



Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial

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Summary

Background There is much uncertainty about the effects of early lowering of elevated blood pressure (BP) after acute intracerebral haemorrhage (ICH). Our aim was to assess the safety and efficiency of this treatment, as a run-in phase to a larger trial.

Methods Patients who had acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated systolic BP (150–220 mm Hg), and no definite indication or contraindication to treatment were randomly assigned to early intensive lowering of BP (target systolic BP 140 mm Hg; n=203) or standard guideline-based management of BP (target systolic BP 180 mm Hg; n=201). The primary efficacy endpoint was proportional change in haematoma volume at 24 h; secondary efficacy outcomes included other measurements of haematoma volume. Safety and clinical outcomes were assessed for up to 90 days. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00226096.

Findings Baseline characteristics of patients were similar between groups, but mean haematoma volumes were smaller in the guideline group (12.7 mL, SD 11.6) than in the intensive group (14.2 mL, SD 14.5). From randomisation to 1 h, mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg, 95% CI 8.9–17.6 mm Hg; $p < 0.0001$); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg, 95% CI 7.7–13.9 mm Hg; $p < 0.0001$). Mean proportional haematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%, 95% CI 0.6–44.5%; $p = 0.04$) at 24 h. After adjustment for initial haematoma volume and time from onset to CT, median haematoma growth differed between the groups with $p = 0.06$; the absolute difference in volume between groups was 1.7 mL (95% CI -0.5 to 3.9, $p = 0.13$). Relative risk of haematoma growth $\geq 33\%$ or ≥ 12.5 mL was 36% lower (95% CI 0–59%, $p = 0.05$) in the intensive group than in the guideline group. The absolute risk reduction was 8% (95% CI -1.0 to 17%, $p = 0.05$). Intensive BP-lowering treatment did not alter the risks of adverse events or secondary clinical outcomes at 90 days.

Interpretation Early intensive BP-lowering treatment is clinically feasible, well tolerated, and seems to reduce haematoma growth in ICH. A large randomised trial is needed to define the effects on clinical outcomes across a broad range of patients with ICH.

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Introduction

Intracerebral haemorrhage (ICH) is estimated to affect over 1 million people worldwide each year,^{1,2} most of whom either die or are left seriously disabled.^{1–3} Early elevation of blood pressure is very common after ICH and is associated with poor outcome,^{4–10} and several non-randomised studies^{11–13} suggest that early lowering of blood pressure is beneficial in hypertensive patients with ICH. Clinical guidelines for the early management of blood pressure in ICH highlight the need for a definitive study, because recommendations are based primarily on expert opinion with no evidence from randomised trials to define either when treatment should be initiated or the extent to which blood pressure should be lowered.^{14–16} We report the results of the first phase of the intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT). This phase was done to establish the

feasibility of early intensive lowering of blood pressure in ICH and to define effects on haematoma growth and key safety parameters. We intended to follow this run-in phase with the main phase of INTERACT, with several thousand patients; however, the executive committee decided in February, 2007, to close the run-in study after follow-up of the required number of patients, which was completed in August, 2007, because recruitment of patients was more rapid than expected and the required number was enrolled before funding was secured for the main phase.

Methods

Participants

This investigator-initiated, multicentre, open, blinded outcome, randomised trial enrolled patients from 44 hospital sites in Australia, China, and South Korea.

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Eligible patients were at least 18 years of age, had spontaneous ICH confirmed by CT and elevated systolic blood pressure (≥ 2 measurements of 150–220 mm Hg, recorded ≥ 2 min apart), and were able to commence the randomly assigned treatment within 6 h of ICH onset in a suitably monitored environment. Patients were excluded for the following reasons: a clear indication for intensive lowering of blood pressure (eg, systolic blood pressure >220 mm Hg or hypertensive encephalopathy); a clear contraindication to intensive lowering of blood pressure (eg, severe cerebral artery stenosis or renal failure); clear evidence that the ICH was secondary to a structural cerebral abnormality (eg, arteriovenous malformation, intracranial aneurysm, or tumour) or the use of a thrombolytic agent; an ischaemic stroke within 30 days; a score of 3–5 on the Glasgow coma scale (GCS), indicating deep coma;¹⁷ significant prestroke disability or medical illness; or early planned decompressive neurosurgical intervention. Written informed consent was given by patients or by legal surrogates for patients who were unable to give consent themselves. The study protocol was approved by the appropriate ethics committee at each participating site.

Procedures

The trial was designed and coordinated, and the data gathered and analysed, by research staff at The George Institute for International Health. An executive committee of specialists in stroke, blood pressure, and cardiovascular disease from Australia, China, the UK,

and the USA finalised the protocol in consultation with other experts who formed national steering committees. An operations committee was responsible for all operational aspects of the trial, including the collection and storage of the data, quality control procedures, and the monitoring of sites. An independent data and safety monitoring committee periodically reviewed safety and efficacy data. All clinical sites were visited several times by trained staff to ensure adherence to the study protocol and to the International Conference on Harmonisation of Good Clinical Practice guidelines.

Patients were randomly assigned to receive either an early intensive strategy to lower blood pressure or the

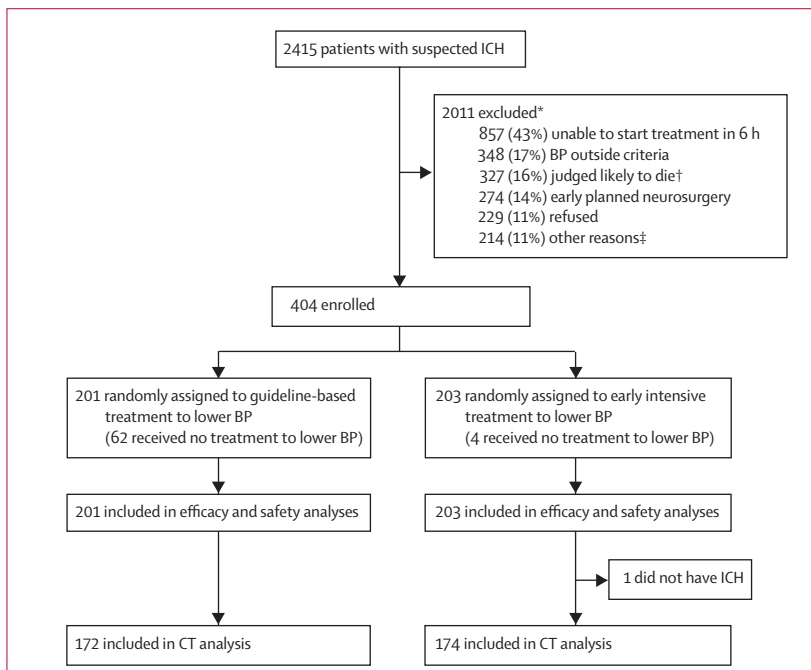


Figure 1: Trial profile

*Reasons for exclusion were not mutually exclusive. †Irrespective of treatment. ‡Including ICH secondary to brain abnormality, prestroke dementia or disability. BP=blood pressure.

	Guideline (n=201)	Intensive (n=203)
Median time from ICH onset to randomisation (h:min)	3:36 (2:54–4:54)	3:42 (2:54–4:48)
Age (years)	62 (13)	63 (12)
Male	139 (69%)	123 (61%)
Country of residence		
China	191 (95%)	193 (95%)
Australia	7 (3%)	6 (3%)
South Korea	3 (1%)	4 (2%)
Medical history*		
Hypertension	149 (74%)	151 (74%)
Previous ICH	19 (9%)	27 (13%)
Ischaemic stroke	24 (12%)	20 (10%)
Acute coronary event	7 (3%)	7 (3%)
Diabetes mellitus	13 (6%)	21 (10%)
Drug use*		
Antihypertensive therapy	90 (45%)	85 (42%)
Antiplatelet therapy	13 (6%)	19 (9%)
Warfarin anticoagulation	1 (0%)	3 (1%)
Clinical features		
Systolic blood pressure (mm Hg)	182 (19)	180 (18)
Diastolic blood pressure (mm Hg)	105 (15)	101 (14)
Heart rate (beats per min)	79 (15)	79 (14)
Median NIHSS score†	9 (5–16)	9 (5–14)
NIHSS score ≥ 14	64 (32%)	61 (30%)
Median GCS score‡	14 (12–15)	14 (13–15)
GCS score <9	16 (8%)	18 (9%)
Location of haematoma§		
Lobar	18 (10%)	15 (8%)
Basal ganglia or thalamus	148 (82%)	149 (83%)
Brainstem	11 (6%)	5 (3%)
Cerebellum	4 (2%)	10 (6%)
Undetermined	..	3 (2%)
Intraventricular extension	36 (21%)	45 (26%)

Data are n (%), mean (SD), or median (IQR). *Percentages do not total 100% because some patients had more than one other disorder and some were taking no relevant drugs at baseline. †NIHSS scores can range from 0 (healthy) to 42 (coma with quadriplegia). ‡GCS scores can range from 3 (deep coma) to 15 (healthy). §Data available for 181 (90%) patients in the guideline group and 179 (88%) patients in the intensive group.

Table 1: Baseline characteristics

recommended best practice standard to lower blood pressure at the time, the 1999 guidelines of the American Heart Association (AHA).¹⁵ Randomisation was done with minimisation through a password protected, internet-based system, with patients stratified according to country of residence and time from onset of ICH (<3 h vs ≥3 h).

For patients allocated to the intensive group, the goal was to achieve a systolic blood pressure of 140 mm Hg within 1 h of randomisation and to maintain this target blood pressure for the next 7 days or until discharge from hospital if this occurred earlier. In each country, a stepped intravenous protocol to lower blood pressure was established before the start of the study on the basis of which drugs were available in that country. The lower limit of systolic blood pressure needed for cessation of intravenous treatment was 130 mm Hg. For patients allocated to the guideline group, treatment was recommended to achieve a target systolic blood pressure of 180 mm Hg. In all other respects, both groups received the best practice standard of care for acute stroke. An oral treatment plan to lower blood pressure was provided in the study protocol, with continuation of antihypertensive therapy recommended for patients who had been taking such treatment before enrolment. The combination of a diuretic and an angiotensin converting enzyme (ACE) inhibitor was recommended to achieve a systolic blood pressure of 140 mm Hg after discharge from hospital for secondary stroke prevention.

CT scanning was done according to standardised techniques at baseline and at about 24 h and 72 h later in all surviving patients. For these analyses, only the 24 h CT scan was used to assess effects on haematoma growth; data from the later scan will be analysed for the effects on cerebral oedema and are not reported here. If the first CT scan was not done within 27 h, this assessment was replaced by the first available scan after 27 h or by the last available scan from between 6 h and 24 h if this was the only CT scan available (ie, the last observation was carried forward). For each patient, uncompressed digital images were sought by the analysis laboratory in DICOM format on a CD-ROM identified only with the patient's unique study number. Haematoma volumes with and without inclusion of any intraventricular component were calculated independently by two trained neurologists (BP and CS) who were blind to clinical data, treatment, and date and sequence of scan. This calculation was done with computer-assisted multislice planimetric and voxel threshold techniques in MISTar software (version 3.2).¹⁸ Inter-reader reliability was tested by reanalysis of 10% of CT scans by both readers after 30% and 60% of the scans were completed, to avoid drift (intraclass correlation coefficient 0.97, 95% CI 0.95–0.98). For the few CT scans received as digital images or plain films, haematoma volume was measured manually by the ABC/2 method.^{19,20}

Vital signs were measured by the attending clinician at enrolment, at initiation of treatment, every 15 min for the first hour, every 6 h for the rest of the first day, every 12 h for the next 6 days, and at 28 days and 90 days. Blood pressure was recorded in the non-paretic arm of

	Guideline (n=201)	Intensive (n=203)
Management of BP in first 24 h after ICH onset		
Median time from onset to IV treatment (h:min)*	4:40 (2:50–7:20)	4:00 (3:00–5:20)
Use of any BP-lowering agent	149 (74%)	199 (98%)
Use of any IV BP-lowering agent	87 (43%)	186 (92%)
Method of IV drug administration†		
Bolus	40 (20%)	107 (53%)
Infusion	55 (27%)	135 (67%)
Number of IV agents used		
1	68 (34%)	133 (66%)
2	17 (8%)	46 (23%)
≥3	2 (1%)	7 (3%)
Types of IV agents used‡		
Furosemide	44 (22%)	71 (35%)
Urapidil	36 (18%)	96 (47%)
Phentolamine	13 (6%)	33 (16%)
Glycerol trinitrate	3 (1%)	20 (10%)
Labetalol	5 (2%)	12 (6%)
Nicardipine	7 (3%)	11 (5%)
Hydralazine	0 (0%)	7 (3%)
Metoprolol	0 (0%)	2 (1%)
Topical nitrate patch	3 (1%)	6 (3%)
Oral drugs		
Calcium channel blocker	69 (34%)	83 (41%)
ACE inhibitor	59 (29%)	71 (35%)
Angiotensin II receptor antagonist	16 (8%)	10 (5%)
Diuretic	15 (7%)	14 (7%)
β blocker	7 (3%)	19 (9%)
Other	7 (3%)	8 (4%)
Background care from ICH onset to day 7		
IV fluids	196 (98%)	198 (98%)
IV mannitol	172 (86%)	165 (81%)
Fever treated	77 (38%)	73 (36%)
Nasogastric feeding	41 (20%)	41 (22%)
Intubation and ventilation	17 (9%)	14 (7%)
Neurosurgical intervention§	14 (8%)	15 (7%)
Fresh frozen plasma or vitamin K	10 (5%)	7 (3%)
rFVIIa	5 (2%)	13 (6%)¶
Data are n (%), mean (SD), or median (IQR). IV=intravenous. BP=blood pressure. ACE=angiotensin-converting enzyme. rFVIIa=recombinant activated factor VII. *Data for 83 (87%) patients in the guideline group and 124 (87%) patients in the intensive group who used IV agents in the first 24 h. †Not mutually exclusive; patients may have received both bolus and infusion. ‡Patients may have received multiple agents. §Evacuation or decompression of the haematoma, or insertion of an intraventricular drain. ¶All in China.		

Table 2: Management of patients

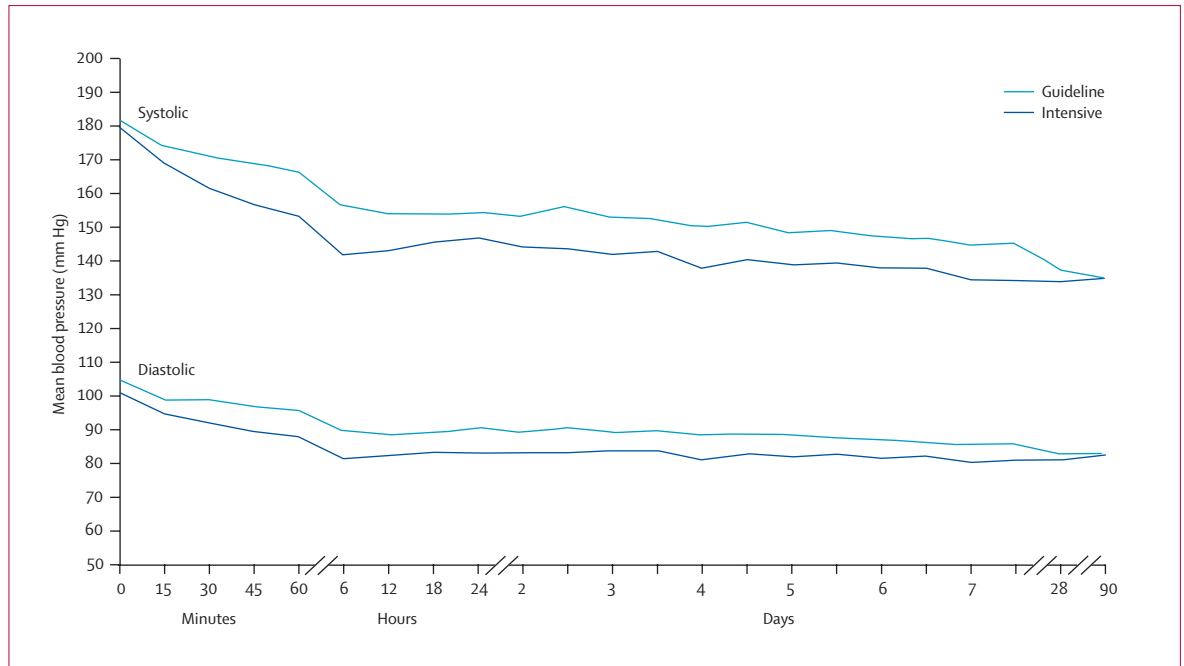


Figure 2: Mean systolic and diastolic blood pressure after randomisation

	Guideline (n=172)	Intensive (n=174)	Difference (95% CI)*	p
Haematoma				
Mean baseline volume (mL)	12.7 (11.6)	14.2 (14.5)
Mean volume at 24 h (mL)	15.4 (14.7)	15.2 (17.5)
Proportional increase (%)				
Mean (95% CI)	36.3% (15.8 to 56.8%)	13.7% (5.9 to 21.5%)	22.6% (0.6 to 44.5%)	0.04
Adjusted median (95% CI)†	16.2% (8.8 to 24.1%)	6.2% (-0.7 to 13.4%)	10.0% (0.0 to 20.5%)	0.06
Absolute increase (mL)				
Mean (95% CI)	2.7 (1.4 to 4.0)	0.9 (-0.9 to 2.7)	1.7 (-0.5 to 4.0)	0.12
Adjusted mean (95% CI)	2.6 (1.1 to 4.2)	0.9 (-0.6 to 2.5)	1.7 (-0.5 to 3.9)	0.13
Substantial growth‡	40 (23%)	26 (15%)	8% (-1.0 to 17.0%)§	0.05
Haematoma plus IVH				
Mean baseline volume (mL)	16.2 (16.1)	16.2 (17.1)
Mean volume at 24 h (mL)	19.2 (20.4)	17.6 (20.2)
Proportional increase (%)				
Mean (95% CI)	40.2% (17.6 to 62.8%)	17.3% (5.8 to 28.8%)	22.9% (-2.5 to 48.2%)	0.08
Adjusted median (95% CI)†	17.6% (10.1 to 25.5%)	7.6% (0.8 to 14.9%)	10.0% (0.0 to 20.8%)	0.06
Absolute increase (mL)				
Mean (95% CI)	3.1 (1.0 to 5.2)	1.4 (-0.4 to 3.2)	1.7 (-1.1 to 4.5)	0.23
Adjusted mean (95% CI)	3.1 (1.2 to 5.1)	1.3 (-0.6 to 3.3)	1.8 (-1.0 to 4.5)	0.21
Substantial growth‡	38 (22%)	26 (15%)	7% (-2.0 to 16.0)¶	0.07

Data are n (%) or mean (SD) except where indicated. Proportional and absolute changes were calculated by ANCOVA and substantial growth by logistic regression. 95% CI for the differences in adjusted medians were calculated using the bootstrap percentile method.²⁹ Adjustments were made for baseline volume of haematoma and time from onset of ICH to CT scan. IVH=intraventricular haemorrhage. Some increases and differences do not equal the differences between data presented here because of rounding to one decimal place. *Differences between groups. †Because of skewed raw data, adjusted medians are reported with 95% CI obtained by back-transformation. ‡An increase in haematoma volume of >33% or >12.5 mL during the first 24 h after ICH onset. §Relative risk reduction 36% (95% CI 0 to 59). ¶Relative risk reduction 32% (95% CI -6 to 57).

Table 3: Effects of early treatment to lower blood pressure on haematoma growth

the supine patient with an automated device. Heart rate and blood pressure were re-checked 5 min and 15 min after patients received an intravenous bolus of treatment to lower blood pressure. The number of occasions on which systolic blood pressure fell below 140 mm Hg and the minimum and maximum systolic blood pressure in the first 24 h were also recorded. Other clinical assessments were done at enrolment and at 24 h, 72 h, 7 days, 28 days, and 90 days after randomisation. These clinical assessments included the GCS,¹⁷ the National Institutes of Health Stroke Scale (NIHSS),²¹ the modified Rankin scale (mRS),²² the Barthel index,²³ the minimal state examination (MMSE),²⁴ and the EuroQol 5D for the calculation of an overall health utility score (EQ5D).²⁵ Assessments were done by investigators who were trained in the use of these scales; where possible, the 28 day and 90 day follow-up assessments were specifically undertaken by an investigator who was not involved in the acute care of the patient, to ensure that they were blind to treatment allocation.

The primary efficacy endpoint was the proportional change or growth in haematoma volume during the first 24 h after randomisation. Secondary efficacy outcomes were absolute and substantial growth of the haematoma and of the haematoma plus any intraventricular haemorrhage. Substantial growth was defined as an increase in volume of more than 33% or more than 12.5 mL in the first 24 h.^{19,20} The main clinical endpoint was the combination of death and dependency (defined by an mRS score of 3–5) at 90 days. The other clinical outcomes at this time were scores on the mRS, NIHSS, Barthel index, MMSE, and EQ5D.

Details of all serious adverse events until day 90 were recorded and reported to the data and safety monitoring committee, which did interim analyses after 184 and 350 patients were enrolled. For the safety analysis, the primary outcome was death from any cause and the secondary outcomes were early neurological deterioration (defined by a fall of ≥ 2 points on the GCS or a gain of ≥ 4 points in the NIHSS from baseline to 72 h), and total and cause-specific serious adverse events. A treatment-blinded endpoint adjudication committee reviewed all serious adverse events.

Statistical analysis

A target sample size of 400 patients was chosen to provide 80% power to detect a minimum absolute difference of 17% ($\geq 60\%$ reduction in relative risk) in proportional mean haematoma growth between the randomised groups, on the assumption that mean growth in the guideline group would be 30% (SD 60). The effects on proportional and absolute changes in haematoma volume were assessed by an analysis of covariance (ANCOVA), with baseline haematoma volume and time from ICH to CT included as covariates: these variables are strong predictors of haematoma growth and were included in primary analyses of the effects of recombinant activated factor VII (rFVIIa) in treatment of ICH.^{26–28} Relative change in haematoma volume was log-transformed to remove skew after addition of 1.1 to eliminate negative values, thus achieving a roughly normal distribution for these analyses. Difference between the treatment groups in substantial haematoma growth was ascertained with logistic regression and the same covariates. Differences in blood pressure were tested at specific timepoints with a *t* test. Binary endpoints such as death and dependency, early neurological deterioration, and serious adverse events were analysed with the χ^2 test; scores on the clinical scales were analysed with the Wilcoxon test. Heterogeneity of the treatment effect on the primary efficacy endpoint was assessed for six prespecified subgroups by addition of an interaction term to the models. Subgroups were based on age at randomisation (<65 vs ≥ 65 years), time from ICH to treatment (<3 vs ≥ 3 h), history of hypertension, systolic blood pressure and diastolic blood pressure (above vs below overall mean in both cases), and NIHSS at baseline (above vs below overall median). We used SAS statistical software (version 9.1) for analyses. This study is registered with ClinicalTrials.gov, number NCT00226096.

Role of the funding source

INTERACT was funded by a grant from the National Health and Medical Research Council of Australia. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study. The executive committee had final responsibility for the decision to submit for publication.

Results

Between November, 2005, and April, 2007, 2415 patients with suspected ICH were screened and 17% were randomly assigned to receive early intensive treatment or guideline-based treatment to lower blood pressure (figure 1). Baseline demographic and clinical characteristics and the median time from ICH onset to randomisation (about 3.5 h) were similar in the treatment groups (table 1). The proportion of patients who received any treatment to lower blood pressure in the first 24 h after ICH onset was lower in the guideline group (table 2), principally because of a greater use of intravenous agents in the intensive group. Intravenous agents were mainly given by infusion in 135 (67%) patients in the intensive group and 55 (27%) patients in the guideline group. Only 50 (20%) patients in the intensive group and 28 (14%) patients in the guideline group had their BP

	Guideline (n=201)	Intensive (n=203)	p*
Death or dependency†	95 (49%)	95 (48%)	0.81
Death	25 (13%)	21 (10%)	0.51
Dependency	70 (36%)	74 (37%)	0.98
Median mRS score‡	2 (1–4)	2 (1–4)	0.66
Median NIHSS score§	2 (1–5)	2 (1–5)	0.97
Median Barthel index score¶	95 (65–100)	95 (65–100)	0.77
Median MMSE score	28 (22–30)	27 (22–30)	0.97
Median EQ5D score**	0.78 (0.59–1.00)	0.75 (0.52–1.00)	0.97
Early neurological deterioration††	30 (15%)	31 (15%)	0.94
Patients with a serious adverse event	42 (21%)	42 (21%)	0.96
Numbers of serious adverse events	61 (30%)	54 (27%)	0.40
Recurrent stroke‡‡	3 (2%)	2 (1%)	..
Acute coronary event	0 (0%)	1 (0%)	..
Other vascular events	3 (1%)	2 (1%)	..
Neurological deterioration§§	28 (14%)	23 (11%)	..
Renal failure	2 (1%)	4 (2%)	..
Non-vascular events	21 (10%)	17 (8%)	..
Pneumonia	15 (7%)	11 (5%)	..
Sepsis	2 (1%)	1 (0%)	..
Fracture	1 (0%)	0 (0%)	..
Other non-vascular events	3 (1%)	5 (2%)	..
Hypotension	4 (2%)	5 (3%)	..
Mild hypotension¶¶	0 (0%)	2 (1%)	..
Severe hypotension	4 (2%)	3 (1%)	..

Data are n (%) or median (IQR). *Based on a χ^2 or Wilcoxon test, as appropriate. †Dependency in survivors at 90 days, defined as an mRS score of 3–5. Percentages calculated with exclusion of patients for whom data were not available (seven in the guideline group and four in the intensive group). Death percentages were calculated with the exclusion of one patient from each group, due to lost to follow-up. ‡mRS scores can range from 1 (no residual symptoms) to 5 (total dependency). §NIHSS scores can range from 0 (healthy) to 42 (coma with quadriplegia). ¶Barthel index scores can range from 0 (complete dependence) to 100 (independence). ||MMSE scores can range from 0 (severe cognitive dysfunction) to 30 (normal cognitive function). **EQ5D scores can range from 0 (worst imaginable health state) to 1 (best imaginable health state). ††A reduction from baseline of ≥ 2 points on the GCS or an increase of ≥ 4 points on the NIHSS during the first 72 h. ‡‡Evidence of a definite ischaemic or new haemorrhagic lesion on CT or, in the absence of a new lesion on CT, from clinical findings consistent with the occurrence of stroke, >24 h after onset of initial symptoms. §§From any cause at any time by day 90. ¶¶Symptomatic hypotension that required only cessation of intravenous treatment. ||||Symptomatic hypotension that required active intervention (eg, use of intravenous fluids, inotrope, or both).

Table 4: Clinical outcomes and serious adverse events at day 90

However, in a post-hoc analysis of 210 patients randomised up to 4 h from ICH onset, substantial haematoma growth was significantly less common in the intensive group (17 [15%] of 110 patients) than the guideline group (30 [30%] of 100 patients) (relative risk reduction 52%, 95% CI 30–88%), and there was a 3.36 mL absolute difference (95% CI 0.3–6.4%) in haematoma volume between groups.

Discussion

In this trial of patients who presented early after the onset of ICH, a management strategy of rapid lowering of blood pressure was applied in routine clinical practice with reasonable efficiency and with careful safety monitoring of patients. Additionally, this treatment seems to attenuate the growth of ICH when compared with a more conservative policy of blood pressure management that was based on a widely used guideline. Because haematoma growth is a strong predictor of morbidity and mortality in ICH,^{26,30} these results provide potentially important new information about possible benefits of rapid physiological control of elevated blood pressure. By contrast with use of rFVIIa,^{26,27} in which any potential clinical benefit derived from effects on haematoma growth might be offset by increased risk of thromboembolism, early intensive lowering of blood pressure holds promise as an intervention without major hazard.

Before this stage of INTERACT was completed, there were few reliable data about the effects of lowering of blood pressure in the acute phase of ICH, as is evident in the similarity between the 1999 and 2007 versions of the AHA guidelines.³¹ In particular, the possibility that early lowering of blood pressure might induce cerebral ischaemia in critically perfused or hypometabolic regions of the brain adjacent to the haematoma has been a major concern,³² although imaging studies have failed to identify any such adverse effect or any significant rim of hypoperfusion in ICH.^{33,34} The results of INTERACT, in conjunction with other recent data,^{35,36} now provide substantial reassurance that early intensive lowering of blood pressure does not seem to be associated with serious harm in these patients. In our trial, most patients had large falls in blood pressure over just a few hours with vigorous use of intravenous drug infusions, with no clear adverse effects on a broad range of clinical outcomes.

Some characteristics and outcomes of the patients in INTERACT are different to those enrolled in other recent trials in acute ICH.^{26–28,37} Although several measures of neurological disability show that the average severity of ICH in INTERACT participants was mild and similar to that in other trials,^{26–28,37} patients in INTERACT had a much lower 90-day fatality rate (10–13%) than did patients in previous studies (20–30%),^{26–28,37} possibly because the haemorrhages were generally smaller at presentation (<20 mL) and located in deeper areas of the brain in INTERACT. These characteristics of ICH might reflect

the predominantly Chinese ethnic origin of the participants. Although different ethnic origin might be associated with slightly different causes and outcomes for ICH,³⁸ demographic features and medical history were otherwise similar to those in other studies, and we have no reason to believe that the findings of INTERACT would not be generally applicable.^{26–28,37}

The mean absolute difference in haematoma volume between the intensive and guideline groups at 24 h (1.7 mL) was much smaller than that between the treated and control groups in a trial of the potent haemostatic agent rFVIIa (about 4 mL).^{27,28} However, the trials of rFVIIa tested that agent within 4 h of onset of ICH, and earlier initiation of treatment to lower blood pressure might produce greater effects on ICH growth. Although we identified no significant interaction between time to treatment and efficacy, the power to show such an interaction was limited by the small sample size, and observational studies show that most haematoma growth occurs soon after stroke onset.^{26,30} The absolute differences in haematoma volume between the treatment groups might also have been smaller than in the rFVIIa trials because the mean baseline volume was smaller in INTERACT. Finally, because many patients in the guideline group in INTERACT received therapy to lower blood pressure, the results almost certainly underestimate the effects of early intensive therapy on haematoma volume in patients with ICH.

The risk that biases were introduced by the unblinded administration of intervention was kept to a minimum by documentation of use of ancillary post-randomisation treatments, assessment of the haematoma outcomes in a standardised masked way, measurement of clinical outcomes with established objective scales, and adjudication of serious adverse events by a central, blinded committee.

Our pragmatic approach to this trial design enabled the recruitment of a broad range of patients with ICH from diverse settings in developed and developing regions in which there is a high burden of ICH. We used prespecified protocols to standardise approaches to lowering of blood pressure but the possibility remains that the different agents used (with variable efficacy and side-effect profiles) might have had different effects on outcomes. For this strategy to be widely implemented, we will need to confirm the beneficial effects on haematoma growth in a larger study with greater power to explore different aspects of the intervention strategy, and particularly to define the effects on clinically meaningful outcomes such as death and disability. Although early use of rFVIIa is associated with a significant reduction in haematoma growth,^{27,28} no effect on the primary endpoint of death or severe disability was recorded in a recently completed phase III trial in several hundred patients with ICH, possibly partly because any effect could have been offset by the adverse effects of rFVIIa.²⁸ Analysis of available data suggests a 7% increased risk of death or disability

for each 1 mL growth in haematoma.²⁶ Therefore, the 1.7 mL less growth of haematoma in our trial of intensive lowering of blood pressure would be expected to translate into a 12% reduction in relative risk of a poor outcome in ICH.

Because intravenous treatment to lower blood pressure is relatively straightforward, is not hazardous, and is of low cost, if applied widely these effects could translate into major absolute benefits. These data provide the basis for us to proceed in 2008 with a new trial, INTERACT2, to determine the effects of the treatment on clinical outcomes in 2800 patients with ICH.

Contributors

CSA, YH, JGW, HA, BN, LBM, and JC contributed to the concept and rationale for the study. CSA, BP, EH, CS, MWP, and SH contributed to data analyses. CSA, HA, BN, EH, MWP, SH, LBM, and JC contributed to the interpretation of the results. All authors participated in the drafting and approval of the final manuscript and take responsibility for the content and integrity of this Article.

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Conflicts of interest

CSA reports receipt of consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi-Aventis, and Servier. JGW reports receipt of consultancy and lecture fees from Bayer, Omron, Pfizer, Sanofi-Aventis, and Takeda, and grants from Mitsubishi-Tanabe via the Shanghai Institute of Hypertension. YH reports receipt of consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Sanofi-Aventis. BN reports receipt of lecture fees from Servier. MWP reports receipt of lecture fees from Boehringer Ingelheim, Sanofi Aventis, and Pfizer. JBM reports receipt of consultancy and lecture fees from AstraZeneca, Merck, and Novo Nordisk. JC reports receipt of lecture fees and research grants administered through the University of Sydney from Servier as co-principal investigator for Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and Action in Diabetes and Vascular Disease (ADVANCE). Automated blood pressure monitors used in Chinese hospitals were donated by Omron (Dalian, China). No other potential conflict of interest relevant to this article was reported.

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