Background and Purpose—Blood pressure (BP) lowering is often conducted as part of general acute management in patients with acute intracerebral hemorrhage. However, the relationship between BP after antihypertensive therapy and clinical outcomes is not fully known.

Methods—Hyperacute (<3 hours from onset) intracerebral hemorrhage patients with initial systolic BP (SBP) >180 mm Hg were included. All patients received intravenous antihypertensive treatment, based on predefined protocol to lower and maintain SBP between 120 and 160 mm Hg. BPs were measured every 15 minutes during the initial 2 hours and every 60 minutes in the next 22 hours (a total of 30 measurements). The mean achieved SBP was defined as the mean of 30 SBPs, and associations between the mean achieved SBP and neurological deterioration (≥2 points' decrease in Glasgow Coma Scale or ≥4 points' increase in National Institutes of Health Stroke Scale score), hematoma expansion (>33% increase), and unfavorable outcome (modified Rankin Scale score 4–6 at 3 months) were assessed with multivariate logistic regression analyses.

Results—Of the 211 patients (81 women, median age 65 [interquartile range, 58–74] years, and median initial National Institutes of Health Stroke Scale score 13 [8–17]) enrolled, 17 (8%) showed neurological deterioration, 36 (17%) showed hematoma expansion, and 87 (41%) had an unfavorable outcome. On multivariate regression analyses, mean achieved SBP was independently associated with neurological deterioration (odds ratio, 4.45; 95% confidence interval, 2.03–9.74 per 10 mm Hg increment), hematoma expansion (1.86; 1.09–3.16), and unfavorable outcome (2.03; 1.24–3.33) after adjusting for known predictive factors.

Conclusions—High achieved SBP after standardized antihypertensive therapy in hyperacute intracerebral hemorrhage was independently associated with poor clinical outcomes. Aggressive antihypertensive treatment may ameliorate clinical outcomes. (Stroke. 2013;44:00-00.)

Key Words: acute intracerebral hemorrhage • antihypertensive therapy • outcome

Blood pressure (BP) lowering therapy is widely performed as part of general acute management in patients with acute intracerebral hemorrhage (ICH). An acute hypertensive response is common in patients with acute ICH, occurring in ≤75%, and elevated BP is associated with hematoma expansion and poor outcome. Recent trials have demonstrated that rapid BP lowering with antihypertensives is feasible and tolerated, and it suppresses hematoma expansion.
expansion. However, the benefit of antihypertensive therapy in acute phase of stroke is still controversial, because the patients with ICH in the recent Scandinavian Candesartan Acute Stroke Trial (SCAST) did not benefit from candesartan, and concerns also exist about excessive depression of BP in the acute phase of ICH, as it may result in renal dysfunction, cerebral ischemia, and death. Given these circumstances, the optimal BP target in patients with acute ICH has not been fully elucidated.

Moreover, although elevated BP in the acute phase is a proven predictor of worse clinical outcomes in patients with ICH, the effect of the response to acute BP lowering on the clinical outcomes of patients with ICH has been relatively unclear, because there have been few prospective studies, and antihypertensive regimens (drugs, dosage, and route) and target BPs were not standardized in most such studies.

We hypothesized that a relatively high mean systolic BP (SBP) after BP lowering therapy was associated with worse clinical outcomes than a low mean SBP. The aims of the present study were to clarify the relationship between mean on-treatment SBP and outcomes, and to determine the optimal SBP threshold to avoid worse clinical outcomes in patients with acute ICH.

Methods

Subjects The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH Study was a prospective, multicenter, observational study to determine the safety and feasibility of early (within 3 hours from symptom onset) SBP reduction to <160 mm Hg with intravenous nicardipine for acute hypertension in patients with spontaneous ICH. The details of the study have been described elsewhere. In brief, acute spontaneous supratentorial ICH patients with hypertension (initial SBP >180 mm Hg), who were treated within 3 hours from onset in 10 Japanese stroke centers were enrolled. Other inclusion criteria were: age 20 years old; total NIHSS score ≥5; computed tomography <2.5 hours from onset demonstrating a supratentorial intraparenchymal hematoma with manual volume measurement <60 mL; and absence of extensive intraventricular hemorrhage. Patients with unreliable time of symptom onset, ICH because of cerebral neoplasms, arteriovenous malformations, aneurysms, trauma, bleeding diathesis, or coagulopathy; candidates for immediate surgical intervention for ICH; current pregnancy, parturition within the previous 30 days or active lactation, thrombolytic time international normalized ratio ≥1.7 because of warfarin intake, and a platelet count <50,000/mm³ were excluded. Each local ethics committee approved this study. Written informed consent was obtained from all patients or their next of kin.

The patients’ clinical background characteristics, including sex, age, cardiovascular risk factors, and comorbidities were collected from medical charts. Routine blood biochemistry examinations were performed on admission. Neurological manifestations were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Functional outcome was estimated using the modified Rankin Scale (mRS).

Hematomas volume was evaluated with noncontrast computed tomography on admission and 24 (±6) hours after the initiation of antihypertensive treatment. The ABC/2 (length×width×height/2) method was used to determine hematoma volume at the bedside by the neurologist or neurosurgeon on admission and at 24 hours.

BP Management and Monitoring

Bolus infusion of 1 mg nicardipine was allowed before the titrating infusion. Titrated of intravenous nicardipine was started within 3 hours of symptom onset and continued for 24 hours, based on a standardized protocol to achieve and maintain the target SBP level <160 mm Hg and >120 mm Hg. BP management after the first 24 hours was at the primary neurologist’s discretion. Oral antihypertensive agents were started after the first 24 hours.

BP and pulse rate were taken using manual or automated sphygmomanometer under established guidelines. All staffs were familiarized with the sphygmomanometer before the study by using it in general practice. The arm was placed horizontal at the level of the heart as denoted by the midster nal level in a recumbent position. BP and pulse rate were measured every 15 minutes during the initial 2 hours and every 60 minutes in the next 22 hours (30 measurements in the initial 24 hours after the initiation of antihypertensive therapy), as well as at 48 and 72 hours. To test the hypothesis, the mean achieved SBP (aSBP) was defined as the mean of a total of 30 SBPs in the initial 24 hours after the initiation of BP lowering therapy.

Clinical Outcomes

The clinical outcomes included: neurological deterioration corresponding to a decrease of ≥2 points from the baseline Glasgow Coma Scale score or an increase of ≥4 points from the baseline NIHSS score at 72 hours after the initiation of treatment; hematoma expansion >33% from baseline to 24 hours; and unfavorable outcome corresponding to patients with modified Rankin Scale scores of 4 to 6 at 3 months after ICH onset. Patients who underwent surgical intervention for ICH were regarded as having an unfavorable outcome regardless of the modified Rankin Scale score.

Statistical Analysis

Clinical background characteristics, including mean aSBP were compared between patients with and without unfavorable outcomes. Univariate analyses were performed using the χ² test, Fisher exact test, or the Kruskal–Wallis test, as appropriate. The data are presented as median values (interquartile range) or frequencies (%). Multivariate logistic regression analyses were performed to elucidate the associations between mean aSBP and outcomes. Sex, age, and prior antithrombotic medication, initial SBP, initial NIHSS score, onset to initial computed tomography examination time, initial hematoma volume, and serum glucose level at baseline, which are known predictors of clinical outcomes based on previous studies, were forced into model 1. In model 1, mean aSBP was entered as a continuous variable or a categorical variable based on quartiles and arbitrarily defined 5 mm Hg interval groups (<130 mm Hg, 130–135 mm Hg, 135–140 mm Hg, 140–145 mm Hg, and ≥145 mm Hg). Alternative model 2 included all variables in Table 1, and a backward stepwise selection procedure was performed using P>0.1 of the likelihood ratio test for exclusion. All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc, Chicago, IL). Results were considered significant at P<0.05.

Results

From July 2009 through June 2011, 211 patients (81 women, median age 65 [interquartile range, 58–74] years, and median initial NIHSS score 13 [8–17]) were included in the SAMURAI-ICH study. Table 1 shows the clinical background characteristics of the included patients. The initial computed tomographic scan was performed at a median of 70 minutes from onset, and baseline hematoma volume was 10.2 (5.6–19.2) mL. The initial SBP was 200 (189–213) mm Hg. The time to reach the target range was 30 (15–45) minutes, and the proportion of time in the target SBP range after having fallen to being within the range was 78.0%. For 7 patients, nicardipine was insufficient, and additional intravenous antihypertensive drugs (diltiazem in 3, nitroglycerin in 3, and isosorbide nitrate in 1) were started.
patients received hematoma evacuation surgery after starting antihypertensive treatment and being regarded as having an unfavorable outcome. As shown by the variables in Table 1, patients with an unfavorable outcome were older (70 [63–79] years versus 62 [55–69] years; \(P<0.001\)) and had a higher initial NIHSS score (15 [12–20] versus 10 [6–15]; \(P<0.001\)) and hematoma volume (14.0 [8.0–25.1] mL versus 9.0 [4.0–17.9] mL; \(P=0.001\)) than those with a favorable outcome. Levels of serum albumin (4.0 [3.8–4.3] g/dL versus 4.2 [4.0–4.5] g/dL; \(P=0.001\)) and total cholesterol (186 [156–211] mg/dL versus 202 [176–226] mg/dL; \(P=0.002\)) were lower in patients with unfavorable than with favorable outcomes. The mean aSBP was higher in patients with unfavorable (139 [134–143] mm Hg) than with favorable (137 [131–141] mm Hg) outcomes (\(P=0.012\)).

Neurological deterioration was observed in 17 (8%), hematoma expansion in 36 (17%), and unfavorable outcome in 87 (41%) patients. Results of multivariate logistic regression analyses are presented in Table 2 and Figures 1 and 2. Every 10 mm Hg increment of mean aSBP was associated with a 4.5-fold increase in neurological deterioration, a 1.8-fold increase in hematoma expansion, and a 2.0-fold increase in unfavorable outcome after multivariate adjustment (Table 2).

Favorable outcome: patients with modified Rankin scale 0–3 at 3 mo from onset. Unfavorable outcome: patients with modified Rankin scale 4–6 at 3 mo from onset or who received hematoma evacuation surgery.

aSBP indicates achieved systolic blood pressure; CT, computed tomography; HR, heart rate; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and SBP indicates systolic blood pressure.

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=211)</th>
<th>Favorable Outcome (n=124)</th>
<th>Unfavorable Outcome (n=87)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>81 (38)</td>
<td>50 (40)</td>
<td>31 (36)</td>
<td>0.566</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>65 (58–74)</td>
<td>62 (55–69)</td>
<td>70 (63–79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>26 (12)</td>
<td>16 (13)</td>
<td>10 (12)</td>
<td>0.834</td>
</tr>
<tr>
<td>Prior antithrombotic medication, n (%)</td>
<td>24 (11)</td>
<td>13 (11)</td>
<td>11 (13)</td>
<td>0.664</td>
</tr>
<tr>
<td>Liver cirrhosis, n (%)</td>
<td>10 (5)</td>
<td>7 (6)</td>
<td>3 (3)</td>
<td>0.530</td>
</tr>
<tr>
<td>Vascular risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>176 (83)</td>
<td>104 (84)</td>
<td>72 (83)</td>
<td>0.853</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (14)</td>
<td>17 (14)</td>
<td>12 (14)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>87 (41)</td>
<td>54 (44)</td>
<td>33 (38)</td>
<td>0.478</td>
</tr>
<tr>
<td>Current smoking</td>
<td>67 (32)</td>
<td>44 (36)</td>
<td>23 (26)</td>
<td>0.179</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>120 (57)</td>
<td>73 (59)</td>
<td>47 (54)</td>
<td>0.572</td>
</tr>
<tr>
<td>SBP on admission, mm Hg, median (IQR)</td>
<td>200 (189–213)</td>
<td>198 (189–212)</td>
<td>200 (190–216)</td>
<td>0.160</td>
</tr>
<tr>
<td>HR on admission, bpm, median (IQR)</td>
<td>80 (70–92)</td>
<td>80 (70–93)</td>
<td>78 (70–90)</td>
<td>0.474</td>
</tr>
<tr>
<td>Initial NIHSS score, median (IQR)</td>
<td>13 (8–17)</td>
<td>10 (6–15)</td>
<td>15 (12–20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset to CT, minutes, median (IQR)</td>
<td>70 (59–94)</td>
<td>74 (58–97)</td>
<td>65 (60–89)</td>
<td>0.181</td>
</tr>
<tr>
<td>Initial hematoma volume, mL, median (IQR)</td>
<td>10.2 (5.6–19.2)</td>
<td>9.0 (4.0–17.9)</td>
<td>14.0 (8.0–25.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematoma on left side, n (%)</td>
<td>101 (48)</td>
<td>61 (49)</td>
<td>40 (46)</td>
<td>0.676</td>
</tr>
<tr>
<td>Hematoma location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>Putamen</td>
<td>121 (57)</td>
<td>76 (61)</td>
<td>45 (52)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>76 (36)</td>
<td>38 (31)</td>
<td>38 (44)</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>14 (7)</td>
<td>10 (8)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Biochemistry sign at admission, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.1 (3.9–4.4)</td>
<td>4.2 (4.0–4.5)</td>
<td>4.0 (3.8–4.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Leukocyte count, /μL</td>
<td>6900 (5400–8300)</td>
<td>6800 (5300–8400)</td>
<td>6900 (5600–8300)</td>
<td>0.662</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>121 (107–144)</td>
<td>121 (105–145)</td>
<td>124 (107–143)</td>
<td>0.595</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>194 (169–224)</td>
<td>202 (176–226)</td>
<td>186 (156–211)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.70 (0.60–0.90)</td>
<td>0.70 (0.60–0.90)</td>
<td>0.70 (0.60–0.90)</td>
<td>0.530</td>
</tr>
<tr>
<td>Mean aSBP, mmHg, median (IQR)</td>
<td>137 (133–142)</td>
<td>137 (131–141)</td>
<td>139 (134–143)</td>
<td>0.012</td>
</tr>
</tbody>
</table>
The thresholds of the mean aSBP quartiles were 132.8, 137.4, and 142.1 mm Hg. Patients with the lowest mean aSBP quartile had a lower rate of neurological deterioration (odds ratio, 0.06; 95% confidence interval, 0.007–0.54), hematoma expansion (0.27; 0.07–0.98), and unfavorable outcome (0.18; 0.06–0.55) compared with those with the highest quartile (Figure 1). Similarly, neurological deterioration (odds ratio could not be estimated because neurological deterioration did not occur in patients with mean aSBP <135 mm Hg) and unfavorable outcome (odds ratio, 0.13; 95% confidence interval, 0.03–0.55) compared with those with the highest quartile (Figure 1). Similarly, neurological deterioration (odds ratio could not be estimated because neurological deterioration did not occur in patients with mean aSBP <135 mm Hg) and unfavorable outcome (odds ratio, 0.13; 95% confidence interval, 0.03–0.51) were less common, and hematoma expansion (0.20; 0.04–1.15) was marginally less common in patients with mean aSBP <135 mm Hg than in those with mean aSBP ≥145 mm Hg (Figure 2). The odds ratios of worse clinical outcomes increased gradually as mean aSBP rose. Leaving out the 7 patients with surgery did not change these findings significantly (Table 2).

### Discussion

This prospective study demonstrated that acute SBP after standardized intravenous antihypertensive therapy was independently associated with neurological deterioration, hematoma expansion, and unfavorable outcome in patients with acute ICH. The rates of poor clinical outcomes increased gradually as mean aSBP rose.

The relationships between elevated BP after antihypertensive therapy and poor clinical outcomes were partly in line with previous studies. Ohwaki et al reported that maximum SBP after nonstandardized antihypertensive treatment was independently associated with hematoma enlargement. We previously reported that mean SBP lowering to <138 mm Hg during the initial 24 hours was associated with more favorable early outcome than SBP of 138 mm Hg or higher after antihypertensive therapy mainly with intravenous nicardipine or nitroglycerin. Leira et al showed that high SBP within 48 hours after nonstandardized antihypertensive therapy with intravenous labetalol or captopril in acute ICH patients with BP >185/105 mm Hg was independently associated with early neurological deterioration. However, few data showed the association between response after standardized BP lowering therapy and clinical/radiological outcomes, such as neurological deterioration, hematoma expansion, and unfavorable outcome. Indeed, a large prospective trial using predefined, standardized antihypertensive strategy found that, although a lower SBP target in acute ICH suppressed hematoma expansion,
the clinical outcome did not differ between the lower and the standard target SBP groups.\textsuperscript{10}

The SAMURAI-ICH was a prospective study that included supratentorial ICH patients within 3 hours from onset treated with a standardized antihypertensive regimen regarding the first-choice drug, administration/titration method, and frequency of BP measurement. These homogeneous factors may reduce possible bias. Moreover, frequent BP measurement may contribute to differentiating between patients with and without worse clinical outcomes. Elevated BP in acute ICH promotes further active bleeding, resulting in hematoma expansion.\textsuperscript{9} Because hematoma expansion is correlated with early neurological deterioration\textsuperscript{20} and poor outcome,\textsuperscript{21} high mean aSBP was independently associated with neurological deterioration and unfavorable outcome through hematoma expansion in the present study. Although perihematomal edema was not measured, increased edema\textsuperscript{22} is also a potential mechanism for the relatively high proportion of neurological deterioration or unfavorable outcome in patients with high mean aSBP.

The rates of poor clinical outcomes increased gradually as mean aSBP rose with standardized BP lowering. Excessive BP reduction in acute ICH patients is considered to be harmful rather than beneficial.\textsuperscript{13-16} The optimal target SBP in patients with acute ICH has been unclear,\textsuperscript{1,2} and the present study showed that patients with the lowest quartile, corresponding to mean aSBP <132.8 mmHg or mean aSBP <130 mmHg, have the lowest proportions of worse clinical outcomes. On the basis of these results, the optimal threshold for worse clinical outcomes was \( \approx 130 \) mmHg, and therefore the optimal target SBP in acute ICH might be \( \approx 130 \) mmHg.

There are some limitations in the present study that need to be addressed. First, because the SAMURAI-ICH study was an observational study that did not compare groups with different SBP targets, the optimal target SBP cannot be determined from the results of the present study. It is difficult to differentiate whether high aSBP is a cause or a consequence of worse clinical/radiological outcomes, although neurological deterioration or hematoma expansion was not reported to be followed by subsequent BP elevation.\textsuperscript{11} Ongoing large randomized trials\textsuperscript{23-25} are expected to resolve these problems. Second, the present target SBP (<160 mmHg) follows the recent guidelines from the American Heart Association/American Stroke Association\textsuperscript{1}; the target level was different from that in the ongoing trials.\textsuperscript{23-25} Third, the use of nicardipine in patients with acute ICH may not be always beneficial, because nicardipine has mild antiplatelet properties,\textsuperscript{26} although there is no direct evidence of hematoma expansion because of the antiplatelet effect of nicardipine.

In conclusion, high SBP after initiation of standardized antihypertensive treatment was independently associated with neurological deterioration, hematoma expansion, and unfavorable functional outcome in acute ICH. A mean aSBP \( \geq 130 \) mmHg was associated with the lowest odds ratios for worse clinical outcomes. Aggressive antihypertensive treatment for such patients may ameliorate clinical outcomes.

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