Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data

Tom J Moullaali, Xia Wang*, Reneé H Martin, Virginia B Shipes, Thompson G Robinson, John Chalmers, Jose I Suarez, Adnan I Qureshi, Yuko Y Palesch, Craig S Anderson*

Summary

Background Uncertainty persists over the effects of blood pressure lowering in acute intracerebral haemorrhage. We aimed to combine individual patient-level data from the two largest randomised controlled trials of blood pressure lowering strategies in patients with acute intracerebral haemorrhage to determine the strength of associations between key measures of systolic blood pressure control and safety and efficacy outcomes.

Methods We did a preplanned pooled analysis of individual patient-level data acquired from the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) and the second Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) trial. These trials included adult patients aged 19–99 years with spontaneous (non-traumatic) intracerebral haemorrhage and elevated systolic blood pressure, without a clear indication or contraindication to treatment. Patients were excluded if they had a structural cerebral cause for the intracerebral haemorrhage, had a low score (3–5) on the Glasgow Coma Scale, or required immediate neurosurgery. Our primary analysis assessed the independent associations between three post-randomisation systolic blood pressure summary measures—magnitude of reduction in 1 h, mean achieved systolic blood pressure, and variability in systolic blood pressure between 1 h and 24 h—and the primary outcome of functional status, as defined by the distribution of scores on the modified Rankin Scale at 90 days post-randomisation. We analysed the systolic blood pressure measures as continuous variables using generalised linear mixed models, adjusted for baseline covariables and trial. The primary and safety analyses were done in a modified intention-to-treat population, which only included patients with sufficient data on systolic blood pressure.

Findings 3829 patients (mean age 63·1 years [SD 12·9], 1429 [37%] women, and 2490 [65%] Asian ethnicity) were randomly assigned in INTERACT2 and ATACH-II, with a median neurological impairment defined by scores on the National Institutes of Health Stroke Scale of 11 (IQR 6–16) and median time from the onset of symptoms of intracerebral haemorrhage to randomisation of 3·6 h (2·7–4·4). We excluded 20 patients with insufficient or no systolic blood pressure data, and we imputed missing systolic blood pressure data in 23 (1%) of the remaining 3809 patients. Overall, the mean magnitude of early systolic blood pressure reduction was 29 mm Hg (SD 22), and subsequent mean systolic blood pressure achieved was 147 mm Hg (15) and variability in systolic blood pressure was 14 mm Hg (8). Achieved systolic blood pressure was continuously associated with functional status (improvement per 10 mm Hg increase adjusted odds ratio [OR] 0·90 [95% CI 0·87–0·94], p<0·0001). Symptomatic hypotension occurred in 28 (1%) patients, renal serious adverse events occurred in 26 (1%) patients, and cardiac serious adverse events occurred in 99 (3%) patients.

Interpretation Our pooled analyses indicate that achieving early and stable systolic blood pressure seems to be safe and associated with favourable outcomes in patients with acute intracerebral haemorrhage of predominantly mild-to-moderate severity.

Funding None.

Introduction

Spontaneous intracerebral haemorrhage is the most serious and least treatable form of acute stroke, affecting approximately 2 million people worldwide each year, with those in low-income to middle-income countries disproportionately affected.[1,2] Elevated systolic blood pressure is a common occurrence early after the onset of intracerebral haemorrhage,[3] and it is associated with expansion of the underlying haematoma[4] and an unfavourable clinical outcome.[5,6] Two large, international, multicentre randomised controlled trials compared early intensive blood pressure lowering with contemporaneous guideline-recommended management (target systolic blood pressure <180 mm Hg).[7] The first, the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) in 2829 patients, showed that intensive

Lancet Neurol 2019; 857–64

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*Joint first authors

The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia (T J Moullaali MBBS, X Wang PhD, Prof J Chalmers PhD, Prof C S Anderson PhD); **Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK** (T J Moullaali); **Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA** (R H Martin PhD, V B Shipes BSc, Prof Y Y Palesch PhD); **Department of Cardiovascular Sciences, University of Leicester, Leicester, UK** (Prof T G Robinson MD); **National Institute for Health Research Leicester Biomedical Research Centre, Leicester, UK** (Prof T G Robinson); **Departments of Anesthesiology and Critical Care Medicine, Neurology, and Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof J I Suarez MD); **Department of Neurology, University of Missouri, Columbia, MO, USA** (Prof A I Qureshi MD); **Zeenat Qureshi Stroke Institute, St. Cloud, MO, USA** (Prof A I Qureshi); **Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, NSW, Australia** (Prof C S Anderson); **and The George Institute China at Peking University Health Science 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

Research in context

Evidence before this study

We searched MEDLINE and Embase, from inception to April 8, 2019, for studies assessing the association between blood pressure and clinical outcome after intracerebral haemorrhage, using the keywords "intracerebral haemorrhage" and "blood pressure". We did not apply any language restrictions. The two largest trials of early intensive blood pressure lowering in patients with acute intracerebral haemorrhage have reported discordant results: Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2; n=2829) showed a modest benefit of treatment on functional recovery and health-related quality of life, whereas Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II; n=1000) reported neutral effects and an excess of renal adverse events. However, participants in both the intensive and guideline treatment groups in ATACH-II received a higher intensity of treatment than their comparators in INTERACT2. Four meta-analyses of aggregate data from these and smaller randomised controlled trials have concluded that early intensive blood pressure lowering has no effect on death or disability in adults with acute spontaneous intracerebral haemorrhage. However, the treatment is feasible and safe, and has a modest effect in attenuating growth of the underlying haematoma. We identified no previous meta-analysis of early systolic blood pressure control in acute intracerebral haemorrhage using individual patient data. Thus, uncertainty persists over the optimal intensity of systolic blood pressure control that balances potential benefits (functional recovery) and risks (cerebral, cardiac, and renal ischaemia).

Added value of this study

To our knowledge, this study involving analysis of pooled individual patient-level data from 3809 participants with sufficient data on systolic blood pressure in the INTERACT2 and ATACH-II trials is the first to show a continuous association between the level of achieved systolic blood pressure in the first 24 h and functional status, potentially to levels as low as 120–130 mm Hg. Moreover, we have shown that achieving such levels is safe with respect to serious adverse events, including renal complications. By confirming the prognostic significance of systolic blood pressure variability across a broad range of clinical outcomes, we provide valuable supporting information to guide early blood pressure management in adult patients with predominantly mild-to-moderate acute intracerebral haemorrhage.

Implications of all the available evidence

Gaps persist in the evidence supporting the optimal approach to early intensive blood pressure lowering as an effective treatment for different types of acute intracerebral haemorrhage. However, with due consideration of the differences in design, analyses, and reporting of the two largest randomised controlled trials, our findings from their pooled analyses provide support for the effectiveness of systolic blood pressure reduction in patients with acute intracerebral haemorrhage. Careful titration and continued smooth control of systolic blood pressure over 24 h, potentially even to levels as low 120–130 mm Hg, can provide benefits to adults who have been admitted to hospital with acute intracerebral haemorrhage of mild-to-moderate severity.

systolic blood pressure reduction within 6 h of the onset of acute intracerebral haemorrhage was safe and feasible across various health-care settings and that it significantly improved the secondary outcomes functional recovery and wellbeing.[8] However, the subsequent second Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) trial, stopped for futility, reported no benefit and an excess of renal adverse events from a strategy of intensive blood pressure lowering in 1000 of a planned 1280 patients.[9]

Blood pressure was controlled differently in these two trials: in ATACH-II, the main treatment was intravenous nicardipine and systolic blood pressure was lowered more intensively than in INTERACT2, in which a range of intravenous and oral agents were used according to local protocols and availability. The discordant results have fuelled controversy over the benefit of intensive blood pressure lowering in patients with acute intracerebral haemorrhage[10] and might have tempered implementation of this management strategy in clinical practice. Moreover, subsequent meta-analyses of these and other smaller studies have shown no overall benefit of early intensive blood pressure lowering, and only a modest effect in reducing haematoma expansion.[10–14] However, such analyses of aggregated data do not allow multivariable analyses to account for confounding factors and differences in the manner and recording of early systolic blood pressure control.[15–18]

We pooled individual participant data from INTERACT2 and the ATACH-II trial to better define associations of key measures of early systolic blood pressure control and safety and efficacy outcomes.[19] We aimed to determine the strength and direction of associations, explore the modifying effects of patient and clinical characteristics, and identify a systolic blood pressure lowering profile that provides an optimal balance between potential benefit (functional recovery) and harm (clinically significant cerebral, cardiac, or renal ischaemia).

Methods

Overview

INTERACT2[8] and ATACH-II[9] were prospective, randomised, open-label, blinded-endpoint trials; INTERACT2 recruited patients between Oct 7, 2008, and Aug 30, 2012, and ATACH-II recruited between May 1, 2011, and Sept 14, 2015. Both trials tested the effectiveness of intensive versus guideline-recommended blood pressure lowering in patients aged 19–99 years with spontaneous

(non-traumatic) intracerebral haemorrhage and elevated systolic blood pressure (defined as 150–220 mm Hg in INTERACT2 and ≥180 mm Hg in ATACH-II), without a clear indication or contraindication to treatment. Patients were excluded if they had a structural cerebral cause for the intracerebral haemorrhage, had a low score (3–5) on the Glasgow Coma Scale,[20] or required immediate neurosurgery. Demographical and clinical characteristics were recorded at the time of enrolment, with neurological severity measured using the Glasgow Coma Scale (scores range from 3 to 15, with lower scores indicating deeper loss of consciousness) and the National Institutes of Health Stroke Scale[21] (NIHSS; scores range from 0 to 42, with higher scores indicating greater neurological deficit).

In INTERACT2, participants were randomly assigned within 6 h of the onset of symptoms to immediate intensive (target systolic blood pressure <140 mm Hg within 1 h of treatment) or guideline (target <180 mm Hg according to the attending clinician's judgment) blood pressure management according to prespecified local treatment protocols, with systolic blood pressure of less than 130 mm Hg prompting treatment cessation. In ATACH-II, participants were randomly assigned within 4·5 h of the onset of symptoms to immediate, more intensive (target systolic blood pressure 110–139 mm Hg) or guideline (140–179 mm Hg) blood pressure management with intravenous nicardipine, with the aim of achieving these target ranges within 2 h after randomisation; systolic blood pressure of less than 110 mm Hg prompted treatment cessation. In both trials, treatment-related symptomatic hypotension was managed with intravenous fluids or vasopressor agents and recorded as a serious adverse event. Systolic blood pressure was recorded at fixed timepoints in the first 24 h post-randomisation, according to the protocol of each trial.[22,23] For the purposes of our analyses, the shared timepoints were time of randomisation, every 15 min within the first hour of treatment (during which we assumed the largest drop in systolic blood pressure had occurred), and then at 6 h, 12 h, 18 h, and 24 h.[19]

Outcomes

Patients were followed up to 90 days post-randomisation by trained staff masked to treatment allocation. Analyses were done in a modified intention-to-treat population, comprising patients with sufficient data on systolic blood pressure. For our analyses, the primary outcome was functional status as defined by the distribution of scores on the modified Rankin Scale (mRS), which range from 0 (no symptoms) to 6 (death), at 90 days post-randomisation. Secondary outcomes were good outcome (defined as scores 0–3 on the mRS) and functional independence measures of recovery from disability (defined as scores 0–2 on the mRS); an increase (absolute >6 mL[24] or relative >33%) in haematoma volume from baseline to the 24 h CT scan; and death within 90 days. Safety outcomes were neurological deterioration, defined as an increase from baseline of 4 points or more on the NIHSS or a decrease from baseline of 2 points or more on the Glasgow Coma Scale over 24 h; 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 definitions, within 90 days.

Data analysis

Variables from INTERACT2 and ATACH-II were exchanged between the George Institute for Global Health (Sydney, NSW, Australia) and Medical University of South Carolina (Charleston, SC, USA), according to our published protocol.[19] These variables related to patient demographics, medical history, baseline clinical assessment, and blood pressure measures in the first 24 h post-randomisation. We independently harmonised and concatenated clinical outcomes into a single data file, which was checked for accuracy of numbers, distributions and categories, and agreed nomenclature. For the primary analysis, we used multiple imputation for missing systolic blood pressure measurements using linear interpolation with cubic splines. For participants who died within 24 h, missing systolic blood pressure data were imputed until the time of death or until the last recorded measurement in those with unknown time of death. We included the following prespecified baseline variables in multivariable analyses: age (<65 years *vs* ≥65 years), Asian versus non-Asian ethnicity, time from the onset of symptoms to randomisation (<4 h *vs* ≥4 h), degree of neurological impairment (NIHSS <10 *vs* ≥10), medical history (presence of diabetes, hypertension, or cardiac disease), presence of intraventricular haemorrhage, and haematoma volume (<15 mL *vs* ≥15 mL).[11]

The following prespecified summary measures of systolic blood pressure control were determined in each participant: magnitude (the difference between systolic blood pressure at randomisation and lowest attained systolic blood pressure within 1 h), achieved (the mean of the systolic blood pressure measurements at five timepoints between 1 h and 24 h), and variability (the SD of the same measures between 1 h and 24 h). Our primary analysis was to determine any significant (two-tailed $p<0·05$) independent association of the systolic blood pressure summary measures, as continuous variables, and the clinical outcomes in generalised linear mixed models, adjusted for the defined covariables and random intercepts for each study. We first included all three summary measures into an adjusted model, and only if this was significant did we proceed to test the significance of each pairing of two measures, and then the individual summary measure in the model using the closed testing procedure. In secondary analyses, we tested the significance of the summary measures across clinically meaningful categories in the models, using a linear component of trend and also with a quadratic component trend if potential U-shaped associations appeared. The data are reported as adjusted odds ratios (ORs) and 95% CIs.

	Combined (n=3829)	INTERACT2 (n=2829)	ATACH-II (n=1000)
Demographics			
Age, years	63·1 (12·9)	63·5 (12·9)	61·9 (13·1)
Sex			
Men	2400 (63%)	1780 (63%)	620 (62%)
Women	1429 (37%)	1049 (37%)	380 (38%)
Asian ethnicity	2490 (65%)	1928 (68%)	562 (56%)
Clinical features			
History of hypertension	2841/3799 (75%)	2048/2826 (72%)	793/973 (82%)
Current use of antihypertensive drugs	1769/3819 (46%)	1274/2826 (45%)	495/993 (50%)
SBP at randomisation, mm Hg	178 (19)	179 (17)	175 (25)
NIHSS score	11 (6–16)	11 (6–16)	11 (6–16)
GCS score	14 (13–15)	14 (12–15)	15 (13–15)
Intracerebral haemorrhage characteristics on brain imaging			
Haematoma volume, mL	10·8 (5·6–19·3)	11 (5·8–19·5)	10·2 (5·1–18·4)
Haematoma location			
Basal ganglia or deep structures	2510/3067 (82%)	1630/2076 (79%)	880/991 (89%)
Lobar	413/3067 (13%)	303/2076 (15%)	110/991 (11%)
Infratentorial or posterior fossa	144/3067 (5%)	143/2076 (7%)	1/991 (<1%)
Intraventricular haemorrhage	1004/3601 (28%)	740/2613 (28%)	264/988 (27%)
Early SBP control			
Time from intracerebral haemorrhage onset to randomisation, h	3·6 (2·7–4·4)	3·7 (2·8–4·7)	3·1 (2·3–3·9)
Treated with multiple agents	1524 (40%)	1309 (46%)	215 (22%)
Achieved SBP, mm Hg*	147 (15)	149 (16)	142 (13)
Magnitude of SBP reduction, mm Hg†	29 (22)	29 (21)	31 (25)
SBP variability, mm Hg‡	14 (8)	14 (8)	12 (6)
Other treatment			
Intubation	326/3771 (9%)	189/2779 (7%)	137/992 (14%)
Neurosurgery			
Evacuation or decompression	125/3771 (3%)	81/2779 (3%)	44/992 (4%)
Intraventricular catheter	155/3771 (4%)	85/2779 (3%)	70/992 (7%)

Data are mean (SD), n (%), n/N (%), or median (IQR). ATACH-II=second Antihypertensive Treatment of Acute Cerebral Haemorrhage trial. GCS=Glasgow Coma Scale. INTERACT2=second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial. NIHSS=National Institute of Health Stroke Scale. SBP=systolic blood pressure. *Mean SBP in 1–24 h. †SBP at randomisation minus minimum SBP within 1 h. ‡SD of SBP in 1–24 h.

Table 1: **Summary of baseline characteristics by trial**

See Online for appendix

For all the analyses involving the primary outcome of functional status (ordinal shift in the distribution of scores on the mRS), we first checked the proportional odds assumption, and if it was violated we used alternative binary cutoff measures for recovery from disability on the mRS. In our prespecified sensitivity analyses to determine any modifying effect of participant characteristics, we added an interaction term for the prespecified baseline covariable in the model, and for any characteristics that yielded a significant (two-sided $\alpha \leq 0 \cdot 10$) interaction subgroup analyses were done in categories of sufficient sample size. We also undertook several post-hoc analyses that included adjustment for location of intracerebral haemorrhage (deep or other); volume of intracerebral haemorrhage as a continuous variable; stratification by randomised blood pressure lowering treatment; and magnitude of systolic blood pressure reduction between 15 min and 24 h. All analyses were done with SAS (version 9.2 or newer) and independently validated by authors from the George Institute for Global Health and Medical University of South Carolina.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all of the data and final responsibility for the decision to submit for publication.

Results

3829 patients with acute intracerebral haemorrhage were randomly assigned in ATACH-II and INTERACT2, of whom 1429 (37%) were women and 2490 (65%) were of Asian ethnicity, and their mean age was 63·1 years (SD 12·9; table 1). Overall median neurological impairment defined by scores on the NIHSS was 11 (IQR 6–16). The overall median time from the onset of symptoms to random allocation of different intensities of blood pressure treatment was 3·6 h (IQR 2·7–4·4), and 1524 (40%) patients were treated with multiple blood pressure lowering agents. We excluded 13 patients without any systolic blood pressure data and seven with too few data before early death, and we imputed missing systolic blood pressure data (due to early death or another reason) in 23 (1%) of the remaining 3809 patients (appendix p 2). Overall, the mean systolic blood pressure summary measures were 29 mm Hg (SD 22) for magnitude of systolic blood pressure fall in 1 h, 147 mm Hg (15) systolic blood pressure achieved over 1 h to 24 h, and 14 mm Hg (8) variability over 1 h to 24 h. 74 (2%) patients had systolic blood pressure less than 120 mm Hg.

There was strong evidence for an association between the three systolic blood pressure summary measures as continuous variables in a combined adjusted model and all safety and efficacy outcomes (table 2). When analysed separately, achieved systolic blood pressure and variability in systolic blood pressure were significantly associated with all outcomes. Inverse linear associations were evident for achieved systolic blood pressure and the primary outcome of favourable shift in functional status (per 10 mm Hg higher systolic blood pressure adjusted OR 0·90 [95% CI 0·87–0·94], p<0·0001) as well as the other disability measures on the mRS, that of good outcome and functional independence. Because the proportional odds assumption was violated in ordinal analysis of the mRS for variability and magnitude (appendix p 3), the alternative disability measures on the mRS were used in analyses of these systolic blood pressure summary measures. These analyses showed that variability was significantly associated with good outcome and functional independence, but there was no evidence for an association between magnitude and these outcomes.

There were significant associations between achieved systolic blood pressure and variability of systolic blood pressure and the secondary outcomes of haematoma

expansion and death, and the safety outcomes of early neurological deterioration and any serious adverse event. During 90 days of follow-up, 28 (1%) of 3809 patients had symptomatic hypotension, 26 (1%) had renal serious adverse events, and 99 (3%) had cardiac serious adverse events. Apart from an association between variability and episodes of hypotension, no clear patterns emerged for these serious adverse events in the relation to the other systolic blood pressure summary measures (appendix p 17).

Our secondary assessment of the systolic blood pressure summary measures as categories produced variation in the shape and significance of associations with outcomes (figure; appendix pp 11–17). Although the general pattern was that lower categories of achieved systolic blood pressure seemed to be associated with better outcomes, down to 120–130 mm Hg, the only significant linear trend was for early neurological deterioration. For variability, there was generally weak evidence for positive associations with adverse outcomes, but the only significant association was for death. Finally, although U-shaped associations were apparent for increasing magnitude, these were only significant when analysed as linear and not quadratic trends for recovery, early neurological deterioration, and death. Moreover, compared with a reference category of less than 20 mm Hg, moderate category reductions in systolic blood pressure of 20–40 mm Hg and 40–60 mm Hg within 1 h seemed to be only weakly associated with both good outcome and functional independence, whereas a large reduction of 60 mm Hg or more within 1 h was significantly associated with lower odds of good outcome but not functional independence on the mRS (appendix pp 12–13).

Associations of the systolic blood pressure summary measures and all outcomes on the mRS were consistent using complete case data in our prespecified sensitivity analysis and several post-hoc analyses (appendix pp 4–6) that included adjustment for location of intracerebral haemorrhage (deep or other); volume of intracerebral haemorrhage as a continuous variable; and a graphical representation of the univariate analyses of the systolic blood pressure summary measures as continuous variables. In addition, there were no significant interactions between prespecified baseline characteristics and systolic blood pressure summary measures with the primary outcome or in stratified analysis by randomised blood pressure lowering treatment. Finally, post-hoc analysis of magnitude of systolic blood pressure reduction between 15 min and 24 h showed no significant trends across any of the outcomes (appendix p 7).

	Adjusted odds ratio* (95% CI)	p value
Primary model (all measures combined)		
Primary outcome, functional status (shift in mRS scores) at 90 days	..	<0·0001
Good outcome (mRS score 0–3) at 90 days	..	<0·0001
Functional independence (mRS scores 0–2) at 90 days	..	<0·0001
Haematoma expansion (>6 mL) from baseline to 24 h	..	<0·0001
Neurological deterioration over 24 h†	..	<0·0001
Death within 90 days	..	<0·0001
Any serious adverse event within 90 days	..	<0·0001
Individual SBP summary measures		
Achieved, mean SBP 1–24 h		
Primary outcome, functional status (shift in mRS scores) at 90 days	0·90 (0·87–0·94)	<0·0001
Good outcome (mRS score 0–3) at 90 days	0·90 (0·85–0·95)	0·0002
Functional independence (mRS scores 0–2) at 90 days	0·91 (0·87–0·96)	0·0009
Haematoma expansion (>6 mL) from baseline to 24 h	1·16 (1·06–1·27)	0·0008
Neurological deterioration over 24 h†	1·12 (1·04–1·20)	0·0022
Death within 90 days	1·24 (1·14–1·34)	<0·0001
Any serious adverse event within 90 days	1·11 (1·04–1·17)	0·0007
Variability, SD of SBP 1–24 h		
Good outcome (mRS score 0–3) at 90 days	0·81 (0·73–0·90)	0·0001
Functional independence (mRS scores 0–2) at 90 days	0·87 (0·79–0·97)	0·0124
Haematoma expansion (>6 mL) baseline to 24 h	1·21 (1·02–1·43)	0·0330
Neurological deterioration over 24 h†	1·41 (1·23–1·61)	<0·0001
Death within 90 days	1·16 (1·01–1·34)	0·0373
Any serious adverse event within 90 days	1·22 (1·09–1·36)	0·0004
Magnitude, from baseline to minimum ≤1 h post-randomisation		
Good outcome (mRS score 0–3) at 90 days	0·97 (0·93–1·01)	0·1186
Functional independence (mRS scores 0–2) at 90 days	0·99 (0·96–1·03)	0·7151
Haematoma expansion (>6 mL) from baseline to 24 h	1·02 (0·96–1·07)	0·5570
Neurological deterioration over 24 h†	1·00 (0·96–1·05)	0·9358
Death within 90 days	1·01 (0·95–1·07)	0·7467
Any serious adverse event within 90 days	1·02 (0·98–1·06)	0·2821

mRS=modified Rankin Scale (0 indicates no symptoms, 1 indicates symptoms without disability, 2 indicates disability but independent function, 3 indicates disability with some assistance, 4 indicates disability with moderate assistance, 5 indicates bedridden, full dependency, and 6 indicates death). SBP=systolic blood pressure. *Odds ratio per 10 mm Hg increase in SBP summary measure, adjusted for age (<65 years *vs* ≥65 years), Asian versus non-Asian ethnicity, time from onset of intracerebral haemorrhage to randomisation (<4 h *vs* ≥4 h), and degree of neurological impairment (National Institutes of Health Stroke Scale [NIHSS] score <10 *vs* ≥10), medical history of diabetes, hypertension, cardiac disease, intracerebral haemorrhage volume (<15 mL *vs* ≥15 mL), and presence of intraventricular haemorrhage at baseline. Odds ratios not calculated if proportional odds assumption violated. †Neurological deterioration defined as an increase of 4 points or more on the NIHSS or a decline of 2 points or more on the Glasgow Coma Scale within 24 h post-randomisation.

Table 2: **Associations of early systolic blood pressure summary measures and outcomes in patients with acute intracerebral haemorrhage**

Discussion

In our preplanned pooled analysis of individual patient-level data derived from the two largest trials of blood pressure lowering treatment commenced early after the onset of acute intracerebral haemorrhage, we showed linear associations between both achieved and sustained systolic blood pressure over 24 h and favourable outcomes, with low risks of serious harms. Every 10 mm Hg reduction in systolic blood pressure was associated with a 10% increase in the odds of better functional recovery, potentially down to 120–130 mm Hg, and similarly of improved outcomes for reduced systolic blood pressure variability. Analyses of magnitude of reduction in systolic blood pressure showed no clear and consistently significant association for any outcome.

An important new finding from these analyses is the continuous association between achieved systolic blood

pressure over 24 h and the various measures of functional recovery on the mRS, which seemed to extend beyond the less than the 140 mm Hg target that is recommended in many guidelines on the basis of the INTERACT2 results.[3] We recognise, however, that we were unable to provide a reliable assessment of the balance of benefits and harms at very low systolic blood pressure because there were few patients (2%) with achieved systolic blood pressure of less than 120 mm Hg. Our results also confirm earlier analyses[18] of an association between variability and adverse outcomes, further supporting potential beneficial effects of smooth control of systolic blood pressure. Lower levels of both achieved and variability of systolic blood pressure were also associated with reductions in haematoma expansion, early neurological deterioration, death, and serious adverse events. Importantly, we also found that renal serious adverse events were infrequent, and without any appreciable trends for harm evident across a wide range of systolic blood pressure levels.

To provide clinically meaningful results, and to determine whether moderate reductions are beneficial and extreme reductions cause harm, we explored the shape of the association of various measures of systolic blood pressure control and outcomes. Compared with INTERACT2, ATACH-II included patients with higher systolic blood pressure that was allowed to be reduced to lower levels before and after randomisation, and almost exclusively with intravenous nicardipine. It follows, therefore, that these participants were likely to have achieved, on average, larger reductions in systolic blood pressure; this key difference between the trials might partly explain their discordant results.[25] However, in our primary analyses, with magnitude of systolic blood pressure as a continuous variable, there was no association with any outcome and there was no significant heterogeneity in the results with analyses stratified by treatment group. Nevertheless, U-shaped curves were apparent for some disability outcomes, early neurological deterioration, and death, when magnitude of early systolic blood pressure reduction was modelled as a categorical variable. These findings suggest that a rapid and large reduction (≥60 mm Hg) within 1 h of the initiation of treatment might cause harm, but this finding might have been due to chance, because there was no such adverse association for the degree of magnitude of reduction over 24 h on these or other outcomes.

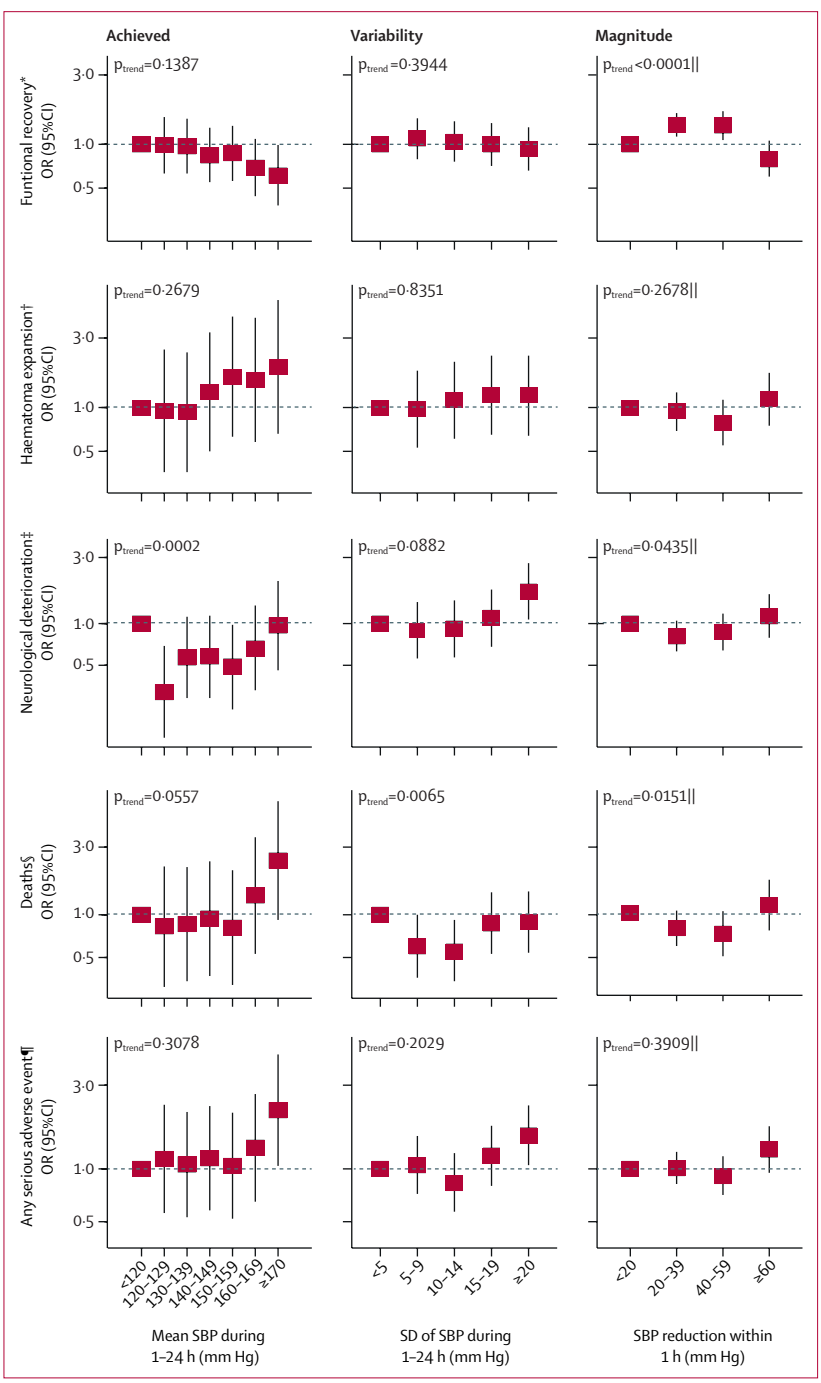

Figure: **Associations of categorised systolic blood pressure summary measures and clinical outcomes**

OR=odds ratio. SBP=systolic blood pressure. OR and 95% CI are comparisons between each category and the reference, adjusted for age (<65 years *vs* ≥65 years), Asian versus non-Asian ethnicity, time from the onset of intracerebral haemorrhage to randomisation (<4 h *vs* ≥4 h), and degree of neurological impairment (National Institutes of Health Stroke scale [NIHSS] score <10 *vs* ≥10), medical history of diabetes, hypertension, cardiac disease, intracerebral haemorrhage volume (<15 *vs* ≥15 mL), and presence of intraventricular haemorrhage at baseline. *Functional recovery at 90 days post-randomisation, defined by functional status (a favourable shift in ordinal scores on the modified Rankin Scale for achieved SBP), and functional independence (according to scores 0–2 on the mRS for variability and magnitude of SBP). †Increase in haematoma volume (>6 mL) from baseline to 24 h on brain imaging. ‡Neurological deterioration defined as an increase of 4 points or more on the NIHSS or a decline of 2 points or more on the Glasgow Coma Scale within 24 h post-randomisation. §Death within 90 days post-randomisation. ¶Any serious adverse event within 90 days post-randomisation. ||p values for quadratic trend: functional recovery p=0·2050; haematoma expansion p=0·8741; neurological deterioration p=0·4317; death p=0·8810; and any serious adverse event p=0·4584.

The strengths of these analyses include the relatively large dataset derived from participants recruited from a broad range of health-care settings, with systematic evaluations and high rates of adherence to treatment and follow-up. Moreover, despite the near-complete data on early systolic blood pressure measurements and outcomes, we further chose to impute missing data to attain the maximum power for multivariable analyses. However, there are several limitations to our study that need to be considered when interpreting the findings. First, our analyses were designed to report the independence, ranking, and shape of associations of early systolic blood pressure control summary measures. Thus, we do not presume causality where there is the potential for incomplete adjustment of important prognostic variables in such cohort analyses, and that multiple testing might have produced some chance associations. Furthermore, the true strength of associations might not have been clearly defined because our prespecified analyses did not include non-linear terms (such as polynomial functions or non-parametric cubic spline terms) to fit the possible U-shaped or J-shaped curves that became evident only in the categorical analyses of the systolic blood pressure summary measures. Another issue is that caution should be taken in extrapolating these findings across the range of cases of intracerebral haemorrhage because these data were derived from clinical trial populations in which the majority of participants were Asian and had deep haematomas causing predominantly mild-to-moderate levels of neurological severity, and blood pressure lowering treatment was commenced within several hours after a clear onset of symptoms. Moreover, as poor prognosis cases of intracerebral haemorrhage were purposefully excluded from these trials, there remains uncertainty over the best approach to blood pressure lowering in people with cerebral oedema, raised intracranial pressure, or requiring decompressive surgery. Finally, although we aimed to minimise bias by imputing missing systolic blood pressure data until the time of death for participants who died within 24 h, we were unable to account for potential confounding occurring as a result of antihypertensive therapy being stopped in such cases.

Our findings pose several questions for future research. First, as the participants in our analyses received a range of systolic blood pressure lowering agents over several hours after being admitted to hospital, we cannot provide insight as to which agents, if any, are better than others, or of the optimal time to achieve a target systolic blood pressure to produce a favourable outcome after intracerebral haemorrhage. In view of the results of the second Rapid Intervention With Glyceryl Trinitrate In Hypertensive Stroke Trial (RIGHT-2;[26] median time to treatment 71 min) and the Scandinavian Candesartan Acute Stroke Trial (SCAST;[27] median time to treatment 18 h), in which subgroup analyses for intracerebral haemorrhage favoured placebo treatment, an individual patient data meta-analysis appraising all the available data across all such blood pressure lowering trials is desirable to inform management by agent and time period from the onset of symptoms. Second, in view of the consistent finding that systolic blood pressure variability is associated with adverse outcomes in patients with intracerebral haemorrhage,[28–30] further studies with careful prospective evaluation to limit confounding factors are needed to resolve uncertainty over how best to identify, quantify, and manage this parameter in clinical practice. Third, although we report associations of individual systolic blood pressure summary measures and outcomes independently of each other, there are likely to be complex interactions between them that require further understanding to identify an optimal approach to treatment.

In summary, our findings indicate that there are benefits to achieving early and smooth control of systolic blood pressure potentially to levels as low as 120–130 mm Hg in adults who have been admitted to hospital with mild-to-moderate acute intracerebral haemorrhage.

Contributors

TJM contributed to planning, analyses, and data interpretation, and wrote the first draft of the report. XW, RHM, and VBS undertook analyses, contributed to planning, data interpretation, and writing of the report. AIQ, YYP, and CSA obtained funding for the original trials, and supervised planning, analyses, data interpretation, and writing of the report. TGR, JC, and JIS contributed to data interpretation and provided comments on the report.

Declaration of interests

TJM reports grants from the British Heart Foundation and holds a British Heart Foundation clinical research training fellowship. CSA has received grant funding from Takeda China, honorarium and travel reimbursement from Boehringer Ingelheim and Amgen, and holds a Senior Principal Research Fellowship of the Australian National Health and Medical Research Council. JC has received a grant from Idorsia for the SPIRIT study of resistant hypertension. JIS is the President of the Neurocritical Care Society, and Chair of the Data Safety Monitoring Board for the INTREPID Study funded by BARD. YYP is a member of the Data Safety Monitoring Committee for a trial sponsored by Brainsgate. TGR is a Senior Investigator of the UK National Institute for Health Research. XW, RHM, VBS, and AIQ declare no competing interests.

Data sharing

Individual, deidentified participant data from INTERACT2 trial used in these analyses will 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 (Sydney, NSW, Australia). The ATACH-II trial data, including deidentified participant data, are available indefinitely at the US National Institute of Neurological Disorders and Stroke data archive. To gain access, requesters will need to sign a data-access agreement.

For the **National Institute of Neurological Disorders and Stroke data archive** see https://www.ninds.nih.gov/

Acknowledgments

We thank Mark Woodward for advice on analyses.

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