentrate administered	332/3188 (10.4%)	289/3775 (7.7%)
Fresh frozen plasma administered	61/3188 (1.9%)	104/3775 (2.8%)
Vitamin K administered	174/3188 (5.5%)	163/3775 (4.3%)
Decompressive surgery	844/3196 (26.4%)	1016/3775 (26.9%)
Mechanical ventilation	646/3196 (20.2%)	806/3775 (21.4%)
Intensive care admission	1105/3196 (34.6%)	1435/3775 (38.0%)
Assisted feeding	1749/3196 (54.7%)	1920/3775 (50.9%)
Decision to withdraw active care	21/3196 (0.7%)	26/3775 (0.7%)

Data are shown as mean (SD), n (%), median (IQR), or n/N (%). *Reached care bundle targets during the 7 days of treatment.

Table 2: Management of patients 7 days after treatment

Figure 2: Physiological measures from random assignment after treatment to day 7

Values are shown for patients with abnormal systolic blood pressure (A) and abnormal diastolic blood pressure (B) in 2905 (90.2%) of 3221 patients in the care bundle group and 3415 (90.7%) of 3767 patients in the usual care group; abnormal glucose (C) in 1094 (34.5%) of 3175 patients in the care bundle and 1319 (37.3%) of 3536 patients in the usual care group; and abnormal body temperature (D) in 52 (1.6%) of 3214 patients in the care bundle and 68 (1.8%) of 3716 patients in the usual care group. Recordings were at 15-min intervals in the first hour after commencing treatment (time 0), hourly from hours 1 to 6, once every 6 h until 24 h, and twice per day until day 7. The overall means per treatment group and overall difference in variables between treatment groups at 1 h and at 24 h were calculated using a repeated-measure linear mixed model with a fixed effect of treatment, a fixed categorical effect of time, a fixed interaction between treatment and time, a repeated patient effect (to model within-patient correlations assuming a compound symmetry structure), and a random site effect, with adjustment for baseline measurements. R indicates time of random assignment.



Compared with usual care, implementation of the time-sensitive care bundle was also associated with improved survival, health-related quality of life, and serious adverse events during the follow-up of patients. Given that 118 of the participating hospitals admitted more than 100 patients with acute intracerebral haemorrhage per year, the size of the beneficial effect equates to an improved outcome for at least several similar such patients per site each year.

To our knowledge, this is the first phase 3 multicentre randomised controlled trial to show a positive outcome for an acute treatment of intracerebral haemorrhage, and one of a few trials that have used a stepped wedge, cluster randomised design across multiple countries.³⁶ Trials in intracerebral haemorrhage have been complicated by uncertainty over the optimal timing of the initiation of interventions and in the assessment of outcomes, and in controlling for confounding from comorbid conditions that are either evident at the time of enrolment or arise as a complication of the intervention or condition of the patient during follow-up.^{13,14,16} Previous trials of early intensive blood pressure lowering in acute intracerebral haemorrhage have produced mixed results, because of the variability in the approaches taken towards this treatment and the use of small sample sizes. Individual patient data meta-analyses, where the reliability of the treatment effect is strengthened by an increase in sample size, the inclusion of a broader range of patients, and adjustment for baseline imbalances in prognostic variables, have shown that a careful, targeted, and sustained reduction in systolic blood pressure is safe and is associated with a better functional outcome after intracerebral haemorrhage.^{8,9} However, because these data were derived from conventional trials with restricted inclusion and exclusion criteria, the results are limited to patients with a generally good prognosis with intracerebral haemorrhage of a mild-to-moderate severity according to standard clinical and imaging criteria. We hypothesised that combining early blood pressure lowering treatment with other simple medical interventions would have additive benefits in intracerebral haemorrhage. Such a multifaceted approach is supported by the Quality in Acute Stroke Care trial,¹⁷ where improved outcomes were seen in patients with acute stroke after nurse-initiated protocols to manage fever, hyperglycaemia, and swallowing dysfunction were implemented at 19 Australian acute stroke units from 2005 to 2010. Moreover, the implementation of a quality improvement protocol involving the reversal of anticoagulation, intensive blood pressure lowering, and rapid triage to neurosurgery and critical care improved survival for patients with acute intracerebral haemorrhage at a large tertiary hospital in the UK.¹⁸

However, complex relationships are likely to exist between the fidelity of implementation and the effect of the intervention. Intensive blood pressure lowering was the central component of the care bundle, because it has

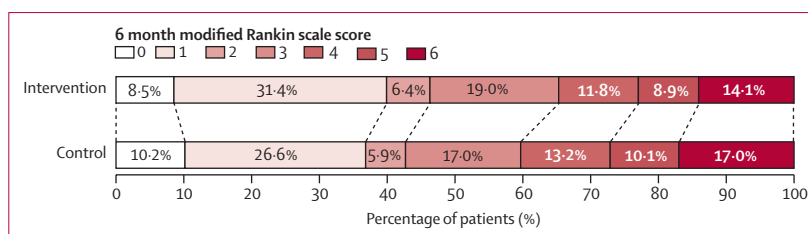


Figure 3: Functional outcome at 90 days in the care bundle and usual care groups, according to scores on the mRS

Raw distribution of scores on the mRS at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 indicating symptoms without clinically significant disability, 2 indicating slight disability, 3 indicating moderate disability, 4 indicating moderately severe disability, 5 indicating severe disability, and 6 indicating death. There was a significant difference between the care bundle group and usual care group in the overall distribution of scores (common odds ratio, indicating a lower odds of worse global function outcome on the mRS, 0.86 [95% CI 0.76–0.97]; $p=0.015$). mRS=modified Rankin Scale.

strong supporting evidence, is applicable to a wide variety of settings, and has a plausible mechanism of action in that attenuating the growth of the intracerebral haemorrhage will reduce the primary injury of dissection and compression of brain tissue. Although the rapid control of blood pressure within an early 6 h inclusion time window was emphasised to investigators in this study, most of the growth in intracerebral haemorrhage occurs within a few hours of the onset of symptoms.³⁷ Moreover, the effect of blood pressure lowering treatment on this intermediate endpoint is modest and does not have a clear time-dependent association defined to date.⁹ The early correction of an abnormal anticoagulation is likely to benefit patients from a similar mechanism of effect,³⁸ but in contrast to ageing populations with ready access to antithrombotic therapies for atrial fibrillation and other cardiovascular disease in high-income countries, only a few patients in our study population presented with anticoagulation-associated intracerebral haemorrhage. Neuroinflammation from the breakdown of red blood cells and blood products is a crucial factor in the cause of secondary brain injury after intracerebral haemorrhage, arising in the perihematoma region and persisting for several days to weeks.³⁹ Because hyperglycaemia⁴⁰ and pyrexia⁴¹ might potentiate this process, their treatment could provide a crucial adjuvant therapeutic strategy.⁴² Once again, these exposures occurred in only a few participants, with small differences in the amounts of control being achieved between randomly assigned groups. Thus, although the overall treatment effect seems to have been driven by intensive blood pressure lowering, the active multifaceted management of physiological variables and the associated, more intensive, monitoring and nursing care could have affected behaviours and attitudes, including self-management in patients, which translated into benefits that extended after discharge from hospital. A mediation analysis is planned to identify the effects of various components of the care bundle and other key aspects of stroke care on outcomes.

The strengths of our trial include that it comprised an evaluation of a complex intervention, for both

	n	Odds ratio or mean difference (95% CI)*	p value†	Intraclass correlation coefficient
Primary outcome				
Ordinal analysis of category scores measured by the mRS*				
Unadjusted	6255	0.86 (0.76 to 0.97)†	0.015	0.05
Adjusted	6069	0.84 (0.73 to 0.97)‡	0.017	0.07
Secondary outcome				
Ordinal analysis of category scores for neurological impairment or death measured by the NIHSS by day 7 of treatment				
	6809	0.89 (0.77 to 1.03)†§	0.12	0.23
Death or disability at 6 months (mRS scores 3–6)				
	6255	0.89 (0.78 to 1.02)†	0.10	0.04
Death at 6 months				
	6440	0.77 (0.63 to 0.95)†	0.015	0.07
Major disability in survivors at 6 months (mRS scores 3–5)				
	5277	0.96 (0.83 to 1.11)†	0.56	0.03
Health-related quality of life measured by the EQ-5D-3L¶				
Mobility	5277	0.87 (0.75 to 1.01)†	0.064	0.02
Self-care	5277	0.93 (0.82 to 1.07)†	0.32	0.02
Usual activities	5277	0.97 (0.85 to 1.10)†	0.62	0.02
Pain or discomfort	5277	0.78 (0.67 to 0.91)†	0.0016	0.02
Anxiety or depression	5277	0.83 (0.69 to 1.00)†	0.046	0.04
Visual analogue scale	5276	1.24 (–0.20 to 2.67)†	0.091	0.02
Mean overall health utility score	6255	0.04 (0.02 to 0.07)†	0.0008	0.06
Hospital discharge by day 7 of treatment				
	7016	0.72 (0.53 to 0.98)†	0.034	0.33
Residence at home at 6 months				
	5277	0.94 (0.65 to 1.35)†	0.73	0.03

EQ-5D-3L=EuroQol Group 5-Dimension Self-Report Questionnaire. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. *The mRS evaluates global disability; scores range from 0 (no symptoms) to 6 (death). A score of 2–5 indicates some degree of disability. The common odds was estimated from an ordinal logistic regression model and indicates the odds of worse functional outcome for the care bundle group compared with the usual care group. †Estimates from a logistic or linear regression model with a random effect of cluster (hospital site) and group assignment (care bundle or usual care) as a fixed effect, and calendar time (6-month window) as a fixed categorical effect. ‡Adjusted for country (grouped as China vs India, Pakistan, Sri Lanka, and Viet Nam vs Brazil, Peru, Chile, Mexico, and Nigeria), pre-stroke mRS score, age, sex, baseline NIHSS score, random effect for cluster (hospital site), and group assignment (care bundle or usual care) as a fixed effect, and calendar time (6-month window) as a fixed categorical effect. §The common odds were estimated from an ordinal logistic regression model and indicate the odds of worse neurological deterioration measured on the NIHSS (separated into seven categories: <5, 5–9, 10–14, 15–19, 20–24, and ≥25) or death for the care bundle group compared with the usual care group. Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶The EQ-5D-3L covers five 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 are combined to provide an overall health utility score that was calculated with population normal values using China normative data for China and UK normative data for countries other than China.

Table 3: Clinical outcomes at 6 months

implementation in real-world settings and clinical effects, on a robust patient-centred outcome assessed at 6 months. The large sample size allowed for the detection of a modest, but still clinically worthwhile, benefit that is generalisable, because an ethnically and sociodemographically diverse population was included from different resource settings. The broad inclusion criteria allowed testing related to the usual triage and care of patients with acute intracerebral haemorrhage, and the analyses followed a prespecified analysis plan. The provision of the protocol, management algorithms, and a short training package, with individual patient management left to the discretion of the treating team and supported by performance monitoring, reflects how this intervention might be adopted more widely. Whether the implementation difficulties already noted to have happened in China,²⁴ in relation to concerns about whether the protocol-defined target concentrations for blood pressure and glycaemic control might harm patients, and whether contextual factors related to staffing

processes and medication supply happened more widely, is under investigation through our embedded process evaluation. Given the broad requirement for the standardisation of best practice and quality requirements of well organised systems to have little unwarranted clinical variation in health care, and the absence of any other clearly proven treatment for intracerebral haemorrhage, we anticipate our findings will also support the implementation and enhancement of protocols for intracerebral haemorrhage in high-income countries.

Our trial has limitations. We chose a stepped wedge cluster randomised design to allow large numbers of patients to be rapidly recruited within routine practice, including those with severe illness and requiring urgent neurosurgery, in whom it can be challenging to obtain early consent. The introduction of the care bundle necessitated a change in practice across different clinical services involved in the flow of patients in hospital. These issues made individual randomisation unfeasible, inequitable, and prone to contamination. However, an

important potential limitation of this study design is confounding effects from secular trends by calendar time, related to the sequential implementation of the intervention across participating sites, and from disruption to the presentation and management of patients created by the COVID-19 pandemic. There was considerable heterogeneity in the recruitment of patients across sites and in the timing of the phases of the trial. Recruitment was also extended for patients in the intervention group towards the end of the trial, which might have introduced a degree of selection bias. To accommodate this heterogeneity, the extent of which was not fully appreciated until the unmasking of the data, we made a post-hoc decision to adjust the analyses according to calendar time instead of by trial period, as recommended in another stepped wedge trial with delays in cluster recruitment.³¹ We could not find any substantial differences in the characteristics of patients or their management by randomised group, overall, and by region, which is especially relevant for the use of decompressive surgery, mechanical ventilation, and early withdrawal of care, because these interventions have the most potential to influence survival from intracerebral haemorrhage. Even so, the possibility of unmeasured confounding from other changes in the management of patients over time cannot be completely excluded. Our trial was not powered to detect differences across secondary outcomes, with statistical significance varying across the secondary outcomes and generally not present after adjustment for patient characteristics. However, the direction of the effect was consistently in favour of the care bundle across all secondary outcomes. There were logistical and practical issues in delivering the intervention, following up patients, and in monitoring the data quality in LMICs. Bias and measurement error are likely to have influenced the assessment of baseline and outcome measures, such as in the primary use of proxies with wide-ranging sociodemographic and cultural backgrounds to assess the health-related quality of life in patients.⁴³

In summary, the findings of our trial provide evidence to support the adoption of an active protocol for intensive blood pressure lowering and the associated management of key abnormal physiological variables within several hours after the onset of signs to improve the recovery of patients presenting with acute intracerebral haemorrhage.

Contributors

CSA, LS, CY, LM, XH, and XC designed the study. LS, XC, and MO provided quality control oversight. QL did statistical analyses and reports. LB wrote the statistical analysis plan with input from CSA and LS. PM-V, AdS, NHT, KWW, JDP, MW, OMP-N, CA, and AA provided comments on the study design and were responsible for data collection and quality control procedures. LS and CSA wrote the first draft of the manuscript. YS, SY, QH, BC, YuL, and EC read the imaging scans. LM, XH, QL, LB, CSA, CY, LS, XC, and JX had full access to all the study data and verified the data, and they had final responsibility for the decision to submit the paper for publication. All authors commented on drafts of the manuscript and approved the final manuscript for submission.

Declaration of interests

LS reports funding from the Medical Research Council of the UK, Sichuan Credit Pharmaceutical, and Takeda China; and speaker fees from Takeda China. CSA has received grants from the National Health and Medical Research Council and Medical Research Futures Fund of Australia, the Medical Research Council of the UK, Penumbra, and Takeda China; is also the chair of the data and safety monitoring boards for several trials; is a board member of WHO; and is the Editor-in-Chief of *Cerebrovascular Disease*. CY has received funding from West China Hospital. All other authors declare no competing interests.

Data sharing

Individual, de-identified participant data used in these analyses will be shared on request from any qualified investigator after the approval of a protocol and signed data access agreement via both the trial steering committee and the research office of The George Institute for Global Health (Sydney, NSW, Australia).

Acknowledgments

The study is supported by an award (grant reference number MR/T005009/1) jointly funded by the Department of Health and Social Care, the Foreign, Commonwealth & Development Office, the Medical Research Council, and the Wellcome Trust (all London, UK); the West China Hospital Outstanding Discipline Development 1–3–5 programme (number ZY2016102); National Health and Medical Research Council of Australia (number APP1149987); Sichuan Credit Pharmaceutical; and Takeda (China). We thank the independent members and patient representatives of the trial steering committee: Thompson Robinson (Chair, University of Leicester, Leicester, UK), J Jaime Miranda (Deputy Chair, Centro de Excelencia en Enfermedades Crónicas, Universidad Peruana Cayetano Heredia, Lima, Peru), Adrian Parry-Jones (University of Manchester, Manchester, UK), Nikola Sprigg (University of Nottingham, Nottingham, UK), Ann Bamford (Manchester, UK), Olivia Smith (Nottingham, UK), and Caroline Harris (Global Health Strategy, Medical Research Council, London, UK). We acknowledge the EuroQol Group for use of the EQ-5D-3L. CSA is a senior investigator fellow for the National Health and Medical Research Council of Australia. We thank the investigators and research staff at the participating sites of the various participating emergency departments, intensive care units, and stroke units, and neurosurgery and neurology departments (appendix pp 4–9), and executive staff at The George Institute for Global Health China for their support of the study. We also thank the participants, their relatives, and their families.

References

- 1 Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet* 2018; **392**: 1257–68.
- 2 GBD 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 Neuro* 2021; **20**: 795–820.
- 3 Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2022; **53**: e282–361.
- 4 Sandset EC, Anderson CS, Bath PM, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur Stroke J* 2021; **6**: II.
- 5 Stroke Foundation. Living Clinical Guidelines for Stroke Management. Chapter 3 Acute medical and surgical management. <https://informme.org.au/en/Guidelines/Living-Clinical-Guidelines-for-Stroke-Management> (accessed Jan 5, 2023).
- 6 Cao Y, Yu S, Zhang Q, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of intracerebral haemorrhage. *Stroke Vasc Neurol* 2020; **5**: 396–402.
- 7 Shoamanesh A, Lindsay MP, Castellucci LA, et al. Canadian stroke best practice recommendations: management of spontaneous intracerebral hemorrhage, 7th edition update 2020. *Int J Stroke* 2021; **16**: 321–41.

- 8 Moullaali TJ, Wang X, Martin RH, et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a pre-planned pooled analysis of individual participant data. *Lancet Neurol* 2019; **18**: 857–64.
- 9 Moullaali TJ, Wang X, Sandset EC, et al. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J Neurol Neurosurg Psychiatry* 2022; **93**: 6–13.
- 10 Zheng J, Li H, Lin S, et al. Perioperative antihypertensive treatment in patients with spontaneous intracerebral hemorrhage. *Stroke* 2017; **48**: 216–18.
- 11 Parry-Jones AR, Paley L, Bray BD, et al. Care-limiting decisions in acute stroke and association with survival: analyses of UK national quality register data. *Int J Stroke* 2016; **11**: 321–31.
- 12 Morgenstern LB, Zahuranec DB, Sánchez BN, et al. Full medical support for intracerebral hemorrhage. *Neurology* 2015; **84**: 1739–44.
- 13 The Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants, The Second HEADS Roundtable Participants. Recommendations for clinical trials in ICH: the second hemorrhagic stroke academia industry roundtable. *Stroke* 2020; **51**: 1333–38.
- 14 Broderick JP, Grotta JC, Naidech AM, et al. The story of intracerebral hemorrhage from recalcitrant to treatable disease. *Stroke* 2021; **52**: 1905–14.
- 15 Morotti A, Arba F, Boulouis G, Charidimou A. Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: a meta-analysis. *Neurology* 2020; **95**: 632–43.
- 16 Dammers R, Beck J, Volovici V, Anderson CS, Klijn CJM. Advancing the surgical treatment of intracerebral hemorrhage: study design and research directions. *World Neurosurg* 2022; **161**: 367–75.
- 17 Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011; **378**: 1699–706.
- 18 Parry-Jones AR, Sammut-Powell C, Paroutoglou K, et al. Intracerebral hemorrhage care bundle is associated with lower case fatality. *Ann Neurol* 2019; **86**: 495–503.
- 19 Song L, Wang X, Ouyang M, et al. Associations of an abnormal physiological score with outcomes in acute intracerebral hemorrhage: INTERACT2 study. *Stroke* 2021; **52**: 722–25.
- 20 Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* 2018; **363**: k1614.
- 21 Song L, Hu X, Ma L, et al. INTensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (INTERACT3): study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials* 2021; **22**: 943.
- 22 Billot L, Song L, Hu X, et al. Statistical analysis plan for the INTensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial: a stepped-wedge cluster randomized controlled trial. *Cerebrovasc Dis* 2022; published online Sept 5. <https://doi.org/10.1159/000526384>.
- 23 American Diabetes Association. Standards of medical care in diabetes—2015: summary of revisions. *Diabetes Care* 2015; **38** (suppl): S4.
- 24 Ouyang M, Anderson CS, Song L, et al. Implementing a goal-directed care bundle after acute intracerebral haemorrhage: process evaluation for the Third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage trial study in China. *Cerebrovasc Dis* 2022; **51**: 373–83.
- 25 Anderson CS, Arima H, Lavados P, et al. Cluster-randomised, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; **376**: 2437–47.
- 26 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.
- 27 Whitehead J. Sample size calculations for ordered categorical data. *Stat Med* 1993; **12**: 2257–71.
- 28 Woertman W, de Hoop E, Moerbeek M, Zuidema SU, Gerritsen DL, Teerenstra S. Stepped wedge designs could reduce the required sample size in cluster randomized trials. *J Clin Epidemiol* 2013; **66**: 752–58.
- 29 Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007; **28**: 182–91.
- 30 Kasza J, Bowden R, Hooper R, Forbes AB. The batched stepped wedge design: a design robust to delays in cluster recruitment. *Stat Med* 2022; **41**: 3627–41.
- 31 Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: an overview. *Stat Methods Med Res* 2021; **30**: 612–39.
- 32 Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. *Trials* 2017; **18**: 101.
- 33 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; **44**: 793–97.
- 34 Abdi H. Holm's sequential Bonferroni procedure. In: Salkind N, ed. *Encyclopedia of research design*. Thousand Oaks, CA: Sage, 2010, 574–89.
- 35 Pocock SJ, Rossello X, Owen R, Collier TJ, Stone GW, Rockhold FW. Primary and secondary outcome reporting in randomized trials: JACC state-of-the-art review. *J Am Coll Cardiol* 2021; **78**: 827–39.
- 36 Vousden N, Lawley E, Nathan HL, et al. Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic, stepped-wedge, cluster-randomised controlled trial. *Lancet Glob Health* 2019; **7**: e347–56.
- 37 Al-Shahi Salman R, Frantzas J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol* 2018; **17**: 885–94.
- 38 Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol* 2016; **15**: 566–73.
- 39 Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; **5**: 53–63.
- 40 Rom S, Zuluaga-Ramirez V, Gajghate S, et al. Hyperglycemia-driven neuroinflammation compromises BBB leading to memory loss in both diabetes mellitus (DM) type 1 and type 2 mouse models. *Mol Neurobiol* 2019; **56**: 1883–96.
- 41 Birg T, Ortolano F, Wieggers EJA, et al. Brain temperature influences intracranial pressure and cerebral perfusion pressure after traumatic brain injury: a CENTER-TBI study. *Neurocrit Care* 2021; **35**: 651–61.
- 42 Kearns KN, Ironside N, Park MS, et al. Neuroprotective therapies for spontaneous intracerebral hemorrhage. *Neurocrit Care* 2021; **35**: 862–86.
- 43 Williams LS, Bakas T, Brizendine E, et al. How valid are family proxy assessments of stroke patients' health-related quality of life? *Stroke* 2006; **37**: 2081–85.