# Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial

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## Summary

**Background** High blood pressure is a prognostic factor for acute stroke, but blood pressure variability might also independently predict outcome. We assessed the prognostic value of blood pressure variability in participants of INTERACT2, an open-label randomised controlled trial (ClinicalTrials.gov number NCT00716079).

**Methods** INTERACT2 enrolled 2839 adults with spontaneous intracerebral haemorrhage (ICH) and high systolic blood pressure (150–220 mm Hg) without a definite indication or contraindication to early intensive treatment to reduce blood pressure. Participants were randomly assigned to intensive treatment (target systolic blood pressure <140 mm Hg within 1 h using locally available intravenous drugs) or guideline-recommended treatment (target systolic blood pressure <180 mm Hg) within 6 h of onset of ICH. The primary outcome was death or major disability at 90 days (modified Rankin Scale score ≥3) and the secondary outcome was an ordinal shift in modified Rankin Scale scores at 90 days, assessed by investigators masked to treatment allocation. Blood pressure variability was defined according to standard criteria: five measurements were taken in the first 24 h (hyperacute phase) and 12 over days 2–7 (acute phase). We estimated associations between blood pressure variability and outcomes with logistic and proportional odds regression models. The key parameter for blood pressure variability was standard deviation (SD) of systolic blood pressure, categorised into quintiles.

**Findings** We studied 2645 (93·2%) participants in the hyperacute phase and 2347 (82·7%) in the acute phase. In both treatment cohorts combined, SD of systolic blood pressure had a significant linear association with the primary outcome for both the hyperacute phase (highest quintile adjusted OR 1·41, 95% CI 1·05–1·90; $p_{trend}$=0·0167) and the acute phase (highest quintile adjusted OR 1·57, 95% CI 1·14–2·17; $p_{trend}$=0·0124). The strongest predictors of outcome were maximum systolic blood pressure in the hyperacute phase and SD of systolic blood pressure in the acute phase. Associations were similar for the secondary outcome (for the hyperacute phase, highest quintile adjusted OR 1·43, 95% CI 1·14–1·80; $p_{trend}$=0·0014; for the acute phase OR 1·46, 95% CI 1·13–1·88; $p_{trend}$=0·0044).

**Interpretation** Systolic blood pressure variability seems to predict a poor outcome in patients with acute intracerebral haemorrhage. The benefits of early treatment to reduce systolic blood pressure to 140 mm Hg might be enhanced by smooth and sustained control, and particularly by avoiding peaks in systolic blood pressure.

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## Introduction

Stroke is a major cause of premature death and disability. The most serious and least treatable form—acute intracerebral haemorrhage—affects more than 1 million people each year worldwide.[1] High blood pressure is a risk factor for stroke, particularly for both incident and recurrent intracerebral haemorrhage, but it also predicts a poor outcome when present in the first 24 h after the onset of intracerebral haemorrhage.[2–4] Thus, early intensive control of blood pressure could be a safe and effective treatment for this disorder.[5,6] INTERACT2 showed improved functional outcomes with little risk for patients with intracerebral haemorrhage who received target-driven, early, intensive treatment to reduce blood pressure.[7] However, the effects did not differ between patients who received treatment within 4 h and those who were treated at 4–6 h, which suggests that other aspects of blood pressure control might be important.

Most guidelines for the management of hypertension[8–12] are based on usual or mean blood pressure, but the different efficacies of different antihypertensive drugs for reducing the risk of stroke and other cardiovascular events cannot be explained by reductions in mean systolic blood pressure alone.[13–15] Blood pressure variability can be defined as the variation in blood pressure during a period of time (standard deviation [SD] or coefficient of variation), with or without adjustment for trends in underlying mean blood pressure (residual standard deviation) or the average absolute difference between successive readings (successive variation). An increase in blood pressure variability might predict outcome after acute stroke,[13] but the few data available are conflicting. Some studies of

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See Online for appendix

patients with acute ischaemic stroke have shown that high beat-to-beat diastolic blood pressure is associated with a poor prognosis,[16] and high systolic blood pressure variability is associated with high risks of death and early neurological deterioration.[17] A small observational study[18] has shown that systolic blood pressure variability independently predicts early haematoma growth and death or early neurological deterioration in patients with intracerebral haemorrhage. However, secondary analyses of two clinical trials—the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS)[19] and Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS),[20] which included patients with intracerebral haemorrhage as well as those with ischaemic stroke—showed no significant association between blood pressure variability in the first 48 h after the onset of symptoms and death or dependency at 2 weeks.[21] We assessed the clinical significance of blood pressure variability in the first 24 h (hyperacute phase) and during days 2–7 (acute phase) in patients with intracerebral haemorrhage who participated in INTERACT2.[7]

## Methods

### Study design and participants

We did this post-hoc analysis with data from INTERACT2 (ClinicalTrials.gov number NCT00716079). The design and main results of INTERACT2 have been outlined elsewhere.[7,22,23] The study included 2839 adult patients with spontaneous intracerebral haemorrhage and high systolic blood pressure (150–220 mm Hg), without a clear indication or contraindication to early intensive treatment to reduce blood pressure. The patients were enrolled from 144 hospitals in 21 countries between 2008 and 2012. Patients were excluded if they had a structural cerebral cause for the intracerebral haemorrhage, deep coma (defined as a score of 3–5 on the Glasgow Coma Scale;[24] low scores indicate reduced consciousness), massive haematoma with a poor prognosis, or if early surgery to evacuate the haematoma was planned. Eligible participants were randomly assigned through a secure internet-based system that used a minimisation algorithm to ensure the groups were balanced according to country, hospital, and time from the onset of symptoms (≤4 h *vs* >4 h).

Participants were assigned to either intensive or guideline-recommended[25,26] blood pressure treatment within 6 h of onset of intracerebral haemorrhage. Neither patients nor investigators were masked to the treatment allocation. Participants allocated to intensive treatment received intravenous treatment and oral drugs according to prespecified treatment protocols based on locally available drugs, with the goal of achieving a systolic blood pressure of less than 140 mm Hg within 1 h of randomisation and to maintain this level while in hospital over the next 7 days. Treatment was halted if systolic blood pressure fell below 130 mm Hg. Symptomatic episodes of severe hypotension were treated with intravenous fluids or vasopressor drugs. Participants allocated to the guideline-treatment group received treatment to reduce blood pressure if their systolic blood pressure was more than 180 mm Hg; no minimum was stipulated. All participants received oral antihypertensive drugs (or topical nitrates) within 7 days (or discharge from hospital, if sooner), via a nasogastric tube if required. If not contraindicated and no other drugs were specifically required, combination treatment with an angiotensin-converting enzyme inhibitor and diuretic was recommended, with the goal of achieving a systolic blood pressure of less than 140 mm Hg during follow-up for the prevention of recurrent stroke. Demographic and clinical characteristics were recorded at enrolment, with stroke severity measured by use of the Glasgow Coma Scale and National Institutes of Health Stroke Scale[27] (NIHSS; scores range from 0 to 42; high scores indicate severe neurological deficit) at baseline, 24 h, and day 7 (or earlier at discharge from hospital). The study was approved by the ethics committees for each hospital and all patients or relevant surrogates gave written informed consent.

### Procedures

The key goals of assessments in the first 24 h were to ensure adherence to and safety of the allocated treatment. Accordingly, blood pressure was recorded with an automated electronic device in the non-paretic arm with the patient supine every 15 min in the first hour from randomisation, every 6 h until 24 h, and twice a day (morning and evening) from days 2–7 (or until discharge or death; figure 1). The number of systolic blood pressure readings less than 140 mm Hg, and minimum and maximum systolic blood pressure in the first 24 h, were also recorded. The primary outcome was death or major disability, defined as a score of 3–6 on the modified Rankin Scale (scores range from 0 [no symptoms] to 5 [severe disability] and 6 [death]), and the secondary outcome was an ordinal analysis of the range of scores on the modified Rankin Scale, done at 90 days by trained local staff who were masked to treatment allocation. Participants who did not receive the allocated treatment or follow the protocol were followed up in full and retained in the analyses as per the intention-to-treat principle.

CT brain scans (or MRI) were done at baseline (to confirm the diagnosis) in all patients, and at 24 h (plus or minus 3 h) in a subset of patients at hospitals where repeat scanning was either part of routine practice or approved for research. In China, collection of CT scans at 24 h ceased in 2009, after 400 consecutive patients had been assessed. Uncompressed digital CT images collected in the Digital Imaging and Communications in Medicine (DICOM) format were analysed centrally for the measurement of haematoma size by trained imaging scientists masked to clinical data, treatment, and date and sequence of scan, with computer-assisted multislice

planimetric and voxel threshold techniques with MIStar software (version 3.2). Inter-reader reliability was checked by periodic reanalysis of 15% of scans by a single neurologist to avoid drift (intraclass correlation coefficients: 0·92 for haematoma volume and 0·96 after removing outliers with volumes >50 mL).

### Statistical analysis

The sample size for INTERACT2 was set at 2800 to provide 90% power with 5% type 1 error and a two-sided significance test to detect a 14% relative reduction (7% absolute difference) for the primary outcome—from 50% in the guideline treatment group to 43% in the intensive treatment group—assuming 10% non-adherence to treatment and 3% loss to follow-up.[7,22,23] For the present analyses, we combined both randomised groups into a single cohort to assess the association between blood pressure variability and clinical outcomes for two early periods after the onset of intracerebral haemorrhage (figure 1). We deemed this approach justified because it increased the sample size and precision of the estimates, and will inform future management of patients for whom two separate time-dependent mechanisms might affect the outcome from intracerebral haemorrhage. We did two analyses to assess these potential mechanisms. The first analysis was for the hyperacute phase (the first 24 h), when the consequences of haematoma expansion are most important, with outcome events included from day 2. The second analysis was for the acute phase (days 2–7) when most perihaematomal oedema occurs, with outcome events included from day 8 onwards.

We calculated blood pressure variability during the hyperacute phase from the five blood pressure measurements recorded at 1 h, 6 h, 12 h, 18 h, and 24 h after randomisation; we excluded measurements taken at 0 mins, 15 mins, 30 mins, and 45 mins from the initial analyses to avoid misclassification of blood pressure variability resulting from treatment to reduce blood pressure, an approach that has been used previously.[15,28] We estimated blood pressure variability during the acute phase from the 12 measurements taken on days 2–7. Patients with missing data for blood pressure or other variables, and those who died within the first 24 h, were excluded from these analyses. We chose SD of systolic blood pressure as the key parameter for blood pressure variability because it is commonly used, relates directly to mean systolic blood pressure, and is simple and meaningful for clinical practice. The other parameters were group-specific or require calculation: coefficient of variation (SD divided by the mean), variation independent of the mean (a transformation of SD uncorrelated with mean blood pressure), residual SD (which takes account of trends in blood pressure over time), and average real variability (which accounts for the order of blood pressure measurements over time).[29] We also used mean, maximum, and minimum systolic blood pressure in the analyses. We applied the same parameters to analyses of diastolic blood pressure and mean arterial pressure.

For assessment of the relation (strength and shape) between blood pressure variability and the primary outcome, we categorised SD of systolic blood pressure into five groups (quintiles), with the lowest fifth used as the reference subgroup for staged logistic regression models. For the secondary outcome—chosen because of its statistical efficiency and clinical relevance to functional status[23,30]—we used proportional odds regression models if the main results showed no violation of the common proportional odds assumption across modified Rankin Scale scores.[7]

We compared baseline characteristics between the five groups with a $\chi^2$ test for categorical variables and Kruskal-Wallis non-parametric test for continuous variables. We selected variables for inclusion in the regression models on the basis of their ability to predict outcome (ie, $p<0·05$; appendix pp 9–10). Model 1 was adjusted for age, sex, and randomised treatment group; model 2 included all covariables in model 1 plus region (China *vs* other countries), NIHSS score (<14 *vs* ≥14), and haematoma

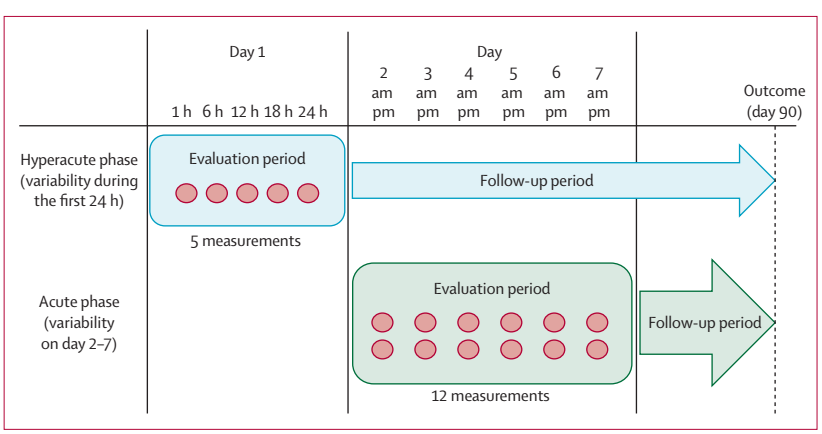


***Figure 1:*** **Measurements used to calculate blood pressure variability**
We excluded measurements taken at 0 mins, 15 mins, 30 mins, and 45 mins after randomisation from calculation of blood pressure variability.

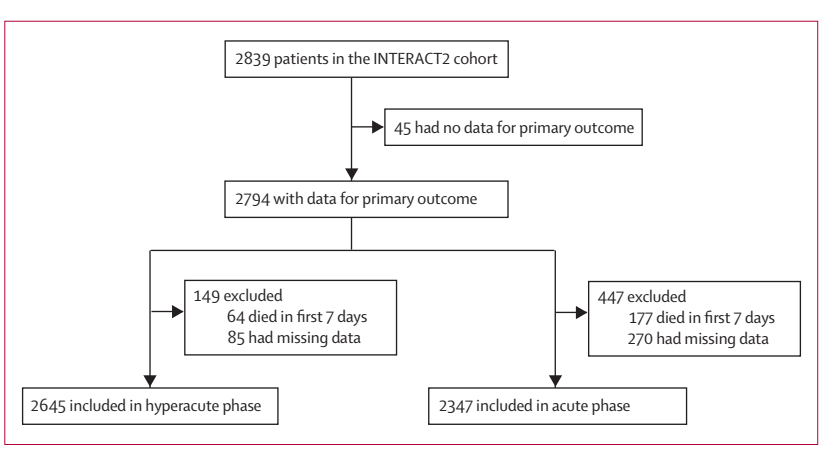


***Figure 2:*** **Trial profile**

volume at baseline (log transformed to remove skew after addition of the value 1·1 mL to eliminate negative values); and model 3 included all variables in model 2 plus mean blood pressure. We analysed the other parameters for blood pressure variability as continuous measures (one SD increase) in the three models. We present results as odds ratios (ORs) and 95% CIs.

We used the variance inflation factor to assess the multicollinearity between models,[31] and the likelihood ratio test to compare the fit of variables between the models. We used the relative integrated discrimination index[32] and Akaike's information criterion to discriminate between the various parameters. Sensitivity analyses included the blood pressure measurements in the first hour after randomisation and using the models including imputation of missing blood pressure measures and other confounding variables.[33] We compared heterogeneity in the associations of blood pressure variability with outcomes by randomised treatment groups, region of recruitment, and between parameters for blood pressure variability by adding an interaction term to model 3. We also investigated the effect of blood pressure variability on death or early neurological deterioration in the first 24 h, defined as an increase from baseline of 4 points or more on the NIHSS. Finally, we assessed the association of blood pressure variability with growth of haematoma for participants in the CT imaging substudy, with and without the blood pressure measurements over the first 24 h, after adjustment for age, sex, region, time from onset to baseline CT scan, location, volume of haematoma at baseline, and randomised treatment. We did the statistical analyses with SAS (version 9.3). We deemed a two-sided p value of less than 0·05 as statistically significant.

| | Hyperacute phase (first 24 h; n=2645) | Acute phase (days 2–7; n=2347) |
|---|---|---|
| Time from onset to randomisation (h) | 3·7 (2·8–4·7) | 3·7 (2·8–4·7) |
| Demographics | | |
| Age (years) | 63·5 (12·9) | 63·0 (12·6) |
| Men | 1643 (62·1%) | 1442 (61·4%) |
| Recruited from China | 1826 (69·0%) | 1714 (73·0%) |
| Clinical features | | |
| Systolic blood pressure (mm Hg) | 179·0 (16·9) | 178·9 (17·0) |
| Diastolic blood pressure (mm Hg) | 101·2 (14·6) | 101·6 (14·4) |
| NIHSS score* | 10 (6–15) | 10 (6–15) |
| GCS score† | 14 (13–15) | 14 (13–15) |
| Hypertension | 1917/2644 (72·5%) | 1703/2346 (72·6%) |
| Drugs for hypertension | 1188/2644 (44·9%) | 1037/2346 (44·2%) |
| Previous intracerebral haemorrhage | 214/2644 (8·1%) | 193/2346 (8·2%) |
| Previous ischaemic or undifferentiated stroke | 300/2644 (11·3%) | 270/2346 (11·5%) |
| Previous acute coronary event | 75/2644 (2·8%) | 59/2346 (2·5%) |
| Diabetes | 279/2644 (10·6%) | 247/2346 (10·5%) |
| Brain imaging intracerebral haemorrhage parameters | | |
| Haematoma volume (mL) | 10·7 (5·7–18·9) | 10·5 (5·7–18·0) |
| Deep location‡ | 2050/2444 (83·9%) | 1820/2167 (84·0%) |
| Intraventricular extension | 680/2444 (27·8%) | 586/2167 (27·0%) |
| Intravenous blood pressure lowering treatment | | |
| Bolus injection | 856 (32·4%) | 497/2346 (21·2%) |
| Continuous infusion | 1329 (50·2%) | 967/2346 (41·2%) |
| None | 1019 (38·5%) | 1194/2346 (50·9%) |
| 1 drug | 1172 (44·3%) | 838/2346 (35·7%) |
| ≥2 drugs | 454 (17·2%) | 314/2346 (13·4%) |
| Oral blood pressure lowering treatment | | |
| None | 1244 (47·0%) | 526/2346 (22·4%) |
| 1 drug | 835 (31·6%) | 697/2346 (29·7%) |
| ≥2 drugs | 566 (21·4%) | 1123/2346 (47·9%) |
| SD of systolic blood pressure | | |
| Initial 24 h (five readings) | 14·3 (7·4) | 14·2 (7·3) |
| Days 2–7 (12 readings) | .. | 13·1 (5·0) |

Data are mean (SD) or median (IQR) for continuous variables, and n (%) for categorical variables. NIHSS=National Institute of Health Stroke Scale. GCS=Glasgow Coma Scale. SD=standard deviation. *Scores range from 0 (normal neurological status) to 42 (coma with quadriplegia). †Scores range from 15 (fully conscious) to 0 (deep coma). ‡Deep location refers to location in the basal ganglia or thalamus.

***Table 1:*** **Baseline characteristics and blood pressure lowering treatment**

### Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the study data. The corresponding author had final responsibility for the decision to submit the paper for publication.

## Results

Of the 2839 participants in INTERACT2, 2645 were included in the analyses of the hyperacute phase and 2347 of the acute phase (figure 2). Baseline characteristics of patients at the time of randomisation were similar between the two phases (table 1). Mean age was 63·5 years, and 62·1% of participants were men, with 1381 participants (52·2%) having the primary outcome (death in 253, major disability in 1128) in the hyperacute phase, and 1179 (50·2%; death in 132, major disability in 1047) in the acute phase.

SD of systolic blood pressure in participants in both the intensive and guideline treatment groups fell from days 1 to 7, with the steepest decrease in the first hour after enrolment (figure 3, appendix p 11). Increasing SD of systolic blood pressure was significantly associated with greater intensity of blood pressure lowering treatment, both oral and intravenous (appendix pp 9–10). However, we detected no significant heterogeneity of associations between SD of systolic blood pressure and the primary outcome by randomised group, which supports our approach to combine both groups into a single cohort for multivariable analyses (appendix p 12).

In the hyperacute phase, SD of systolic blood pressure had a significant linear association with the primary outcome in all models (the highest quintile of SD of systolic blood pressure in model 3 adjusted OR 1·41, 95% CI 1·05–1·90; $p_{trend}$=0·0167; figure 4). All other parameters of systolic blood pressure variability were

significantly associated with the primary outcome in the fully adjusted model (table 2). The robustness of these data is supported by likelihood ratio tests, which show improved fitting of the variables for model 3 versus model 2 (appendix p 13). Similar patterns of association for SD of systolic blood pressure in the hyperacute phase were evident within each randomised group, although the trends were not significant (appendix pp 22–23).

SD of systolic blood pressure during the hyperacute phase had a similar linear association with the secondary outcome (the highest quintile in model 3 adjusted OR 1·43, 95% CI 1·14–1·80; $p_{trend}$=0·0014; appendix pp 15, 16). All other indices of systolic blood pressure variability were also significantly associated with the secondary outcome in the hyperacute phase (appendix p 16).

For the acute phase, SD of systolic blood pressure was significantly associated with the primary outcome for all models, although the relationship was much weaker than for the hyperacute phase. The association was only evident in the highest fifth of SD of systolic blood pressure (model 3 OR 1·57, 95% CI 1·14–2·17; $p_{trend}$=0·0124; figure 4). Similarly, we noted a modest non-linear association with the secondary outcome for all models. The association was only evident for the highest fifth of SD of systolic blood pressure (model 3 OR 1·46, 95% CI 1·13–1·88; $p_{trend}$=0·0044; appendix p 24). All other parameters of systolic blood pressure variability except average real variability were significantly associated with the primary and secondary outcomes in model 3 (table 2; appendix pp 14, 16).

The associations in both the hyperacute and acute phases were strong for participants outside of China but weak for participants in China; regional differences showed significant heterogeneity in the acute phase (appendix p 15).

Although minimum and maximum systolic blood pressures are highly correlated with mean systolic blood pressure, minimum systolic blood pressure was only significantly associated with outcome when adjusted for mean systolic blood pressure in model 3 (table 2). This finding suggests that assessing the risk of minimum systolic blood pressure in patients with high mean

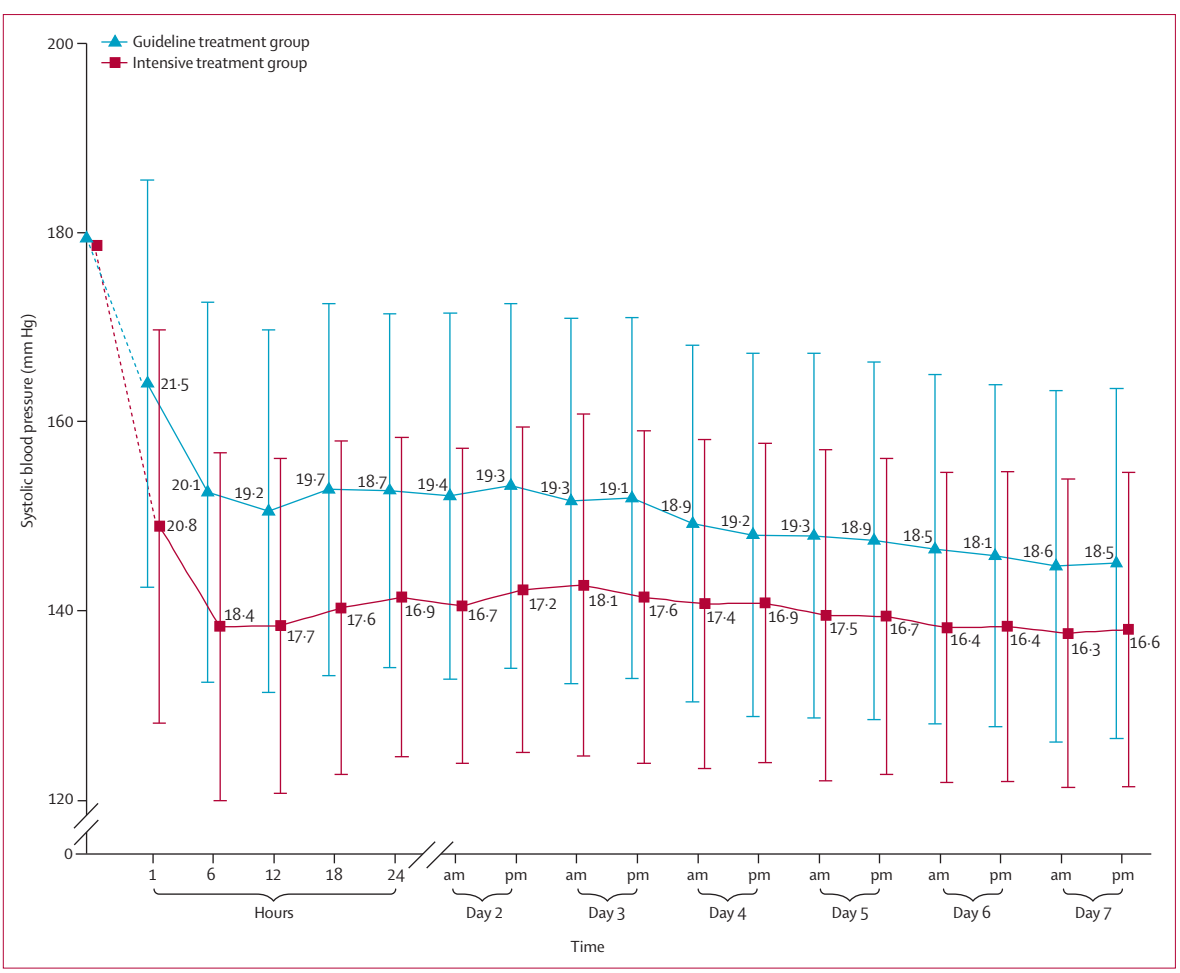


*Figure 3:* **Within-group mean systolic blood pressure and standard deviation of systolic blood pressure over time**
Note, the axes are broken.

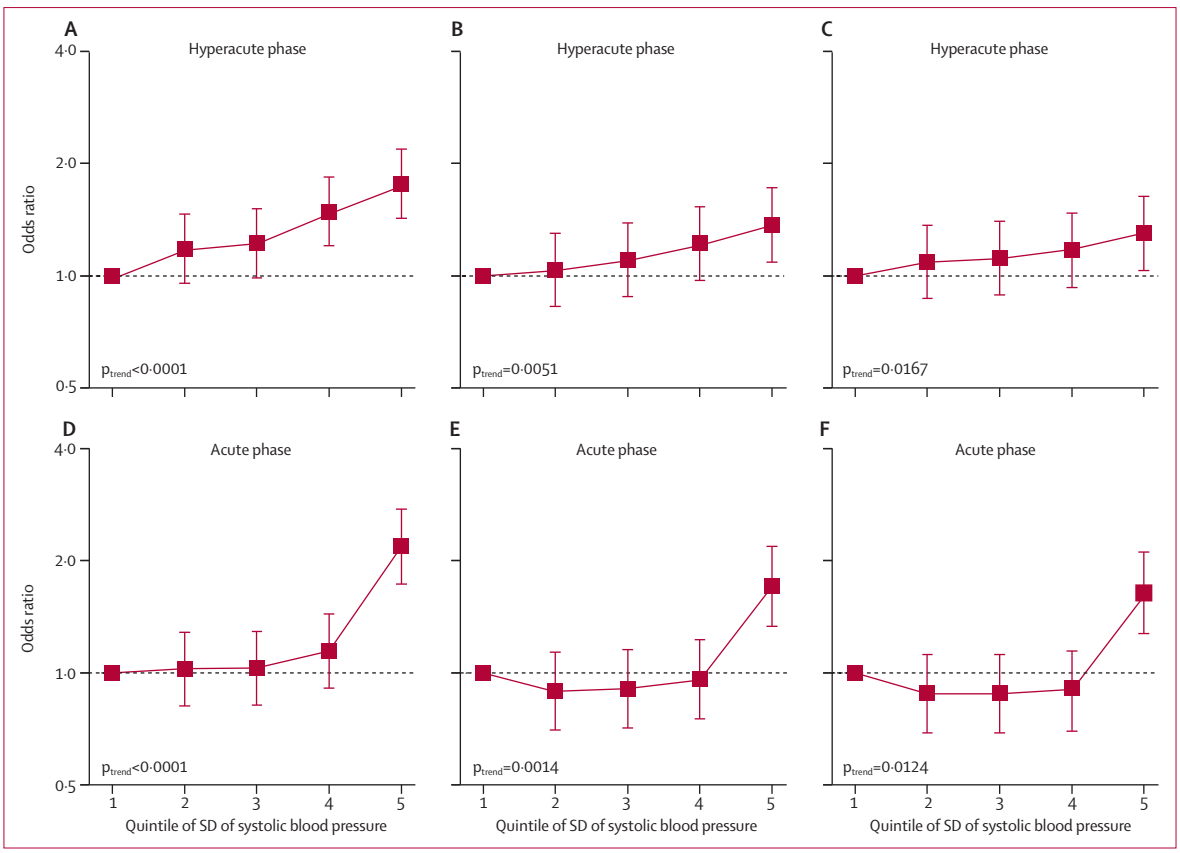


***Figure 4:*** **Association between quintiles of SD of systolic blood pressure and death or major disability at 90 days**
According to models 1–3 for the hyperacute phase (A–C) and models 1–3 for the acute phase (D–F). Lowest quintile is reference.

systolic blood pressure is complex. Although the ORs overlapped for the other parameters of blood pressure variability in model 3, results for the relative integrated discrimination index and Akaike's information criterion both indicate that the best predictors of outcome were maximum systolic blood pressure in the hyperacute phase and SD of systolic blood pressure in the acute phase (table 3). The associations between maximum systolic blood pressure and SD of systolic blood pressure in model 3 showed no heterogeneity, and we detected no co-linearity across any of the indices (all with variance inflation factor <5).

The degree of fall in systolic blood pressure was moderately correlated with both maximum systolic blood pressure (Spearman's correlation coefficient=0·48) and SD of systolic blood pressure (Spearman's correlation coefficient=0·45) in the hyperacute phase, but they were only weakly correlated in the acute phase (Spearman's correlation coefficients 0·18 and 0·21, respectively). The correlation between mean systolic blood pressure and each of SD of systolic blood pressure, maximum systolic blood pressure, and minimum systolic blood pressure was moderate-to-strong (Spearman's correlation coefficients >0·58) but the other parameters for blood pressure variability had only weak-to-moderate correlation in both hyperacute and acute phases (appendix pp 17–18). The associations between SD of systolic blood pressure during the acute phase and both primary and secondary outcomes were much the same for blood pressure measurements taken in the morning and evening, and when missing systolic blood pressure and other values were imputed in the models (data not shown). For the separate components of the primary outcome (ie, death and major disability), the associations between SD of systolic blood pressure and death had much the same patterns in the hyperacute and acute phases, but these associations were significant in the acute phase only; SD of systolic blood pressure was not associated with major disability at 90 days in either of the phases in the fully adjusted model (appendix pp 25–26). SD of systolic blood pressure in the first hour was not significantly associated with the primary outcome (data not shown). Moreover, SD of systolic blood pressure in the hyperacute phase and outcomes were not significantly associated when measurements taken in the first hour were included in the models (appendix p 27), nor if blood pressure data for only days 2–3 were assessed (data not shown). We noted significant effects of diastolic blood pressure and mean arterial pressure on the secondary outcome for both phases but not for the primary outcome (appendix pp 28–31).

959 patients were included in the 24 h CT scan substudy. SD of systolic blood pressure at 1–24 h after onset of intracerebral haemorrhage was not significantly associated with absolute haematoma growth at 24 h (4·5 mL in the highest fifth *vs* 2·2 mL in the lowest fifth of SDs of systolic blood pressure; $p_{trend}$=0·0277; appendix p 32). We also noted no association when these analyses were limited to or included the four measures taken in the first hour (0–24 h blood pressure measurements, 3·7 mL in the highest fifth *vs* 2·0 mL in the lowest fifth; $p_{trend}$=0·34).

## Discussion

We have shown that within-patient variation in systolic blood pressure from visit to visit—in both the hyperacute (within 24 h) and acute (over the subsequent week) periods after intracerebral haemorrhage—is an important determinant of outcome, independent of mean systolic blood pressure. The greater the variation of systolic blood pressure, the stronger the association with a poor outcome at 90 days, defined either by the conventional measure of death or major disability, or by the level of physical functioning according to the modified Rankin Scale score. Of the different parameters to measure blood pressure variability, mean and maximum systolic blood pressure are probably the most practical and were the most significant predictors of poor outcome. Our findings suggest, therefore, that it is important not only to rapidly reduce high systolic blood pressure soon after the onset of intracerebral haemorrhage, but also to ensure that blood pressure control is smooth and sustained for several days.

Our results are consistent with a small-scale, single-centre, observational study, which showed that systolic blood pressure variability (derived from resting measurements every 15 min) and systolic blood pressure load (percentage of measurements >180 mm Hg) in the first 24 h after intracerebral haemorrhage were independently associated with death or early neurological deterioration within 90 days (panel, appendix p 19).[18] These findings accord with several studies[34–36] of patients with ischaemic stroke who had received thrombolytic treatment, which showed significant associations between measures of systolic blood pressure variability and poor outcomes including death, secondary symptomatic intracerebral haemorrhage, and asymptomatic haemorrhagic transformation of cerebral infarction. Moreover, in a post-hoc analysis of a large clinical trial,[17] systolic blood pressure variability within the first 48 h after ischaemic stroke was significantly associated with death or early neurological deterioration within 10 days. Conversely, our findings differ from those of an analysis[21] of nearly 1000 patients enrolled in the CHHIPS and COSSACS trials, in which no significant associations were noted between early systolic blood pressure variability and death or dependency. However, this analysis was based on only a few measurements of blood pressure, short duration of follow-up (2 weeks), and a predominance of patients with ischaemic stroke recruited within 36 h (CHHIPS) and 48 h (COSSACS) after the onset of symptoms.

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| **Systolic blood pressure variability in first 24 h*** | | | | | | |
| Mean | 1·21 (1·11–1·33) | <0·0001 | 1·20 (1·08–1·33) | 0·0006 | .. | .. |
| SD | 1·27 (1·17–1·38) | <0·0001 | 1·18 (1·07–1·30) | 0·0007 | 1·16 (1·05–1·28) | 0·0029 |
| CV | 1·24 (1·14–1·34) | <0·0001 | 1·16 (1·05–1·27) | 0·0030 | 1·17 (1·06–1·29) | 0·0017 |
| Maximum | 1·31 (1·20–1·43) | <0·0001 | 1·23 (1·11–1·36) | <0·0001 | 1·21 (1·02–1·43) | 0·0309 |
| Minimum† | 0·97 (0·89–1·06) | 0·4995 | 0·95 (0·86–1·05) | 0·3451 | 1·31 (1·11–1·56) | 0·0020 |
| VIM | 1·24 (1·15–1·35) | <0·0001 | 1·16 (1·06–1·28) | 0·0020 | 1·16 (1·06–1·28) | 0·0020 |
| RSD | 1·26 (1·17–1·37) | <0·0001 | 1·16 (1·06–1·28) | 0·0019 | 1·15 (1·04–1·26) | 0·0052 |
| ARV | 1·27 (1·17–1·38) | <0·0001 | 1·20 (1·09–1·33) | 0·0002 | 1·18 (1·07–1·31) | 0·0006 |
| **Systolic blood pressure variability on days 2–7‡** | | | | | | |
| Mean | 1·25 (1·14–1·37) | <0·0001 | 1·17 (1·06–1·30) | 0·0028 | .. | .. |
| SD | 1·30 (1·19–1·42) | <0·0001 | 1·21 (1·09–1·33) | 0·0003 | 1·17 (1·05–1·30) | 0·0037 |
| CV | 1·25 (1·14–1·36) | <0·0001 | 1·17 (1·06–1·29) | 0·0023 | 1·16 (1·05–1·28) | 0·0041 |
| Maximum | 1·31 (1·20–1·44) | <0·0001 | 1·20 (1·09–1·33) | <0·001 | 1·19 (1·00–1·43) | 0·0505 |
| Minimum† | 0·97 (0·89–1·06) | 0·4579 | 0·97 (0·88–1·07) | 0·5688 | 1·20 (1·03–1·40) | 0·0167 |
| VIM | 1·23 (1·13–1·34) | <0·0001 | 1·16 (1·05–1·28) | 0·0041 | 1·16 (1·05–1·28) | 0·0041 |
| RSD | 1·31 (1·20–1·43) | <0·0001 | 1·20 (1·08–1·32) | 0·0005 | 1·16 (1·05–1·29) | 0·0053 |
| ARV | 1·24 (1·14–1·36) | <0·0001 | 1·11 (1·01–1·23) | 0·0363 | 1·07 (0·97–1·19) | 0·1828 |

Model 1 was adjusted for age, sex, and randomised group; model 2 was adjusted for all variables in model 1 plus region, haematoma volume at baseline, and high scores on the National Institutes of Health Stroke Scale; model 3 was adjusted for all variables in model 2 and mean SBP in each period. SD=standard deviation. CV=coefficient of variation. VIM=variation independent of mean. RSD=residual standard deviation. ARV=average real variability. OR=odds ratio. *From five measurements at 1 h, 6 h, 12 h, 18 h, and 24 h; patients who died during the first 24 h were excluded. †Per one SD decrement. ‡12 measurements from day 2 to 7 (morning and evening each day); patients who died during first 7 days were excluded.

***Table 2:*** **Effects of one SD increment of systolic blood pressure variability on major disability and death at 90 days**

| | Hyperacute phase (first 24 h) | | Acute phase (days 2–7) | |
|---|---|---|---|---|
| | rIDI (%) | AIC | rIDI (%) | AIC |
| Mean | 1·81% | 2701·06 | 1·54% | 2445·65 |
| SD | 1·65% | 2701·08 | 2·34% | 2441·29 |
| CV | 1·22% | 2703·93 | 1·65% | 2445·26 |
| Maximum | 2·47% | 2696·43 | 2·21% | 2441·82 |
| Minimum | 0·17% | 2711·94 | 0·03% | 2454·28 |
| VIM | 1·32% | 2703·14 | 1·47% | 2446·29 |
| RSD | 1·34% | 2703·06 | 2·12% | 2442·21 |
| ARV | 1·94% | 2698·37 | 0·80% | 2450·20 |

Adjusted for age, sex, randomised group, region, haematoma volume at baseline, and high score on the National Institutes of Health Stroke Scale. The rIDI is the percentage improvement in the average sensitivity and specificity of the fitted model when the index variable is added to the prediction model (higher scores are better). A low value for AIC indicates a close fit of the model to the true odds. rIDI=relative integrated discrimination index. AIC=Akaike's information criteria. SD=standard deviation. VIM=variation independent of the mean. RSD=residual standard deviation. ARV=average real variability.

***Table 3:*** **Discrimination between indices of systolic blood pressure variability and odds of major disability or death at 90 days**

The exact mechanism by which systolic blood pressure variability affects outcome of intracerebral haemorrhage is unknown. Large fluctuations in systolic blood pressure as a result of impaired cerebral autoregulatory control in microvascular channels could promote haematoma expansion, while oncotic or hydrostatic pressure gradients in the perihaematomal region might enhance the formation of cerebral oedema.[37] Although some[4,38] but not all[39,40] observational studies have shown an association between high systolic blood pressure and haematoma growth, the INTERACT2 CT scan substudy showed only a modest non-significant reduction in haematoma growth at 24 h after intensive treatment to reduce blood pressure,[7] and our other findings showed no association of blood pressure variability and haematoma growth. These results suggest that any modest beneficial effects of early reduction of blood pressure on the initial haemorrhage or cerebral oedema might take time to manifest. Blood pressure instability (and baroreceptor sensitivity) has been correlated with cerebral oedema in intracerebral haemorrhage in one observational study.[41] However, a rigorous but small randomised assessment of early rapid blood pressure reduction for patients with moderate size intracerebral haemorrhage did not show any alteration in perihaematomal perfusion or oedema.[42,43]

### *Panel:* Research in context

**Systematic review**

We searched Medline (from Jan 1, 1946) and Embase (from Jan 1, 1966) on Nov 14, 2013, with relevant text words and medical subject headings in any language that included "intracerebral haemorrhage" and "blood pressure variability". Studies were eligible for inclusion if they assessed the effect of blood pressure variability on the risk of clinical outcome. We identified no randomised trials or meta-analyses.

**Interpretation**

We identified only one single-centre hospital-based study[18] of 117 patients, which showed that systolic blood pressure variability in the first 24 h after the onset of intracerebral haemorrhage is an independent predictor of death or early neurological disability at 90 days. However, the strength of association was not reported in relation to one SD increases in systolic blood pressure variability, and reverse causality cannot be excluded. Our study of a large group of patients with predominantly mild-moderate size intracerebral haemorrhage from a randomised controlled trial (INTERACT2) shows that systolic blood pressure variability in both the hyperacute (the first 24 h) and acute phase (next several days) is associated with poor outcome independent of mean systolic blood pressure. These results further support early rapid lowering of high systolic blood pressure with an emphasis on smooth and sustained target-driven control (140 mm Hg) over several days to improve the chances of recovery after intracerebral haemorrhage. Further research will clarify whether different approaches to such treatment have beneficial effects.

Strengths of this study include the large sample size and number of blood pressure measurements, and the staged approach to development of multivariable models, which provide reassurance about the precision and reliability of the estimates of association. Furthermore, our results were consistent across different analyses, including within each randomised treatment group, and the generalisability of these results is strengthened by the wide range of patients who were included from a variety of hospitals in many countries, along with the use of several different blood pressure lowering regimens. However, the reason for the weaker association between systolic blood pressure variability and outcome for Chinese patients is not obvious. It could relate to differences in background treatment, including the common concurrent use of intravenous mannitol for acute treatment[7] in China.

The association of large and persistent fluctuations in systolic blood pressure with clinical outcomes provides useful insights into the mechanisms that might underlie the adverse effects of acute intracerebral haemorrhage. Particularly, we report a large difference for the predictive value of systolic and diastolic blood pressure variability in the acute phase of intracerebral haemorrhage. This finding is discordant with the epidemiological data, which show that mean systolic and diastolic blood pressure have similar risk associations for stroke and other major cardiovascular events.[44–47]

Our study has some limitations. Selection bias might have arisen because we excluded a population of patients with a poor prognosis—those who had a massive intracerebral haemorrhage or deep coma—and patients who had early surgery planned. Similarly, exclusion of patients who died during the hyperacute and acute phases might have introduced further selection bias. Moreover, patients enrolled in the trial had to present with persistent systolic blood pressure of 150–220 mm Hg, although this restriction might have limited the strength of association between blood pressure variability and outcome. Although we adjusted the models for several variables, residual confounding and reverse causality might still have occurred if patients with large haematomas and severe neurological deficits had high systolic blood pressure variability. Although based on prospectively collected data, our analysis was post-hoc and therefore prone to chance and confounding. However, because the data for blood pressure variability were based on a small number of measurements, particularly during the acute phase with twice daily resting measurements, we might have underestimated the true significance of blood pressure variability for outcome. Analysis of the prognostic value of visit-to-visit variability in other cohorts has shown steep increases in the reproducibility of measurement of variability[48] and strength of risk associations[15] with increasing number and frequency of measurements. Finally, the heterogeneity of treatments used creates uncertainty as to the best drug and approach (intermittent bolus *vs* infusion) to use in practice.

We believe our study has several implications for clinical practice. First, episodic hypertension, isolated high systolic blood pressure readings, and large fluctuations in systolic blood pressure in the first 24 h—and indeed over several days after intracerebral haemorrhage—are all associated with an increased risk of a poor outcome, independent of mean systolic blood pressure, which is often measured infrequently after a patient is admitted to hospital. Moreover, evidence now exists of a steep rise in systolic blood pressure in the days before the onset of intracerebral haemorrhage, suggesting that episodic hypertension is involved in triggering this illness in addition to affecting outcome.[49] Second, contrary to popular belief,[25,26] mean arterial pressure seems to be of little use because it has minimal prognostic value, possibly because it takes diastolic blood pressure into account. Thus, although the results of INTERACT2 reinforce the importance of early reduction of high systolic blood pressure, our results show that efforts should also be undertaken to ensure that blood pressure control is consistent and sustained over the first few days in hospital. Clinicians should not be falsely reassured by the presence of a few normal blood pressure readings in patients whose systolic blood pressure is fluctuating widely or is often high. The frequency and intensity of blood pressure monitoring might therefore need to be tailored to ensure consistency in the fall and stability of systolic blood pressure throughout the period in hospital. Taken together with reports by Rothwell and colleagues[14,50] on the potential different effects of different antihypertensive drugs on blood pressure variability, the therapeutic effects of targeting blood pressure variability in patients with intracerebral haemorrhage warrants further investigation.

#### Contributors

LM interpreted the data and wrote the first draft of the report. YH did the analyses and wrote the report. TGR, JC, RL, and CSA obtained funding, planned and supervised the study, interpreted data, and wrote the report. HA supervised and contributed to analyses, and wrote the report. XW, JW, EH, CD, BN, PL, SMD, CT, YH, CS, and MW provided comments on the report. PR interpreted the data and wrote the report.

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#### Declaration of interests

YH has been reimbursed for travel expenses from Osaka Pharmaceuticals. JW has received consulting fees from Novartis, Omron Healthcare, Pfizer, and Takeda; grant support from Novartis, Omron Healthcare, and Pfizer; lecture fees from A&D Pharma, Omron Healthcare, Novartis, Pfizer, and Servier; and reimbursement for travel expenses from Pfizer and Takeda. The other authors declare that they have no competing interests.

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