Lower Treatment Blood Pressure Is Associated With Greatest Reduction in Hematoma Growth After Acute Intracerebral Hemorrhage

Hisatomi Arima, Craig S. Anderson, Ji Guang Wang, Yining Huang, Emma Heeley, Bruce Neal, Mark Woodward, Christian Skulina, Mark W. Parsons, Bin Peng, Qing Ling Tao, Yue Chun Li, Jian Dong Jiang, Li Wen Tai, Jin Li Zhang, En Xu, Yan Cheng, Lewis B. Morgenstern, John Chalmers, for the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial Investigators

Abstract—The pilot phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) showed that rapid blood pressure (BP) lowering can attenuate hematoma growth in acute intracerebral hemorrhage. We sought to define the systolic BP level associated with greatest attenuation of hematoma growth. INTERACT included 404 patients with computed tomographic–confirmed intracerebral hemorrhage, elevated systolic BP (150 to 220 mm Hg), and capacity to commence BP lowering treatment within 6 hours of onset. Computed tomography was done at baseline and at 24 hours using standardized techniques, with digital images analyzed centrally, blinded to clinical data. Associations of baseline and achieved on-treatment (mean during the first 24 hours) systolic BP levels with the primary outcome of increase in hematoma volume were explored. There were 346 patients with duplicate computed tomographic scans. There was no significant association between baseline systolic BP levels and either the absolute or proportional growth in hematoma volume (P trend = 0.26 and 0.12, respectively). By contrast, achieved on-treatment systolic BP levels in the first 24 hours were clearly associated with both absolute and proportional hematoma growth (both P trend = 0.03). Maximum reduction in hematoma growth occurred in the one third of participants with the lowest on-treatment systolic BP levels (median: 135 mm Hg). Intensive BP reduction to systolic levels between 130 and 140 mm Hg is likely to provide the maximum protection against hematoma growth after intracerebral hemorrhage. (Hypertension. 2010;56:852-858.)

Key Words: stroke • intracerebral hemorrhage • hypertension • blood pressure lowering • clinical trial

A

acute intracerebral hemorrhage (ICH) is estimated to affect >1 million people worldwide each year,1 many of whom either die or are left seriously disabled.1,2 Early elevation of blood pressure (BP) is very common after ICH,3 with a number of observational studies showing strong associations of increasing levels of BP at presentation, with hematoma growth4,5 and subsequent poor outcome.6,7 The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) pilot phase was a randomized, controlled trial, which demonstrated that early intensive BP lowering was clinically feasible, well tolerated, and reduced hematoma growth in patients treated within 6 hours after the onset of ICH.8,9 The aims of this report are to determine the associations of baseline and achieved on-treatment systolic BP levels with hematoma growth and to define the BP target likely to provide maximum benefit in the acute phase of ICH.

Methods

Overview

INTERACT has been described in detail elsewhere.8–10 Briefly, 404 patients were recruited from a network of hospital sites in China, South Korea, and Australia during 2005–2007. Eligible patients were
aged ≥18 years with computed tomography (CT)–confirmed spontaneous ICH and elevated systolic BP (≥2 measurements of 150 to 220 mm Hg recorded ≥2 minutes apart), with the capacity to commence randomly assigned BP lowering treatment within 6 hours of ICH in a suitably monitored environment. Exclusion criteria were as follows: (1) a clear indication for, or contraindication to, intensive BP lowering; (2) ICH secondary to a structural cerebral abnormality or the use of a thrombolytic agent for any disease; (3) an ischemic stroke within 30 days; (4) deep coma; (5) significant prestroke disability or medical illness; and (6) early planned neurosurgical intervention.

**Treatment and Outcome Assessments**

Patients were randomly assigned to receive either an early intensive BP lowering treatment strategy or the recommended best practice standard of BP lowering at that time based on the American Heart Association guidelines published in 1999. For patients allocated to the intensive group, the goal was to achieve a systolic BP of 140 mm Hg within 1 hour of randomization and subsequently to maintain this target level for the next 7 days. In each country, a stepped intravenous protocol to lower BP was established before the start of the study on the basis of which drugs were available in that country. The lower limit of systolic BP needed for cessation of intravenous treatment was 130 mm Hg. For patients allocated to the guideline group, treatment was recommended to achieve a target systolic BP of ≤180 mm Hg.

BP levels were recorded in the nonparetic arm with the patient supine using an automated device with a standard cuff. Baseline BP was measured in duplicate with an interval of ≥2 minutes, and the mean of the 2 measurements was used. Likewise, achieved on-treatment BP was measured at 1, 6, 12, 18 and 24 hours after randomization, and the mean of these 5 measurements was calculated (the mean achieved BP). Groups of participants defined by tertiles of BP levels were used for the analyses of baseline BP and those of achieved BP.

Sites were required to perform CT scans on patients according to standardized techniques at baseline and at 24±3 hours after the initial CT. If the 24-hour CT was not done within the specified time period, this assessment was replaced by the first available scan after 27 hours or by the last available scan done between 6 and 21 hours. For each patient, uncompressed digital images were sought by the analysis laboratory in Digital Imaging and Communications in Medicine format identified only by the patient’s unique study number. Hematoma volumes were calculated independently by 2 trained neurologists who were blind to clinical data, treatment, and outcome. Hematoma volume was also log-transformed to remove skewness. All of the data were analyzed with SAS version 9.2 (SAS Institute).

**Results**

Of the 404 patients recruited, a total of 346 patients (85%) had baseline and 24-hour CT scans available for analyses. Patients with and without 2 CT scans had broadly similar baseline characteristics except for history of acute coronary events (2% with CT and 10% without CT; P=0.002), median time from onset to randomization (3.6 hours [interquartile range: 2.8 to 4.8 hours] and 4.0 hours [interquartile range: 3.0 to 5.1 hours]; P=0.05), median National Institutes of Health Stroke Scale score (9 [interquartile range: 5 to 14] and 13 [interquartile range: 7 to 18]; P=0.03), and median Glasgow Coma Scale score (14 [interquartile range: 13 to 15] and 14 [interquartile range: 11 to 15]; P=0.005). Among the 58 patients without repeat CT, 2 were dead and 7 had neurosurgical intervention before the 24-hour CT.

Table 1 shows the baseline characteristics of 346 patients with repeat CT scans according to tertiles of baseline and achieved on-treatment systolic BP levels. There were no clear differences in baseline characteristics across the tertile groups defined by baseline systolic BP. Conversely, patients with higher achieved systolic BP had higher baseline and National Institutes of Health Stroke Scale scores and lower baseline Glasgow Coma Scale scores and they were more likely to have intraventricular extension at admission and less likely to be assigned to receive early intensive BP lowering.

During the first 24 hours, 226 patients (65%) had their BP controlled using intravenous agents (104 [30%] urapidil, 96 [28%] frusenemide, 41 [12%] phenolamine, 20 [6%] glycerol trinitrate, 16 [5%] labetalol, 16 [5%] nicardipine, 7 [2%] hydralazine, and 2 [1%] metoprolol), 8 (2%) used topical nitrate patches, and 208 (60%) used oral drugs (129 [37%] calcium channel blocker, 116 [34%] angiotensin-converting enzyme inhibitor, 21 [6%] angiotensin II receptor antagonist, 21 [6%] diuretic, 26 [8%] β-blocker, and 15 [4%] some other agent). Patients with higher baseline systolic BP were more likely to receive both intravenous (frusenemide, urapidil, and phenolamine) and oral agents (calcium channel blocker, angiotensin-converting enzyme inhibitor, and β-blocker; all P<0.05). Achieved systolic BP was also associated with increased use of oral drugs (angiotensin-converting enzyme inhibitor and β-blocker, both P=0.02), whereas there was slightly decreased use of several intravenous agents (labetalol and hydralazine) among patients with higher achieved BP (both P<0.05). Among 174 patients who received early intensive BP lowering, 78 (45%) and 118 (68%) achieved the target systolic BP of 140 mm Hg within 1 hour and 6 hours postrandomization, respectively. Higher percentages of target BP achievement were observed in patient groups with lower baseline and achieved systolic BP (both P trend<0.004).

Among 346 patients with repeat CT scans, 254 (63%) had their 24-hour CT within the prespecified time window; only 32 patients (9%) with non-Digital Imaging and Communications in Medicine format CT scans had their hematoma volumes analyzed using the ABC/2 method. For the 3 groups defined by tertiles of baseline systolic BP of <171, 171 to 190, and ≥191 mm Hg, the median values were 162, 180, and...
Table 1. Baseline Characteristics by Tertiles of Baseline and Achieved On-Treatment Systolic BP Levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Systolic BP, mm Hg</th>
<th>Achieved Systolic BP, mm Hg</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic (Baseline Systolic BP, mm Hg)</td>
<td>(&lt;171 (n=117))</td>
<td>(171 \text{ to } 190 (n=113))</td>
<td>(190 \text{ to } 210 (n=116))</td>
</tr>
<tr>
<td>Median time from ICH onset to randomization, h</td>
<td>3.6 (2.7 to 4.8)</td>
<td>3.7 (2.9 to 4.9)</td>
<td>3.6 (2.8 to 4.4)</td>
</tr>
<tr>
<td>Age, y</td>
<td>64 (12)</td>
<td>61 (12)</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Asian</td>
<td>96</td>
<td>96</td>
<td>97</td>
</tr>
</tbody>
</table>

| Medical history                                     |                            |                              |         |
| Hypertension                                       | 66                          | 82                           | 73       | 0.19  |
| Previous ICH                                       | 10                          | 20                           | 4        | 0.16  |
| Ischemic stroke                                    | 11                          | 10                           | 11       | 0.98  |
| Acute coronary event                               | 4                           | 2                            | 1        | 0.08  |
| Diabetes mellitus                                  | 8                           | 8                            | 9        | 0.62  |

| Medication                                         |                            |                              |         |
| Antihypertensive therapy                           | 38                          | 48                           | 41       | 0.65  |
| No. of antihypertensive drug types \(\geq 2\)      | 9                           | 10                           | 12       | 0.96  |
| Types of antihypertensive drugs                    | 17                          | 17                           | 16       | 0.88  |
| Calcium channel blocker                            | 17                          | 17                           | 16       | 0.88  |
| ACE inhibitor                                       | 7                           | 9                            | 9        | 0.62  |
| Angiotensin II receptor antagonist                  | 2                           | 4                            | 2        | 0.99  |
| Diuretic                                           | 6                           | 4                            | 4        | 0.54  |
| \(\beta\)-Blocker                                  | 3                           | 5                            | 3        | 0.72  |
| Others                                             | 19                          | 23                           | 17       | 0.77  |
| Antiplatelet therapy                               | 11                          | 7                            | 5        | 0.09  |
| Warfarin anticoagulation                           | 2                           | 1                            | 0        | 0.16  |
| Lipid-lowering agent                               | 6                           | 5                            | 8        | 0.58  |
| Glucose lowering treatment                         | 3                           | 2                            | 2        | 0.65  |

| Clinical features                                   |                            |                              |         |
| Baseline systolic BP, mm Hg                         | 161 (6)                     | 180 (6)                      | 202 (8)  | <0.0001 |
| Baseline diastolic BP, mm Hg                        | 95 (11)                     | 103 (12)                     | 110 (13) | <0.0001 |
| Heart rate, bpm                                     | 78 (15)                     | 78 (14)                      | 80 (13)  | 0.32  |
| Median NIHSS score                                  | 9 (5 to 13)                 | 8 (5 to 14)                  | 10 (6 to 15) | 0.22 |
| Median GCS score                                    | 14 (13 to 15)               | 15 (12 to 15)                | 14 (13 to 15) | 0.97 |
| Baseline hematoma volume, mL                        | 8.9 (4.9 to 13.3)           | 11.2 (4.8 to 20.7)           | 8.9 (4.5 to 17.6) | 0.26 |
| Location of hematoma                                |                             |                              |         |
| Lobar                                              | 6                           | 12                           | 7        | 0.53 |
| Basal ganglia or thalamus                           | 89                          | 79                           | 83       | 0.53 |

(Continued)
Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Systolic BP, mm Hg</th>
<th>Achieved Systolic BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;171 (n=117)</td>
<td>171 to 190 (n=113)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Early intensive BP lowering</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

Data are %, mean (SD), or median (interquartile range). ACE indicates angiotensin-converting enzyme; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.

*Data are based on an ANCOVA, a Wilcoxon test, or a χ² test.

201 mm Hg, respectively. Absolute growth in hematoma volume was not significantly associated with baseline systolic BP levels (Figure 1; P trend=0.26); neither was proportional growth in hematoma volume (Figure 2; P trend=0.12). For the 3 groups defined by tertiles of achieved on-treatment systolic BP of <144, 144 to 158, and ≥159 mm Hg, the median values were 135, 150, and 167 mm Hg, respectively. The association of absolute hematoma growth with achieved on-treatment systolic BP was strong and continuous in the range of achieved systolic BP levels of 135 to 167 mm Hg (Figure 1). These associations remained strong after controlling for age, sex, hematoma location, baseline hematoma volume, time from onset of ICH to CT, and study treatment (P trend=0.03). Similar associations were observed between achieved-on-treatment systolic BP and proportional hematoma growth (Figure 2; P trend=0.03). Similar effects of baseline and achieved on-treatment systolic BP were observed for proportional increase in hematoma volume after excluding baseline hematoma volume from the multivariate model. There were no clear differences in the effects of baseline or achieved on-treatment BP on either absolute or proportional growth of hematoma obtained for patient groups defined by age (<65 versus ≥65 years), sex, randomized treatment allocation, location of hematoma (lobar versus other), method of CT analysis (multislice planimetric and voxel threshold techniques versus the ABC/2 method), and time of 24-hour CT (within versus beyond 3 hours; all P homogeneity >0.1). In contrast to systolic BP, neither baseline nor achieved on-treatment diastolic BP was significantly associated with absolute and proportional hematoma growth (all P trend >0.2).

Figure 3 also shows that there were significant associations of achieved systolic BP with absolute and proportional increase in hematoma volume (P=0.01 and 0.04, respectively). Table 2 shows the results of multiple regression analysis, where achieved on-treatment systolic BP was positively associated with absolute and proportional increase in hematoma volume, but these associations did not reach standard levels of statistical significance (P=0.06 and 0.13 for absolute and proportional increase, respectively).

Achieved on-treatment systolic BP was associated with hematoma volume at 24 hours as well, being 9.5 (95% CI: 8.6 to 10.5), 10.1 (95% CI: 9.1 to 11.3), and 11.3 (95% CI: 10.3 to 12.5) ml for the 3 groups defined by tertiles of achieved on-treatment systolic BP after controlling for age, sex, hematoma location, baseline hematoma volume, time from onset of ICH to CT scan, and study treatment (P trend=0.004).

**Discussion**

The main results from the pilot phase of INTERACT showed that early intensive BP lowering reduced hematoma growth in patients treated within 6 hours after the onset of ICH.8,9

Figure 1. Absolute increase in hematoma volume according to tertiles of baseline and achieved on-treatment systolic BP (SBP) levels. Estimates and P values were controlled for age, sex, hematoma location, baseline hematoma volume, time from onset to CT scan, and study treatment. Solid boxes represent estimates of hematoma growth. Centers of the boxes are placed at the estimates and at median values of SBP; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Vertical lines represent 95% CIs. P trend=0.26 for baseline and 0.03 for achieved SBP.
although the effect just missed statistical significance when adjustments were made for baseline imbalances between groups. The current analysis now demonstrates strong and continuous associations of achieved on-treatment systolic BP levels during the first 24 hours and measures of hematoma growth. Moreover, these data reveal that the maximum treatment effect was observed in patients who achieved the lowest systolic BP levels (median: 135 mm Hg). Because hematoma growth is a strong predictor of poor outcome in ICH, these analyses suggest that early intensive BP reduction to lower BP levels is likely to be maximally beneficial in patients with acute ICH. This agrees with the conclusion from a recent meta-regression analysis, which investigated the relationship between therapeutic BP reduction and clinical outcomes in this patient group.

Several observational studies have demonstrated strong and continuous associations between baseline BP levels and hematoma growth in acute ICH, whereas others involving patients whose BP levels were assessed within just a few hours of ICH have not showed such clear associations. The present analyses of INTERACT provide some explanation for the discrepancy in these findings of previous reports: associations between baseline BP levels and hematoma growth were not statistically significant, whereas strong and continuous associations were observed between achieved on-treatment BP levels and hematoma growth at 24 hours. Potential beneficial effects of early BP lowering are, therefore, supported by achieved BP levels after the initiation of such treatment being stronger predictors of hematoma growth than baseline BP levels in acute ICH.

Existing guidelines for the management of acute ICH generally recommend treatment in patients with systolic BP levels of >160 mm Hg, but they also acknowledge uncertainty as to the most appropriate lower BP target. In a prospective observational study, a reduction of BP to a target of 160/90 mm Hg was associated with hematoma expansion of 9%, which is lower than has been seen in other studies. Another prospective observational study, for example, demonstrated a lower risk of hematoma growth among patients treated with target systolic BP levels of 150 mm Hg compared with those treated with target systolic BP levels of ≥160 mm Hg. These observational analyses of INTERACT are consistent with the hypothesis generated by such previous studies concerning the likely optimal BP target for prevention of hematoma growth: patients with acute ICH might have the lowest risk of hematoma growth if their systolic BP was reduced to 130–140 mm Hg and have this level sustained for 24 hours.

Key strengths of INTERACT are the relatively large sample size of patients with early and rigorous evaluations made after acute ICH. However, the trial still had relatively limited power to define significant effects of achieved on-treatment systolic BP in each set of analyses. Moreover, because the present evaluation was restricted to those patients...
with repeat CT at 24 hours, who had better clinical status (lower National Institutes of Health Stroke Scale and higher Glasgow Coma Scale scores) at baseline, and who did not die or have surgical evacuation of the hematoma during the first 24 hours, the findings may not be applicable to patients with severe ICH. Although the relationship between achieved on-treatment BP and hematoma growth may have arisen from BP elevating effects of ongoing bleeding during the first 24 hours, the randomized evidence of beneficial effects of intensive BP lowering on hematoma growth in INTERACT\textsuperscript{8,9} supports the role of achieved on-treatment BP lowering being an important determinant of attenuation of hematoma growth.

**Perspectives**

The present data reaffirm hypotheses about potential beneficial effects of early intensive BP lowering treatment on the hematoma growth in ICH. They also support the idea that the maximum beneficial effects against hematoma growth and subsequent poor outcome in this condition are likely to be obtained in those patients who achieve the lowest BP levels during the first 24 hours after onset, particularly those who achieve on-treatment levels of systolic BP between 130 and 140 mm Hg. However, although these results may appear persuasive, they cannot be seen as definitive given that the data presented are observational and secondarily derived from a single study. Moreover, intensive BP reduction may lower cerebral perfusion pressure and induce ischemia in a zone of hypoperfused tissue surrounding the hematoma,\textsuperscript{21} and there remains uncertainty over the clinical benefits to be derived from modest reduction in hematoma growth. Indeed, the Factor Seven for Acute Hemorrhagic Stroke Trial failed to show any improvement in survival or functional outcome resulting from a reduction in hematoma growth from early use of recombinant activated Factor VIIa, although this study was likely complicated by imbalances in baseline prognostic factors among randomized groups, comorbid effects of residual disability in older patients, thromboembolic adverse effects, and limited statistical power.\textsuperscript{22} Therefore, we do not recommend an updating of present guidelines for the management of BP in acute stroke\textsuperscript{23} but rather continuation of efforts to resolve this area of clinical equipoise, such as with the ongoing second (main phase) INTERACT2 study, which is powered to assess the effects of early BP lowering on substantive clinical end points in ICH.\textsuperscript{24}

**Sources of Funding**

The INTERACT was supported by a program grant (358395) from the National Health and Medical Research Council of Australia.

**Disclosures**

H.A. holds a postdoctoral research fellowship from the University of Sydney. C.S.A. holds a senior principal research fellowship from the National Health and Medical Research Council and has received consulting and lecture fees from Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi-Aventis, and Servier. J.G.W. has received consulting and lecture fees from Astra-Zeneca, Novartis, Omron, Pfizer, and Servier. B.N. has received consulting fees from Pfizer, Roche, and Takeda; lecture fees from Amgen, Astra Zeneca, GlaxoSmithKline, Pfizer, Roche, Sanofi Aventis, Servier, and Tanabe; and research support from Johnson and Johnson, Merck Schering Plough, Servier, and the United Healthcare Group. M.W. has received consulting and conference fees from Astra Zeneca, Roche, Glaxo Smith Kline, Pfizer, and Servier. L.B.M. is on a medical adjudication board for Wyeth. J.C. has received lecture fees and research grants administered through the University of Sydney as coprincipal investigator for the Perindopril Protection against Recurrent Stroke Study and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial from Servier.

**References**


**Table 2. Predictors of Absolute and Proportional Increase in Hematoma Volume**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Absolute Increase, β (95% CI)</th>
<th>Proportional Increase, β (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved on-treatment systolic BP, per 10 mm Hg</td>
<td>0.692 (−0.019 to 1.403)</td>
<td>0.021 (−0.006 to 0.049)</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>−0.749 (−1.672 to 0.174)</td>
<td>−0.038 (−0.074 to −0.003)</td>
</tr>
<tr>
<td>Sex, male vs female</td>
<td>−0.169 (−2.498 to 2.160)</td>
<td>0.013 (−0.076 to 0.102)</td>
</tr>
<tr>
<td>Location of hematoma, lobar vs others</td>
<td>2.221 (−1.882 to 6.324)</td>
<td>0.168 (0.011 to 0.326)</td>
</tr>
<tr>
<td>Log of baseline hematoma volume, per 1</td>
<td>−0.138 (−1.268 to 0.992)</td>
<td>−0.080 (−0.124 to −0.037)</td>
</tr>
<tr>
<td>Time from ICH onset to CT, per 1 h</td>
<td>−0.668 (−1.685 to 0.348)</td>
<td>−0.036 (−0.075 to 0.003)</td>
</tr>
<tr>
<td>Randomized treatment, intensive vs standard</td>
<td>−0.912 (−3.266 to 1.441)</td>
<td>−0.053 (−0.143 to 0.037)</td>
</tr>
</tbody>
</table>

Values were calculated by a linear regression model.

*Proportional increase in hematoma volume was log-transformed to remove skewness after additional of the value 1.1 to eliminate negative values.
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Hypertension. 2010;56:852-858; originally published online September 7, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.154328

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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