



Effects of blood pressure lowering in relation to time in acute intracerebral haemorrhage: a pooled analysis of the four INTERACT trials

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Summary

Background Uncertainty remains about the effects of intensive blood pressure (BP) lowering in acute intracerebral haemorrhage, particularly the impact of treatment timing. This study aimed to assess the safety and effectiveness of early intensive BP-lowering treatment and its dependence on timing in patients with intracerebral haemorrhage.

Methods We undertook an individual patient-data pooled analysis of the four Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials: INTERACT1 (n=404), INTERACT2 (n=2829), INTERACT3 (n=7036), and INTERACT4 (n=1043). INTERACT1–3 included adults with acute intracerebral haemorrhage who presented within 6 h of the onset of symptoms and had an elevated systolic BP (>150 mm Hg). INTERACT4 included patients with suspected acute stroke that caused a motor deficit and an elevated systolic BP (≥150 mm Hg) within 2 h after the onset of symptoms, among whom 1029 had a haemorrhagic form of stroke. Patients were randomly assigned to receive intensive (target systolic BP <140 mm Hg within 1 h) or guideline-recommended (target systolic BP <180 mm Hg within 1 h) BP-lowering treatment using locally available drugs. The primary outcome was functional recovery, defined by the distribution of scores on the modified Rankin scale (mRS). In a CT substudy, radiological outcomes were relative (≥33%) and absolute (≥6 mL) changes in haematoma volume from baseline to 24 h. The treatment effects were determined in logistic regression models adjusting for trial and baseline haematoma volume. Heterogeneity in the effects across groups by time from onset to randomisation (continuous) and baseline severity according to the intracerebral haemorrhage score were assessed by adding interaction terms to the models. These trials are registered at ClinicalTrials.gov (INTERACT1 NCT00226096; INTERACT2 NCT00716079; INTERACT3 NCT03209258; INTERACT4 NCT03790800). This pooled analysis is registered with PROSPERO (CRD420251001539).

Findings Among 11312 patients (mean age 63 years [SD 12·7], 4066 [35·9%] female and 7246 [64·1%] male), the median time from the onset of symptoms to randomisation was 2·9 h (IQR 1·8–4·1). At 1 h, the mean systolic BP was 149·6 mm Hg (SD 21·8) in the intensive treatment group and 158·8 mm Hg (22·8) in the guideline group (difference 9·13 mm Hg, 95% CI 8·28–10·00; $p < 0·0001$). Intensive BP-lowering treatment significantly decreased the chances of poor physical function (mRS scores of 3–6; odds ratio [OR] 0·85, 95% CI 0·78–0·91). Compared with guideline treatment, intensive BP-lowering treatment significantly reduced odds of neurological deterioration within 7 days (OR 0·76, 95% CI 0·66–0·88; $p = 0·0002$), death (0·83, 0·75–0·94; $p = 0·002$), and any serious adverse event (0·84, 0·76–0·92; $p = 0·0003$). In the CT substudy involving 2921 patients, there was no apparent effect of intensive treatment on relative (0·85, 0·70–1·03; $p = 0·09$) or absolute (0·84, 0·68–1·04; $p = 0·12$) haematoma growth compared with guidelines treatment. In the same substudy, the treatment effects on functional recovery and relative haematoma growth decreased with increasing time from onset to randomisation, with a cutoff point in the effect crossing unity at 3 h ($p = 0·002$ and $p = 0·01$ for interaction, respectively).

Interpretation Intensive BP-lowering initiated within several hours of intracerebral haemorrhage onset was safe and improved functional recovery, without a clear effect on haematoma growth. The greatest benefits for both outcomes occurred when treatment was commenced within 3 h of symptom onset. These findings underscore the importance of early intervention and inform the design of future trials targeting patients at highest risk of haematoma expansion.

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Introduction

Blood pressure (BP) is commonly elevated after the onset of spontaneous intracerebral haemorrhage, and it independently predicts a range of adverse outcomes from this common and serious condition.^{1,2} However, until recently, randomised trials^{3–5} have been unable to clearly demonstrate that early intensive BP-lowering treatment improves the chances of recovery from intracerebral haemorrhage. The first two international multicentre randomised trials of intensive BP-lowering treatment—the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2)³ and the second Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH-II)⁴—produced conflicting results in findings

with a borderline significant (INTERACT2) and null effect (ATACH-II) on functional outcome. A follow-up meta-analysis of patient-level data from a broad range of randomised trials, including INTERACT2 and ATACH-II, further indicated only a modest effect of early intensive BP-lowering treatment on the reduction of haematoma growth and no effect on functional recovery.⁵

According to a large pooled analysis of multiple different prospective studies, the likelihood of haematoma growth is greatest within the first few hours after the onset of intracerebral haemorrhage.⁶ Post-hoc analysis of ATACH-II suggests that the benefits of intensive BP-lowering treatment could be greatest when initiated within 2 h of the onset of symptoms.⁷ Attenuation of haematoma growth is the most plausible

Research in context

Evidence before this study

We searched Medline and Embase from inception to Jan 11, 2025, with the relevant text words and medical subject headings in any language that included “intracerebral haemorrhage” and “blood pressure”. Studies were eligible for inclusion if they assessed the effects of blood pressure (BP) lowering in relation to time in acute intracerebral haemorrhage. We identified no studies of a similar design to ours in assessing the effects of BP lowering regarding the timing of treatment initiation in acute intracerebral haemorrhage. Meta-analyses of aggregate data from randomised controlled trials have concluded that early intensive BP-lowering treatment does not significantly reduce death or disability in adults with acute spontaneous intracerebral haemorrhage. However, the treatment is feasible, safe, and has a modest effect in reducing haematoma growth, which is considered the most plausible mechanism through which BP lowering could improve outcomes in acute intracerebral haemorrhage. The neutral results observed in these trials might be attributed to the overall median time from symptom onset to randomisation being about 3–8 h and the inclusion of many patients at low risk of haematoma expansion, which might have diluted the potential benefits of intensive BP lowering. Most recently, the fourth Intensive Ambulance-Delivered Blood Pressure Reduction in Hyperacute Stroke Trial (INTERACT4) demonstrated that initiating BP-lowering treatment within 2 h of the onset of symptoms in the pre-hospital setting improved outcomes in patients with intracerebral haemorrhage. Furthermore, evidence highlights the importance of not only achieving rapid BP reduction soon after intracerebral haemorrhage but also ensuring smooth and sustained BP control over several days to maximise potential benefits. However, uncertainty remains regarding the optimal timing for treatment initiation, warranting further investigation to refine clinical strategies and improve patient outcomes.

Added value of this study

In this pooled analysis of the four INTERACT trials in acute intracerebral haemorrhage, early intensive BP-lowering treatment compared with the more conservative level of BP control recommended in guidelines at the time reduced haematoma growth and improved functional recovery when treatment was initiated within 3 h. This finding underscores the highly time-sensitive nature of treatment of intracerebral haemorrhage, which is similar to the use of reperfusion therapy for acute ischaemic stroke. Since haematoma growth generally occurs within the first few hours after the onset of intracerebral haemorrhage, any delay in achieving the target for BP control diminishes the potential benefits to improving the functional recovery of patients.

Implications of all the available evidence

Our pooled individual patient data analysis of four randomised trials indicates that initiating BP-lowering treatment within the first 3 h after onset of intracerebral haemorrhage reduces the likelihood of haematoma growth and improves functional recovery. Importantly, the earlier treatment is initiated, the greater the reduction in haematoma expansion, with a critical threshold of 3 h identified for maximum benefit. These findings emphasise the need for rapid BP control following intracerebral haemorrhage. While early and aggressive BP reduction is crucial in the acute phase, maintaining smooth and consistent BP management over the following days is equally important. This insight can inform future clinical trials by guiding the selection of participants at high risk of haematoma expansion, ensuring that interventions are targeted at those most likely to benefit from early treatment, ultimately improving outcomes for patients with intracerebral haemorrhage.

mechanism by which BP lowering can improve outcome after acute intracerebral haemorrhage.^{8–10} Thus, the neutral results of trials might be explained by the delay in the initiation of treatment (overall median time from the onset of symptoms to randomisation of 3·8 h),⁵ which, in turn, could have resulted in the inclusion of many patients at low risk of haematoma expansion, and thus could have diluted the potential benefits of intensive BP lowering treatment. Most recently, the fourth Intensive Ambulance-Delivered BP Reduction in Hyperacute Stroke Trial (INTERACT4) showed that the initiation of BP-lowering treatment within 2 h of the onset of symptoms in the pre-hospital ambulance setting improved outcomes in participants with intracerebral haemorrhage.

The four INTERACT studies^{3,11–13} were all randomised controlled trials that investigated the effects of BP lowering according to consistent treatment protocols in patients with acute intracerebral haemorrhage. Herein, we present a detailed analysis of the treatment effects on functional outcome, haematoma growth, and safety, focusing on the timing of initiation and baseline severity of neurological impairment.

Methods

Study design and participants

The INTERACT1¹¹ and INTERACT2³ studies, and the third Intensive Care Bundle with BP Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3),¹² were international, multicentre, open-label, blinded-endpoint, randomised controlled trials that included adults with acute intracerebral haemorrhage who presented within 6 h of the onset of symptoms and had an elevated systolic BP (>150 mm Hg). Patients were allocated to receive intensive (target systolic BP <140 mm Hg within 1 h) or guideline-recommended (target systolic BP <180 mm Hg within 1 h) BP-lowering treatment. In brief, INTERACT1 recruited 404 participants from hospitals in Australia, China, and South Korea in 2005–07, and INTERACT2 recruited 2829 participants from hospitals in 21 countries in 2008–12. INTERACT3¹² used a multicentre, stepped wedge, cluster randomised controlled trial design that incorporated early intensive BP-lowering treatment as part of a care bundle of protocols being implemented in 7036 patients at 121 hospitals in nine low-income and middle-income countries and one high-income country. Finally, INTERACT4¹³ was an open-label, blinded-endpoint, randomised controlled trial conducted in 51 hospitals in China, which included 2404 adult patients with suspected acute stroke that caused a motor deficit and an elevated systolic BP (\geq 150 mm Hg) within 2 h after the onset of symptoms. Of these participants, 1043 had a haemorrhagic form of stroke and were randomly assigned in the ambulance to receive either immediate BP-lowering treatment (target systolic BP 130–140 mm Hg within 30 min) or usual BP management (usual care upon arrival at hospital).^{14–16}

In selected centres with CT perfusion capability, a CT substudy was conducted. Brain CT scans were undertaken according to standardised techniques at baseline and at 24 h after randomisation, as per the usual standard of practice. In INTERACT1 and INTERACT4, all enrolled patients underwent a repeat brain CT scan at 24 h after randomisation. In INTERACT2, the effect of treatment on haematoma expansion was assessed at 24 h in a subsample of patients using a prespecified protocol similar to that used in INTERACT1; sites that wished to participate in this substudy were identified before they were started recruiting patients. In INTERACT3, the first ten patients at each site were required to undergo a repeat scan at 24 h. For each participant, uncompressed digital images were sought for central analysis in Digital Imaging and Communications in Medicine (DICOM) format on a CD-ROM identified only with the patient's unique study number. Haematoma volumes with and without the inclusion of any intraventricular component were calculated independently by two trained neurologists at The George Institute for Global Health who were masked 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).¹⁷ The radiological outcomes related to haematoma growth were only available in the CT substudy.

The trials are registered at ClinicalTrials.gov, NCT00226096 (INTERACT1), NCT00716079 (INTERACT2), NCT03209258 (INTERACT3), and NCT03790800 (INTERACT4). The studies complied with the Declaration of Helsinki, the ethics committee at each site approved the research protocol, and written informed consent was obtained from all participants or relevant surrogates. This pooled analysis is registered with PROSPERO (CRD420251001539) and the protocol is available online.

Exposure measures

BP was measured in the non-paretic arm in a supine position using either an automated device or a manual sphygmomanometer with an appropriately sized cuff. Baseline BP was measured twice at 2 min intervals, and the mean of the two measurements was used. For INTERACT1, INTERACT2, and INTERACT3, BP was measured at 15 min, 30 min, 45 min, 1 h, 6 h, 12 h, 18 h, and 24 h after randomisation. For INTERACT4, patients had their BP monitored every 5 min for the first 30 min after randomisation and then every 15 min until 60 min while in the ambulance during transport. After arrival at the receiving hospital, BP was measured at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h, 18 h, and 24 h after hospital admission. We assumed there was a 10 min transfer time from the ambulance to the hospital emergency centre in INTERACT4 to allow a pooling of the BP measurements in the ambulance and hospital for a continuous measure of time from randomisation.

For the study protocol see <https://www.crd.york.ac.uk/PROSPERO/PROSPEROFILES/b975a8ff3791bb52fa69a113000e3e81.pdf>

Outcomes

The primary outcome was physical function according to the distribution of scores on the seven levels of the modified Rankin scale (mRS) at the end of follow-up—90 days in INTERACT1, INTERACT2 and INTERACT4, and 180 days in INTERACT3 after randomisation. Safety outcomes were neurological deterioration; treatment-related symptomatic hypotension requiring corrective therapy within 24 h; and any fatal or non-fatal, cardiac, or renal serious adverse events, according to standard MedRA definitions, within 90 days. Neurological deterioration was defined as an increase from baseline of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS) over 7 days. This definition was

modified from the original definition in the study protocol, which also included a decrease from baseline of ≥ 2 points on the Glasgow Coma Scale (GCS), since INTERACT3 did not collect data for GCS at day 7. The primary and safety outcomes were assessed in the INTERACT full cohort.

The radiological outcomes, which were assessed in the CT substudy, were absolute (continuous and ≥ 6 mL) and proportional ($\geq 33\%$) haematoma growth between the baseline and 24 h CT scans. In INTERACT4, however, the baseline measure of haematoma volume was on the diagnostic CT scan performed on arrival at hospital; as the median time from randomisation to arrival at hospital was 58 min (IQR 40–86), haematoma growth was assumed to be at 25 h post randomisation.

Statistical analysis

We estimated the effects of randomised BP-lowering treatment on physical functional recovery using proportional odds regression models, and the effects on haematoma growth using logistic regression models. The models were adjusted for trial, baseline haematoma volume, and a trial-by-treatment interaction in the event of heterogeneity of treatment effect across trials. We first assessed the significance of the regression coefficient for the trial-by-treatment interaction effects and, if not significant, we ran the reduced model without the interaction term. We did a sensitivity analysis by further adjusting for the baseline severity of neurological impairment on the NIHSS (scores <21 vs ≥ 21). For all analyses involving the primary outcome of functional status, the ordinal shift in the distribution of mRS scores was first tested for the proportional odds assumption. If this assumption was violated, we planned to use the alternative binary cutoff measure of mRS scores 3–6. Number needed to treat (NNT) was estimated based on the use of proportions of patients with the outcome (ie, π_0 , the risk in the control group and π_1 , the risk in treatment group), according to formula: $NNT=1/(\pi_1-\pi_0)$.¹⁸ We ascertained the heterogeneity in the effects across groups by time according to the time from the onset of symptoms to randomisation (continuous) and to overall baseline severity of the illness according to the intracerebral haemorrhage score (ICH score; 0, 1, 2, and 3–5 for increasing severity)¹⁹ by adding interaction terms to the models. The ICH score is a clinical tool used to predict mortality and severity in patients with intracerebral haemorrhage. The score ranges from 0 to 6, based on scores on the Glasgow coma scale (GCS; categories 3–4, 5–12, and 15), haematoma volume (<30 vs ≥ 30 cm³), any intraventricular haemorrhage, infratentorial origin, and age (<80 vs ≥ 80 years), with higher scores indicating worse prognosis. We initially tested for potential non-linearity by incorporating a log transformation, squared (X^2), or cubed (X^3) term of time from onset to randomisation into the regression model, but the model performed best when time was included in its original

	All (n=11 312)	Intensive BP- lowering treatment (n=5345)	Guideline treatment (n=5967)
Median time from onset to randomisation, h	2.9 (1.8–4.1)	2.9 (1.8–4.0)	3.0 (1.8–4.1)
Mean age, years	63 (12.7)	62 (12.7)	63 (12.7)
Sex			
Female	4066/11 312 (35.9%)	1916/5345 (35.8%)	2150/5967 (36.0%)
Male	7246/11 312 (64.1%)	3429/5345 (64.2%)	3817/5967 (64.0%)
Region			
China	9814/11310 (86.8%)	4550/5345 (85.1%)	5264/5965 (88.2%)
India	766/11310 (6.8%)	378/5345 (7.1%)	388/5965 (6.5%)
South America	175/11310 (1.5%)	105/5345 (2.0%)	70/5965 (1.2%)
North America/Europe/Australia	555/11310 (4.9%)	312/5345 (5.8%)	243/5965 (4.1%)
Mean systolic BP, mm Hg	176.9 (25.3)	176.9 (24.9)	176.9 (25.6)
Mean diastolic BP, mm Hg	100.3 (16.9)	100.6 (16.7)	100.2 (17.0)
Median NIHSS score*	12.0 (7.0–20.0)	12.0 (7.0–20.0)	12.0 (7.0–20.0)
Median GCS score†	13.0 (10.0–15.0)	13.0 (10.0–15.0)	13.0 (10.0–15.0)
History of hypertension	8013/11 308 (70.9%)	3762/5344 (70.4%)	4251/5964 (71.3%)
Current use of antihypertensive drugs	4658/11 304 (41.2%)	2249/5342 (42.1%)	2409/5962 (40.4%)
Previous intracerebral haemorrhage	884/11 308 (7.8%)	417/5344 (7.8%)	467/5964 (7.8%)
Previous ischaemic stroke	976/11 308 (8.6%)	441/5344 (8.3%)	535/5964 (9.0%)
Diabetes	1185/11 308 (10.5%)	569/5344 (10.6%)	616/5964 (10.3%)
Use of warfarin anticoagulation	246/11 302 (2.2%)	125/5340 (2.3%)	121/5962 (2.0%)
Use of aspirin or other antiplatelet drug	715/11 305 (6.3%)	306/5342 (5.7%)	409/5963 (6.9%)
Haematoma location			
Cortical	779/5089 (15.3%)	370/2511 (14.7%)	409/2578 (15.9%)
Deep‡	4000/5089 (78.6%)	1996/2511 (79.5%)	2004/2578 (77.7%)
Brainstem, cerebellar, or primary ventricular	310/5089 (6.1%)	145/2511 (5.8%)	165/2578 (6.4%)
Median haematoma volume	11.9 (5.9–23.4)	11.6 (5.9–22.3)	12.1 (5.9–24.4)
Intraventricular extension of haemorrhage	1604/5164 (31.1%)	794/2556 (31.1%)	810/2608 (31.1%)
Median intraventricular haematoma volume, mL	7.9 (2.8–16.4)	7.8 (2.5–16.5)	7.9 (3.1–16.3)
Median perihematoma oedema volume, mL	4.0 (1.6–9.5)	3.8 (1.5–9.2)	4.2 (1.8–9.9)

Data are n (%), mean (SD), or median (IQR). BP=blood pressure. GCS=Glasgow coma scale. NIHSS=National Institutes of Health stroke scale. *Scores range from 0 (normal) to 42 (coma with quadriplegia). †Scores range from 15 (normal) to 3 (deep coma). ‡Location in the basal ganglia or thalamus.

Table 1: Baseline characteristics of participants by randomised treatment

form, as indicated by the lowest Akaike Information Criterion. Thus, we assumed a linear effect of time from the onset of intracerebral haemorrhage to randomisation in analyses. Analyses were performed according to the modified principle of intention-to-treat in patients with available outcome data. Two-sided *p* values are reported with a value lower than 0.05 being considered statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used in all analyses.

Role of the funding source

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

Results

Pooled INTERACT cohort

Overall, 11 312 participants (mean age 63 years [12.7]; 4066 [35.9%] female and 7246 [64.1%] male) were included in these analyses, of whom 5345 (47.3%) were assigned to receive early intensive BP-lowering treatment and 5967 (52.7%) to receive guideline-recommended treatment (table 1; figure 1; appendix 2 p 11). The baseline characteristics were balanced between the two randomised groups, except for region and use of aspirin or other antiplatelet drugs (table 1). The median time from the onset of intracerebral haemorrhage to randomisation was similar between the intensive treatment group (2.9 h, IQR 1.8–4.0) and the guideline group (3.0 h, 1.8–4.1; *p*=0.84). The mean systolic BP differed significantly between the two groups at all timepoints from 15 min to 24 h after randomisation (appendix 2 p 12). At 1 h, the mean systolic BP was 149.6 mm Hg (SD 21.8) in the intensive treatment group (with 1797 [35.2%] of 5102 patients achieving the target BP of <140 mm Hg) compared with 158.8 mm Hg (22.8) in the guideline group (with 4320 [82.3%] of 5247 patients achieving a target BP of <180 mm Hg). The mean difference in systolic BP between the two groups at 1 h after randomisation was 9.13 mm Hg (95% CI 8.28–10.00; *p*<0.0001). The mean difference in systolic BP between the two groups in the first 24 h was 5.60 mm Hg (95% CI 5.30–5.90; *p*<0.0001).

The odds of having a poor physical functional recovery, measured by achieving an mRS score of 3–6, at the end of follow-up were significantly reduced in patients receiving intensive BP-lowering treatment (2726 [54.7%] of 4988) compared with guideline treatment (3209 [58.6%] of 5478; figure 2; *p*=0.003 for proportional odds assumption, justifying use of a binary outcome; odds ratio [OR] 0.85, 95% CI 0.78–0.91, *p*<0.0001, when model adjusted for trial; OR 0.83, 0.77–0.91, *p*<0.0001 when adjusted for trial and NIHSS). The absolute risk reduction between the randomised treatment groups was 3.9% (95% CI 2.00–5.80). The corresponding number needed to treat was 25.5 (95% CI 17.20–49.30), indicating that for every 25.5 patients managed with

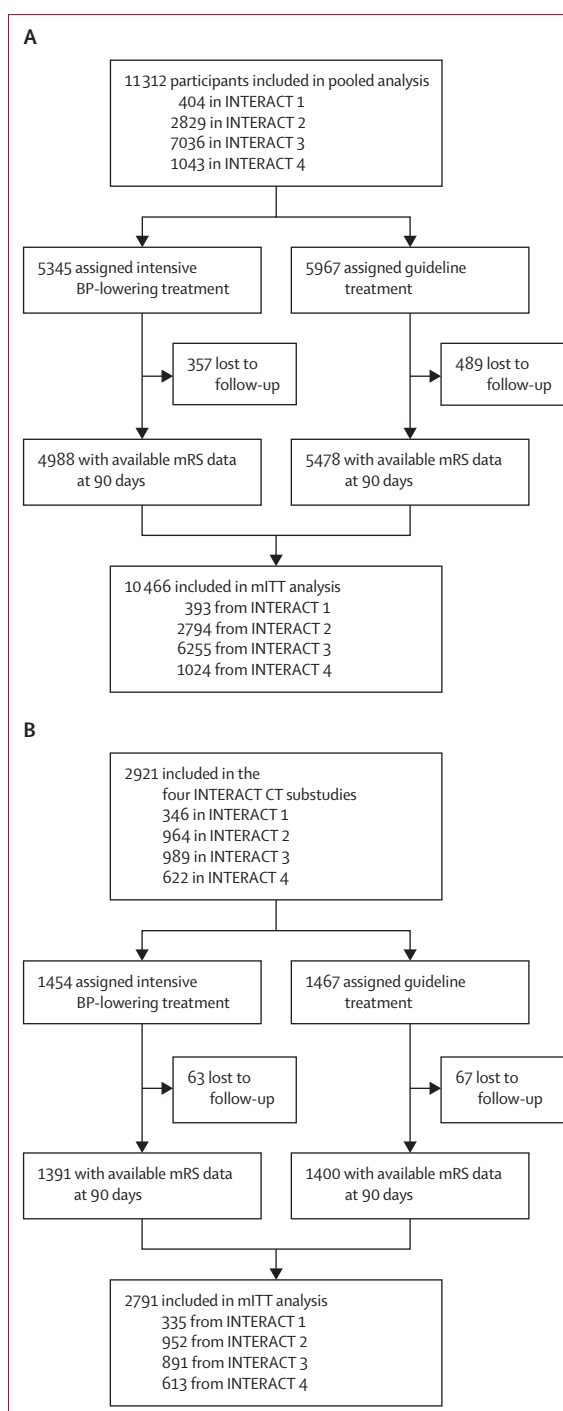


Figure 1: Study flowchart for the pooled analysis (A) and the CT substudy (B)

intensive BP-lowering treatment, one additional patient would be prevented from experiencing a poor functional outcome (mRS 3–6), relative to standard guideline-based treatment. This finding translates into a 14.9% relative risk reduction in the proportion of patients with mRS scores of 3–6 in the guideline group, assuming optimal implementation of the intervention. There was no

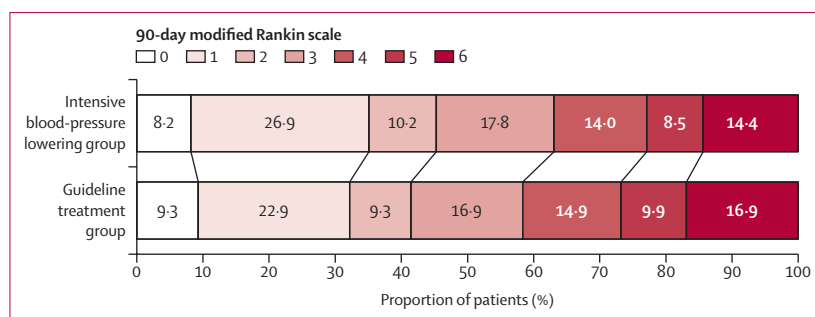


Figure 2: Distribution of 90-day modified Rankin scale scores by randomised treatment in the INTERACT full cohort

	Group		Model 1*		Model 2†	
	Intensive	Guideline	OR (95% CI)	p	OR (95% CI)	p
Neurological deterioration‡	367/5011 (7.3%)	509/5539 (9.2%)	0.77 (0.66–0.88)	<0.0001	0.76 (0.66–0.88)	0.0002
Death	719/4988 (14.4%)	922/5478 (16.8%)	0.83 (0.74–0.92)	0.001	0.83 (0.75–0.94)	0.002
Any serious adverse events	1023/5345 (19.1%)	1311/5967 (22.0%)	0.83 (0.75–0.91)	<0.0001	0.84 (0.76–0.92)	0.0003
Any cardiac serious adverse events	39/5343 (0.7%)	48/5964 (0.8%)	0.86 (0.56–1.31)	0.478	0.86 (0.56–1.32)	0.499
Any renal serious adverse events	14/5343 (0.3%)	26/5964 (0.4%)	0.58 (0.30–1.11)	0.097	0.57 (0.30–1.10)	0.094
Any hypotension serious adverse events	8/5345 (0.2%)	6/5967 (0.1%)	1.37 (0.47–3.98)	0.563	1.39 (0.48–4.04)	0.547

Data are n/N (%) or OR (95% CI). OR=odds ratio. NIHSS=National Institute of Health Stroke Scale. *Model 1: adjusted for trial. †Model 2: further adjusted for NIHSS (<21 vs ≥21). ‡Neurological deterioration was defined as an increase from baseline of 4 points or more on scores of the NIHSS at day 7.

Table 2: Blood pressure lowering treatment effect on safety outcomes

significant interaction between BP-lowering treatment and the time from onset to randomisation ($p=0.66$ for interaction).

Intensive BP-lowering treatment was shown to be safer than guideline treatment. It was associated with a significantly lower risk of neurological deterioration within 7 days (OR 0.76, 95% CI 0.66–0.88; $p=0.0002$), death (0.83, 0.75–0.94; $p=0.002$), or any serious adverse event (0.84, 0.76 to 0.92; $p=0.0003$; table 2).

When the analysis was restricted to patients with available data on baseline haematoma volume with or without 24 h CT scan ($n=5134$), intensive BP-lowering treatment was shown to significantly improve functional recovery according to an ordinal analysis of scores on the mRS ($p=0.39$ for proportional odds assumption), compared with guideline treatment (OR 0.87, 95% CI 0.79–0.96; $p=0.0052$). The effects of intensive BP-lowering treatment on functional recovery showed decreasing levels of function with increasing time from the onset of symptoms to randomisation ($p=0.01$ for interaction, appendix 2 p 13). Compared with the guideline group, the intensive treatment group had significantly better functional recovery in patients who were randomised within 3 h after the onset of

intracerebral haemorrhage than in patients randomised after 3 h (data not shown). Sensitivity analyses with further adjustment for baseline scores on the NIHSS in the model showed similar results ($p=0.02$ for interaction; data not shown).

INTERACT CT substudy

Overall, 2921 patients (mean age 64.0 years [SD 12.6]; 1008 [34.5%] female and 1913 [65.5%] male) with available sequential brain CT were included in the INTERACT CT substudy, of whom 1454 were assigned to receive early intensive BP-lowering treatment and 1467 to receive guideline-recommended treatment (figure 1B, appendix 2 p 3). The baseline characteristics were balanced between the randomised groups (appendix 2 p 3). The median time from the onset of intracerebral haemorrhage to randomisation was similar between the intensive treatment group (2.58 h, IQR 1.45–3.97) and the guideline group (2.74 h, 1.45–4.04; $p=0.29$). The distribution of time from onset to randomisation by trial in the INTERACT CT substudy is shown in appendix 2 (p 15), and the characteristics of patients by time from onset to randomisation are shown in appendix 2 (p 7). The mean systolic BP differed significantly between the two groups at all timepoints from 15 min to 24 h after randomisation (appendix 2 p 16). At 1 h, the mean systolic BP was 147.7 mm Hg (SD 21.3) in the intensive treatment group (with 429 [38.3%] of 1121 patients achieving the target BP of <140 mm Hg) compared with 159.9 mm Hg (22.8) in the guideline group (with 868 [81.5%] of 1065 patients achieving a BP target of <180 mm Hg). The mean difference in systolic BP at 1 h was 12.2 mm Hg (95% CI 10.3–14.0; $p<0.0001$). The mean difference in systolic BP between the intensive-treatment group and guideline group in the first 24 h was 7.7 mm Hg (7.0–8.3; $p<0.0001$).

Intensive BP-lowering treatment was shown to significantly improve the odds of functional recovery according to an ordinal analysis of scores on the mRS ($p=0.20$ for proportional odds assumption) compared with guideline treatment (OR 0.87, 95% CI 0.76–0.99; $p=0.04$). Appendix 2 (p 17) shows the distribution of mRS by randomised treatment group. The effects of BP-lowering treatment on functional recovery showed decreasing levels of function with increasing time from onset of symptoms to randomisation ($p=0.02$ for interaction, figure 3A). Compared with the guideline group, the intensive treatment group had significantly improved functional recovery in patients who were randomised within 3 h after the onset of intracerebral haemorrhage (figure 3A). Sensitivity analyses with further adjustment for baseline scores on the NIHSS showed similar results ($p=0.03$ for interaction; data not shown).

Overall, there was no effect of intensive BP-lowering treatment on either relative (OR 0.85, 95% CI 0.70–1.03; $p=0.09$) or absolute (0.84, 95% CI 0.68–1.04, $p=0.12$)

haematoma growth at 24 h. However, the effects of treatment on relative haematoma growth decreased with increasing time from onset to randomisation ($p=0.01$ for interaction, figure 3B). Although there was a significantly decreasing effect of intensive BP-lowering treatment on relative haematoma growth in patients randomised within 3 h of intracerebral haemorrhage, the effect on absolute haematoma growth remained constant regardless of the time from onset to randomisation ($p=0.63$ for interaction; figure 3C). Sensitivity analyses with further adjustment for scores on the NIHSS showed similar results ($p=0.002$ and $p=0.43$ for interaction, for relative and absolute growth, respectively; data not shown).

Compared with the guideline group, there was less haematoma growth in the intensive group for patients with smaller ICH scores (the p for trends 0.003 for absolute haematoma growth and 0.03 for relative haematoma growth (appendix 2 pp 9, 18). A similar trend was also observed for physical function, although it was not significant ($p=0.08$ for trend; appendix 2 pp 9, 18). Sensitivity analyses with further adjustment for NIHSS score showed similar results (appendix 2 p 9).

Discussion

In our pooled analysis of the INTERACT trials involving over 11 000 patients with acute intracerebral haemorrhage, intensive BP-lowering treatment was shown to improve the likelihood of functional recovery without affecting haematoma growth compared with a more conservative treatment for BP control. However, in nearly a quarter of the patients with serial CT scans, early intensive BP-lowering treatment was shown to improve functional recovery and reduce haematoma growth when the treatment was initiated within 3 h of symptom onset (cutoff value at 2.6 h). Additionally, early intensive BP-lowering produced greater reductions in haematoma growth in patients with mild-to-moderate levels of severity according to the ICH score system.

Our study integrated data from four international multicentre clinical trials involving patients with a broad range of characteristics in diverse health-care settings worldwide, and which used robust and independently assessed endpoints. The findings indicate that the treatment of intracerebral haemorrhage is highly time-sensitive, similar to the treatment of acute ischaemic stroke. Since haematoma growth generally occurs within the first few hours after onset,^{6,20} any delay in achieving BP control to a target reduces the effect on functional outcome.²¹ Some observational evidence^{7,22} has shown that intensive BP reduction attenuates haematoma growth within this therapeutic window. A post-hoc analysis of ATACH II,⁷ for example, which included a subgroup of 354 participants who received intravenous nicardipine within 2 h of onset, found that nicardipine-based intensive BP lowering was associated with improved functional outcome and a reduction in

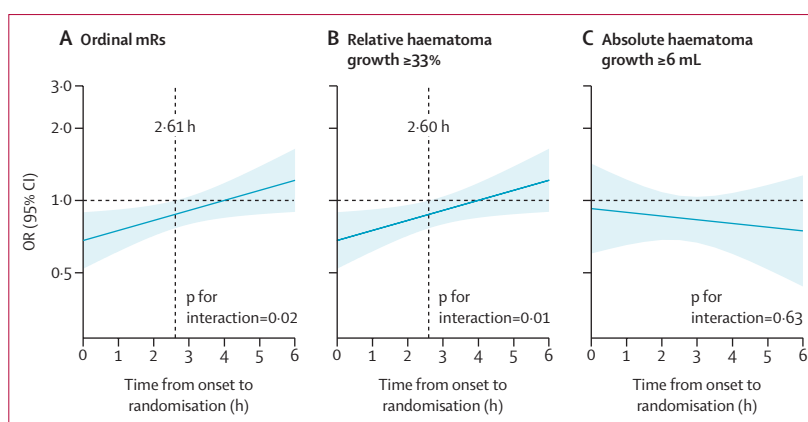


Figure 3: Effect of blood pressure-lowering treatment on physical function recovery and relative and absolute haematoma growth, by time from onset to randomisation in the INTERACT CT substudy

Poor physical function recovery was defined as achieving an mRS score of 3–6. Data shown are estimates of OR of the outcomes (intensive treatment group vs guideline treatment group), with shading representing 95% CIs. The dashed horizontal line represents no significant effect (95% CI crosses 1). p for interaction was obtained by adding interaction terms to statistical models. OR=odds ratio. mRS=modified Rankin scale.

haematoma growth. Secondary analyses of INTERACT²² showed that a reduction in systolic BP is associated with a reduction in haematoma growth when the target BP is achieved early and maintained consistently. Thus, our data reaffirm the time-sensitive nature of the effect of BP-lowering treatment. We found no significant interaction of intensive BP-lowering treatment and the time from onset to randomisation in the full INTERACT cohort, but this finding might readily be explained by a dilution effect from later-presenting patients. In the CT substudy, which included a greater proportion of patients who presented early, the time-sensitive treatment effect was significant.

We acknowledge that intensive BP-lowering treatment is a complex intervention, and many of the patients in our trials did not achieve the target BP as rapidly as intended, which might also have influenced the observed treatment effects. In this analysis, the mean systolic BP in the intensive treatment group remained around 150 mm Hg in the first hours post-randomisation and required 6–12 h to reach the target of less than 140 mm Hg. Conversely, in the guideline treatment group, the target systolic BP of less than 180 mm Hg was maintained at levels just above 160 mm Hg. Again, this delay in achieving optimal BP control might have weakened the potential impact of early intervention, particularly within the critical window for reducing haematoma expansion. Notably, during the first 24 h after admission to hospital, achieving the optimal systolic BP range (120–140 mm Hg) 1 h earlier was associated with a 2% reduction in the likelihood of a poor functional outcome.²³ Given the time-dependent nature of the benefit of BP lowering, this delay in reaching the target BP probably diminished the ability to realise a significant treatment effect in this pooled dataset. These findings highlight the need to optimise treatment protocols for

achieving faster BP control, particularly within the crucial early hours following intracerebral haemorrhage onset, in both clinical practice and future trials.

We also found that intensive BP-lowering treatment in patients with less severe intracerebral haemorrhage can more effectively prevent haematoma growth. In less severe cases, lowering BP can optimise cerebral blood flow without any potential risk of hypoperfusion, which could be a concern in more severe cases with larger haematomas with significant perihematomal oedema.^{24–26} Moreover, patients with less severe intracerebral haemorrhage might be more resilient to intensive BP-lowering treatment and allow more consistent adherence to target BP levels.⁵

Intracerebral haemorrhage remains a devastating disease with limited treatment options. Randomised trials are essential to assess the effectiveness of interventions and establish causality, but designing and conducting them for intracerebral haemorrhage is highly challenging.²⁷ At the second Haemorrhagic Stroke Academia Industry (HEADS) roundtable meeting, researchers discussed these challenges and recommended optimising patient selection to identify a responder group most likely to benefit from interventions.²⁸ Our findings support this approach, suggesting that future trials targeting haematoma expansion should prioritise ultra-early BP-lowering treatment within 3 h of the onset of intracerebral haemorrhage, as its benefits on haematoma growth and functional recovery seem to diminish over time, with a critical threshold at 3 h. All patients within this window should be included, while those presenting between 3–6 h should be selectively enrolled based on risk factors for haematoma expansion, such as anticoagulation use,²⁹ neuroimaging markers³⁰ (eg, irregular shape), or the presence of a spot sign on CTA.³¹ This targeted strategy enhances trial efficiency and efficacy by ensuring BP-lowering interventions focus on those most likely to benefit.

Our study has some limitations. First, although using a range of drug therapies was a strength, it added complexity to the assessment of the effects across different drugs. Additionally, the open assignment of interventions led to potential confounding from varying management strategies between the groups, beyond those documented. Second, in INTERACT1, INTERACT2, and INTERACT3, many participants received BP-lowering treatment before randomisation, which was not captured in the database, and the time from the onset of symptoms to randomisation was used as a surrogate measure of the time to the initiation of treatment. Third, the generalisability of our results to patients with more severe intracerebral haemorrhage is less certain due to small numbers. While sensitivity analyses adjusting for baseline haematoma volume and NIHSS score (as a marker of severity) showed consistent results, future studies should explore the effects of intensive

BP-lowering treatment in a broader range of intracerebral haemorrhage severity, particularly in patients with higher ICH scores who might have different responses to treatment.

In summary, our pooled analysis shows that early intensive BP-lowering treatment improves functional recovery compared with guideline-recommended control of BP in patients with acute intracerebral haemorrhage. Initiating treatment soon after the onset of intracerebral haemorrhage reduces haematoma growth and enhances outcomes, with the greatest benefit apparent within 3 h. These findings can inform improvements in systems of care around CODE-ICH and the design of future trials targeting high-risk patients for early intervention.

Contributors

CSA conceived the study, obtained funding, and supervised the planning, analyses, data interpretation, and writing of the report. XW and XR did the statistical analysis and wrote the first draft of the manuscript. All authors participated in the revisions of subsequent drafts. All authors read and approved the final version. All other authors contributed to data collection, analysis, interpretation, and report writing. XW and XR directly accessed and verified the data. All authors were responsible for the decision to submit the manuscript for publication.

Declaration of interests

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Data sharing

Individual, de-identified participant data used in these analyses may be shared by request from any qualified investigator following approval of a protocol and signed data access agreement via the Research Office of The George Institute for Global Health, Australia.

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