Stroke

CLINICAL TRIAL

Temporal Trajectory of Systolic Blood Pressure and Outcomes in Acute Intracerebral Hemorrhage: ATACH-2 Trial Cohort

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BACKGROUND: To highlight the heterogeneity of acute temporal blood pressure (BP) changes in the ATACH-2 trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage-2) and associations with the outcomes of intracerebral hemorrhage.

METHODS: One thousand patients with acute intracerebral hemorrhage, who had been randomized to intensive (110–139 mm Hg) or standard (140–179 mm Hg) systolic BP (SBP) lowering with intravenous nicardipine in ATACH-2 from 2011 to 2015, were analyzed about temporal changes in hourly maximum SBP up to 24 hours after randomization using group-based trajectory modeling. Outcomes included death or disability (modified Rankin Scale score 4–6) at 3 months, neurological deterioration within 24 hours (≥2-point decrease in Glasgow Coma Scale score or ≥4-point increase in National Institutes of Health Stroke Scale score), and acute kidney injury (≥0.3 mg/dL within 48 hours or ≥1.5-fold increase in serum creatinine) within 7 days after onset.

RESULTS: Group-based trajectory modeling revealed 4 SBP trajectory groups: moderate SBP (from ≈190 mm Hg at hospital arrival to 150–160 mm Hg after randomization; n=298), moderate-to-low SBP (from ≈190 mm Hg to <140 mm Hg; n=395), high-to-low SBP (from >210 mm Hg to <140 mm Hg; n=134), and high SBP (from >210 mm Hg to 160–170 mm Hg; n=173). Patients with intensive treatment accounted for 11.1%, 88.6%, 85.1%, and 1.7% of each group, respectively. Compared with the moderate-to-low SBP group, the high-to-low SBP group showed increased risks of death or disability at 3 months (adjusted odds ratio, 2.29 [95% CI, 1.24–4.26]) and acute kidney injury (adjusted odds ratio, 3.50 [95% CI, 1.83–6.69]), while no increase in neurological deterioration was seen in this group (adjusted odds ratio, 0.48 [95% CI, 0.20–1.13]). The moderate SBP and high SBP groups showed no significant risk differences for such outcomes.

CONCLUSIONS: Data-driven observation using a group-based trajectory modeling approach may be useful to clarify the relationship between antihypertensive treatment, temporal SBP changes, and outcomes in acute intracerebral hemorrhage.

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Key Words: acute kidney injury ■ antihypertensive agents ■ blood pressure ■ cerebral hemorrhage ■ nicardipine

Elevated blood pressure (BP) is frequently observed in acute intracerebral hemorrhage.[1] Past observational studies have suggested that early reduction of BP using antihypertensive agents has the potential to lower the risk of hematoma growth and neurological deterioration.[2,3] In this context, intensive reduction of systolic

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Nonstandard Abbreviations and Acronyms

ATACH	Antihypertensive Treatment of Acute Cerebral Hemorrhage
BIC	Bayesian Information Criterion
GBTM	group-based trajectory modeling
OR	odds ratio
SBP	systolic blood pressure

BP (SBP) has been evaluated in randomized clinical trials but has demonstrated either only a small magnitude benefit or no benefit at all.[4,5] In genuine clinical settings, some patients show good response to antihypertensive agents, whereas others require a higher dosage or use of additional antihypertensives. This may be attributed to differences in the strength of the acute hypertensive response,[6] which may be associated with differences in the outcomes of BP lowering between observational studies and randomized clinical trials and could be reflected in the heterogeneity of hourly BP changes in response to antihypertensive treatments aimed at target BP ranges.

To observe the heterogeneity of temporal BP changes in acute intracerebral hemorrhage, data from the ATACH-2 trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage) may be suitable since BP goals were randomly assigned and the first-line antihypertensive agent was designated as intravenous nicardipine in the predetermined plan for dose adjustment.[5] As a methodology for objective and reproducible modeling of time-based longitudinal data, group-based trajectory modeling (GBTM) is reportedly applicable to disclose the distinctive trajectories of BP in patients with acute stroke.[7,8] This modeling approach provides an exploratory capacity to identify previously unrecognized SBP trajectories that emerge from the data itself, rather than assuming the existence of trajectories of a specific form before the statistical analysis of data begins. The objective of this study was to highlight the heterogeneity of temporal SBP changes in the ATACH-2 trial using GBTM and associations with the outcomes of acute intracerebral hemorrhage.

METHODS

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Study Population

The ATACH-2 trial was an international, randomized, 2-group, open-label trial to determine the efficacy of rapid lowering of SBP in patients with acute spontaneous intracerebral hemorrhage. A detailed description of the protocol has been provided elsewhere.[5] Briefly, patients with Glasgow Coma Scale score ≥5 and SBP ≥180 mm Hg on hospital arrival and intraparenchymal hematoma showing a volume <60 mL on initial noncontrast computed tomography were centrally randomized to undergo either intensive SBP lowering (target SBP: 110–139 mm Hg) or standard SBP lowering (target SBP: 140–179 mm Hg) in a 1-to-1 ratio within 4.5 hours of symptom onset from 2011 to 2015. Intravenous nicardipine infusion was initiated at 5 mg/h, then increased by 2.5 mg/h every 15 minutes as needed, up to a maximum of 15 mg/h to reduce the hourly minimum SBP to the target level within 2 hours of randomization, and to maintain this level through 24 hours for each subject. Once the target SBP level was reached, the infusion rate was adjusted by 1 to 2.5 mg/h to maintain SBP within the specific range. If SBP was greater than the target despite infusion of the maximum dose of nicardipine for 30 minutes, a prespecified secondary agent (intravenous labetalol, diltiazem, or urapidil) was used. Informed consent was obtained from each subject, their legally authorized representative, or their next of kin.

Data Collection

SBP data were collected from the timing of hospital arrival through the first 24 hours after randomization. SBP data were collected every 15 minutes for the first 1 hour after randomization followed by every 1 hour for the remainder of the first 24 hours. For each time interval, maximum and minimum SBP data were collected. A detailed protocol for BP measurement can be found in the Supplemental Methods.

The following demographic and clinical data were collected: recruitment site (Asia or not), sex, age, past clinical history including hypertension, diabetes, hyperlipidemia, atrial fibrillation, stroke/transient ischemic attack before the index event, coronary heart disease, and congestive heart failure, smoking habit, prescription of antihypertensive agents, Glasgow Coma Scale, National Institutes of Health Stroke Scale score, white blood cell count, platelet count, blood glucose, and serum creatinine. Glasgow Coma Scale and National Institutes of Health Stroke Scale score were measured by a physician at baseline and by nursing staff or a physician 24 hours after treatment initiation. Laboratory measurements were performed at baseline and 24, 48, and 72 hours after treatment initiation. Noncontrast computed tomography was performed at baseline and 24 hours after initiation of treatment and analyzed by a reader who was blinded to treatment assignment, clinical findings, and time points of image acquisition. Parenchymal hematoma volume was measured using automated delineation with manual correction by computer software on each slice containing the hematoma. Maximum dose of intravenous nicardipine in each time interval corresponding to SBP data was collected.

Postdischarge follow-up included telephone contact at 1 month to collect information on serious adverse events and deaths, and in-person clinical evaluation at 3 months to assess modified Rankin Scale, including deaths, by blinded study investigators trained and certified in the use of the structured interview method of obtaining the modified Rankin Scale score. All adverse events were coded using the Medical Dictionary for Regulatory Activities.

Group-Based Trajectory Modeling

We adopted a GBTM approach using the Stata traj plugin to identify SBP trajectories from the timing of hospital arrival through the first 24 hours after randomization. This is a specialized form of finite mixture modeling, and longitudinal SBP

data were fitted by a maximum likelihood method as a mixture of multiple latent trajectories in a censored normal model with a polynomial function of time.[8] Each trajectory can be linear or take more complex shapes according to the polynomial functions. In this study, we set 29 time points from hospital arrival to 24 hours after randomization. These set time points were as follows: (1) hospital arrival time was allocated as 90 minutes before randomization (median actual time interval from hospital arrival to randomization =89 minutes); (2) timing at randomization was allocated as 0 minute; (3–6) 15, 30, 45, and 60 minutes after randomization; and (6–29) 120 to 1440 minutes with an interval of 60 minutes (Table S1). We modeled 363 combinations of the number of groups and degree of polynomials as follows: (1), (2), (3), (1 1), (1 2), (1 3), (2 1), (2 2), (2 3), (3 1), (3 2), (3 3), …, (3 3 3 3 1), (3 3 3 3 2), and (3 3 3 3 3). Considering the study objective and model parsimony, we assumed that the number of groups should be up to 4, but to reduce the possibility of unintentionally eliminating the optimal model, we created models with a maximum of 5 groups. Candidate models were selected if the Bayesian Information Criterion (BIC) for the total number of observations was ≥95th percentile of the BIC set of models sharing the same group number. In the context of GBTM, selection of the model with the largest (least-negative) BIC is recommended,[8] and this accepted practice was followed in the present study. For every participant, we calculated the posterior probability of being a member of each group in the selected model. Odds of correct classification based on the posterior probabilities of group membership were also calculated to test the adequacy of the model. The proportion of the smallest group was specified as >5%. Missing data were handled by fitting the model using maximum likelihood estimation in which data were assumed to be missing at random. We assigned a descriptive label for each trajectory group on the basis of the patterns of SBP changes over time.

Outcomes

The primary outcome of this study was death or disability (modified Rankin Scale score 4–6) at 3 months. Secondary outcomes were as follow: (1) death within 3 months; (2) hematoma expansion of ≥33% in volume on computed tomography images obtained at 24 hours compared with the baseline scan; (3) neurological deterioration within 24 hours (decrease from baseline of ≥2 points in Glasgow Coma Scale score or an increase from baseline of ≥4 points in National Institutes of Health Stroke Scale score); (4) acute kidney injury within 7 days (increase in serum creatinine by ≥0.3 mg/dL within 48 hours or increase in serum creatinine to ≥1.5 times baseline within 7 days)[9]; (5) renal adverse events within 7 days; (6) cardiac adverse events within 7 days; and (7) brain infarction adverse events within 7 days. Severity of acute kidney injury was classified into (1) stage 1, 1.5 to 1.9 times baseline serum creatinine; (2) 2.0 to 2.9 times baseline; and (3) stage 3, ≥3.0 times baseline.[9] Serious adverse events were defined as adverse events that resulted in death, a life-threatening adverse experience, new or prolonged hospitalization, or persistent or significant disability or incapacity.[5] Renal, cardiac, and brain infarction adverse events were classified with the use of terminology from Medical Dictionary for Regulatory Activities.[5]

Statistical Analysis

Data were summarized with mean (SD) or median (interquartile range) for continuous variables and frequencies and percentages for categorical variables. Statistical differences were assessed using 1-way ANOVA, the Kruskal-Wallis test, or Pearson χ^2 test among the trajectory groups, as appropriate.

Logistic regression models were created to elucidate the association of primary and secondary outcomes with trajectory grouping. Multivariable adjustments were made for sex, age, recruited sites (Asia or non-Asia), prescribed antihypertensive medication, baseline National Institutes of Health Stroke Scale score, white blood cell count, serum creatinine, baseline hematoma volume, time from onset to randomization, treatment assignment (intensive or standard SBP lowering), SBP at randomization, maximum dosage of nicardipine, use of secondary antihypertensive agents, and mechanical ventilation. Odds ratios (ORs) with 95% CIs were calculated.

To examine the robustness of SBP trajectory grouping, we performed a sensitivity analysis with a model with the next highest BIC. Subgroup analysis for evaluation of 2-way interactions was not performed due to the insufficient sample size in this study.

In analyses using the selected trajectory model, missing data were handled using a pairwise-deletion approach. All statistical analyses were performed using Stata/MP statistical package, version 16.1 (Stata Corp LP, College Station, TX).

RESULTS

The 1000 randomized subjects with acute intracerebral hemorrhage from 110 clinical sites from 6 countries were analyzed. The brute-force search with GBTM approach found 20 candidate models for SBP trajectories from hospital arrival to 24 hours after randomization (Table S2). Among the candidate models, a 4-group model with 4 cubic terms showed the highest BIC (Figure). Averages for the posterior probability of assignment to each group were high (>0.90). The odds of correct classification also exceeded 5.0 for all groups, indicating that the model offered high assignment accuracy. A close correspondence was seen between the estimated proportion of a group and the proportion of individuals classified to the group. Descriptive labels were assigned to each of the 4 trajectory groups: Group 1, Moderate SBP group; Group 2, Moderate-to-low SBP group; Group 3, High-to-low SBP group; and Group 4, High SBP group. A study flow chart is shown in Figure S1.

Measured hourly maximum and minimum SBPs in each trajectory group are shown in Table 1. The moderate SBP group (Group 1, n=298) showed SBP of ≈190 mm Hg on hospital arrival and hourly maximum SBPs ranging from ≈150 to 160 mm Hg after randomization. In the moderate-to-low SBP group (Group 2, n=395), SBP was ≈190 mm Hg on arrival at the hospital, and both hourly maximum SBP and hourly minimum SBP remained at <140 mm Hg until 1440 minutes after randomization. The high-to-low SBP group (Group 3,

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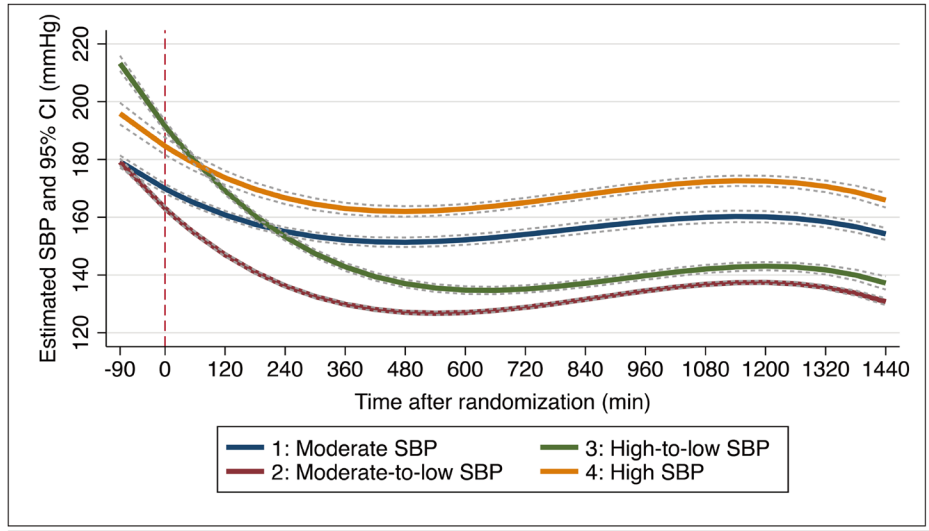

Group	n (%)	Average posterior probability	Odds of correct classification	Estimated proportion for each group
1	298 (29.8%)	0.91	25.22	29.1%
2	395 (39.5%)	0.97	59.41	39.3%
3	134 (13.4%)	0.93	92.09	13.8%
4	173 (17.3%)	0.93	60.74	17.8%

Figure. Trajectory groups of 24-h systolic blood pressure and model fit statistics.
SBP indicates systolic blood pressure.

n=134) showed SBP >210 mm Hg on hospital arrival and hourly minimum SBP was immediately lowered to <140 mm Hg at 120 minutes after randomization but hourly maximum SBP remained >140 mm Hg up to 480 minutes after randomization. The high SBP group (Group 4, n=173) indicates hourly maximum SBPs ranging from 160 to 170 mm Hg after randomization with a SBP >210 mm Hg on hospital arrival.

Baseline data for the 4 SBP trajectory groups are summarized in Table 2. Among the 4 groups, the high-to-low SBP group was youngest ($P<0.01$) and showed a relatively higher rate of current smokers ($P=0.06$). White blood cell count was highest in the high-to-low SBP group ($P<0.01$). Creatinine level ($P=0.02$) and baseline hematoma volume ($P=0.07$) were higher in the high-to-low and high SBP groups than in the moderate and moderate-to-low SBP groups.

Treatment characteristics were distinctively different among the 4 groups (Table 3). The moderate-to-low and high-to-low SBP groups were assigned to intensive SBP lowering in 88.6% and 85.1% of patients, respectively, and the moderate and high SBP groups were assigned to receive intensive treatment in 11.1% and 1.7%, respectively ($P<0.01$). The maximum dosage of nicardipine was highest in the high-to-low SBP group ($P<0.01$), and the use of secondary antihypertensive agents was most frequent in this group ($P<0.01$). More than half of the antihypertensive agents used as a secondary agent were labetalol (Table S3). Mechanical ventilation was used most frequently in the high-to-low SBP group ($P<0.01$).

Outcomes

Using the moderate-to-low SBP group as a reference, the high-to-low SBP group showed significantly higher risks of death or disability at 3 months (adjusted OR, 2.29 [95% CI, 1.24–4.26]), acute kidney injury within 7 days (adjusted OR, 3.50 [95% CI, 1.83–6.69]), renal adverse events within 7 days (adjusted OR, 2.84 [95% CI, 1.22–6.62]), and cardiac adverse events within 7 days (adjusted OR, 2.26 [95% CI, 1.10–4.64]), but no increase in the risk of neurological deterioration (adjusted OR, 0.48 [95% CI, 0.20–1.13]; Table 4). The incidence of hematoma expansion was lowest in the high-to-low SBP group, but no significant differences were seen among the 4 groups ($P=0.09$).

Death or disability at 3 months was more common in patients with hematoma expansion (55.5% [101/182]) than in those without (34.2% [266/779]; $P<0.01$), and it was also more frequent in patients with neurological deterioration (78.0% [71/91]) than in those without (34.0% [296/870]; $P<0.01$).

Among the total of 126 cases with acute kidney injury, the distribution of severity was 82.5% for stage 1, 11.9% for stage 2, and 5.6% for stage 3. The severity distribution of acute kidney injury and details of renal and cardiac adverse events by the SBP trajectory groups are shown

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Table 1. Mean Hourly SBP Measured at Set Time Points in Each Trajectory Group

Set time point, min	−90*	0	60	120	180	240	300	360	420	480
Group 1: Moderate SBP, mean±SD, mm Hg										
Hourly maximum	194.3±23.1	169.9±21.1	154.4±16.2	157.3±14.9	155.0±14.3	153.7±14.6	154.8±15.7	155.8±15.4	153.9±15.9	154.8±16.2
Hourly minimum	…	…	146.3±16.3	137.6±15.9	136.3±15.7	136.1±16.0	139.5±15.9	138.9±16.2	137.6±16.6	138.4±16.5
Group 2: Moderate-to-low SBP, mean±SD, mm Hg										
Hourly maximum	194.6±24.3	167.6±21.2	141.4±15.6	140.9±15.7	136.1±14.7	134.3±14.9	131.8±13.3	131.9±14.8	131.6±13.5	131.3±12.4
Hourly minimum	…	…	132.5±15.1	122.6±15.8	119.4±13.1	118.9±12.6	119.2±12.1	118.5±12.9	118.0±11.7	119.7±11.7
Group 3: High-to-low SBP, mean±SD, mm Hg										
Hourly maximum	215.8±29.0	195.9±27.0	170.6±21.8	166.9±20.1	153.0±21.1	146.9±21.5	144.8±17.9	140.6±14.9	141.6±13.8	140.6±15.5
Hourly minimum	…	…	157.5±20.3	133.7±21.2	127.7±17.3	126.2±16.7	125.3±15.9	122.9±15.1	124.4±13.1	124.2±13.9
Group 4: High SBP, mean±SD, mm Hg										
Hourly maximum	213.2±28.5	184.2±26.0	166.4±20.5	172.2±20.0	167.1±18.0	166.4±17.2	165.7±19.6	165.0±17.5	164.1±15.6	163.5±13.3
Hourly minimum	…	…	155.2±19.7	143.5±17.4	143.1±17.9	145.4±15.7	143.3±17.2	144.2±15.9	145.8±16.0	145.9±17.1
Set time point, min	540	600	660	720	840	960	1080	1200	1320	1440
Group 1: Moderate SBP, mean±SD, mm Hg										
Hourly maximum	155.2±17.7	155.5±14.7	155.4±14.2	155.5±13.1	157.7±14.2	156.2±14.2	158.2±14.7	157.1±13.9	157.8±14.5	157.7±15.4
Hourly minimum	139.6±15.7	140.7±16.0	140.8±15.6	141.7±14.8	142.8±14.4	142.9±16.2	144.3±15.8	144.9±15.7	144.6±16.2	144.6±16.5
Group 2: Moderate-to-low SBP, mean±SD, mm Hg										
Hourly maximum	131.9±12.5	131.5±12.4	131.7±12.1	132.0±11.6	131.8±12.2	132.1±12.8	132.5±12.8	134.2±12.9	135.5±10.8	136.1±11.5
Hourly minimum	119.7±12.0	120.0±11.4	120.7±12.1	121.5±11.2	120.8±11.0	120.8±12.3	122.0±11.6	123.7±11.8	125.2±11.2	126.8±11.7
Group 3: High-to-low SBP, mean±SD, mm Hg										
Hourly maximum	139.6±16.5	138.3±14.4	138.7±12.2	138.2±11.2	138.1±10.9	138.3±12.9	138.3±14.2	140.1±12.3	140.5±12.8	142.9±13.5
Hourly minimum	124.2±14.1	123.3±13.0	126.1±12.0	126.1±11.7	125.9±11.4	125.0±12.3	126.8±12.7	128.1±13.5	128.6±14.3	129.4±15.2
Group 4: High SBP, mean±SD, mm Hg										
Hourly maximum	166.3±13.1	167.5±14.8	167.4±14.7	169.5±16.8	168.1±14.2	168.6±14.7	169.3±14.8	170.6±17.9	170.4±15.7	170.2±19.8
Hourly minimum	147.5±15.5	148.1±15.8	149.7±17.1	149.4±16.7	149.9±15.8	150.2±15.0	150.6±15.7	152.0±16.4	152.9±17.9	152.1±15.7

SBP indicates systolic blood pressure.
*At hospital arrival.

in Tables S4 through S6. The causes of the total of 67 deaths were respiratory arrest in 26.9%, cardiovascular events in 19.4%, brain herniation in 14.9%, infection in 7.5%, and others in 31.3%. Causes of deaths in each group are demonstrated in Table S7.

Percentages of death or disability at 3 months were 35.2% (295/837) for patients without acute kidney injury and 58.1% (72/124) for those with acute kidney injury ($P<0.01$). These percentages were 37.4% (339/906) for patients without renal adverse events and 50.9% (28/55) for those with renal adverse events ($P=0.04$), and 36.2% (313//864) for patients without cardiac adverse events and 55.7% (54/97) for those with cardiac adverse events ($P<0.01$; Figure S2). Death or disability at 3 months were encountered in 38.7% of patients in the intensive SBP treatment group and in 37.7% in the standard treatment group ($P=0.75$).

Sensitivity Analysis Using a Model With the Next Highest BIC

A 5-group model with 3 cubic terms and 2 linear terms, which showed the highest BIC next to the 4-group model in the main analysis, was used for sensitivity analysis (Figure S3). Similar trajectories to those in the main analysis model were identified in this 5-group model; a newly found disparate trajectory was the high-to-moderate SBP trajectory. As with the main analysis, risks of death or disability (adjusted OR, 2.60 [95% CI, 1.41–4.81]), acute kidney injury (adjusted OR, 4.31 [95% CI, 2.22–8.36]), renal adverse events (adjusted OR, 2.94 [95% CI, 1.25–6.88]), and cardiac adverse events (adjusted OR, 2.21 [95% CI, 1.08–4.52]) were significantly higher in the high-to-low SBP group when compared with the moderate-to-low SBP group (Table S8). In the high-to-moderate SBP group, hematoma expansion was more common than in the high-to-low SBP group, but other outcomes were less frequent than in the high-to-low SBP group.

DISCUSSION

The present exploratory analysis of ATACH-2 data using the GBTM approach suggested the presence of distinct groups of SBP trajectories up to the first 24 hours from randomization. We identified 4 unique SBP trajectories:

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Table 2. Baseline Characteristics

	Group 1: Moderate SBP (n=298)	Group 2: Moderate-to-low SBP (n=395)	Group 3: High-to-low SBP (n=134)	Group 4: High SBP (n=173)
Male	187 (62.8%)	238 (60.3%)	81 (60.4%)	114 (65.9%)
Age, y, mean (SD)	61.0 (13.1)	63.9 (12.8)	59.1 (12.7)	61.4 (13.4)
Recruited at sites in Asia	155 (52.0%)	217 (54.9%)	75 (56.0%)	90 (52.0%)
Past medical history				
Hypertension	230 (78.5%)	313 (81.5%)	113 (86.3%)	137 (83.0%)
Diabetes	49 (16.4%)	78 (19.7%)	22 (16.4%)	37 (21.4%)
Hyperlipidemia	69 (24.4%)	109 (29.4%)	24 (19.5%)	39 (23.9%)
Atrial fibrillation	9 (3.0%)	20 (5.1%)	2 (1.5%)	5 (2.9%)
Stroke/transient ischemic attack	52 (17.4%)	56 (14.2%)	24 (18.2%)	32 (18.7%)
Coronary heart disease	10 (3.4%)	22 (5.7%)	5 (3.8%)	7 (4.1%)
Congestive heart failure	11 (3.7%)	15 (3.8%)	2 (1.5%)	9 (5.3%)
Current smoking	74 (24.8%)	92 (23.3%)	45 (33.6%)	53 (30.6%)
Prescribed antihypertensive medication	142 (48.0%)	200 (50.9%)	63 (47.4%)	90 (52.6%)
Glasgow Coma Scale score, median (IQR)	15.0 (13.0–15.0)	15.0 (14.0–15.0)	15.0 (12.0–15.0)	14.0 (13.0–15.0)
NIHSS score, median (IQR)	11.0 (7.0–16.0)	11.0 (6.0–16.0)	11.0 (6.0–16.0)	11.0 (7.0–15.0)
White blood cell count, $\times 10^3/\mu L$, median (IQR)	7.4 (5.9–9.3)	7.3 (5.9–9.4)	8.2 (6.5–10.3)	7.8 (6.4–9.7)
Platelet count, $\times 10^3/\mu L$, median (IQR)	212.0 (180.0–256.0)	214.0 (178.0–254.0)	218.0 (181.0–270.0)	214.0 (181.0–255.0)
Glucose, mg/dL, median (IQR)	120.2 (106.0–153.0)	119.5 (105.0–148.0)	126.0 (110.0–152.0)	126.0 (107.0–153.0)
Creatinine, mg/dL, median (IQR)	0.8 (0.7–1.1)	0.8 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.2)
Baseline hematoma volume, mL, median (IQR)	10.1 (5.1–17.9)	9.5 (4.9–17.1)	11.2 (5.4–20.8)	11.3 (6.1–20.6)
Location of hematoma				
Basal ganglia	168 (56.6%)	219 (55.4%)	76 (56.7%)	99 (57.2%)
Thalamus	87 (29.3%)	131 (33.2%)	48 (35.8%)	54 (31.2%)
Lobar	41 (13.8%)	45 (11.4%)	10 (7.5%)	20 (11.6%)
Pons/cerebellum	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraventricular extension	80 (27.1%)	90 (23.0%)	36 (27.1%)	52 (30.4%)
Hydrocephalus	39 (13.2%)	51 (13.0%)	18 (13.5%)	25 (14.6%)

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

moderate, moderate-to-low, high-to-low, and high SBP. Among these 4 SBP trajectory groups, the high-to-low SBP group showed increased risks of death or disability at 3 months after onset. The risks of acute kidney injury and renal and cardiac adverse events also increased in the high-to-low SBP group, but the risk of neurological deterioration did not.

In this analysis, the high-to-low SBP group displayed the lowest frequency of hematoma expansion, but the highest frequency of acute kidney injury and renal and cardiac adverse events, which may have increased the risks of death or disability in this patient group. The rates of such adverse events in the moderate-to-low SBP group were similar with the moderate SBP and high SBP groups, although the hourly minimum SBP was maintained at 120 to 130 mm Hg in both the moderate-to-low SBP group and the high-to-low SBP group. In a previous subanalysis of ATACH-2 for SBP levels achieved after intracerebral hemorrhage, hematoma expansion was increased, but cardiorenal adverse events were decreased in the group with an average hourly minimum SBP of 140 to 150 mm Hg or ≥150 mm Hg compared with the group of 120 to 130 mm Hg, suggesting that beneficial effects of lowering and maintaining SBP at 120 to 130 mm Hg on clinical outcomes by suppressing hematoma expansion are offset by cardiorenal complications.[10] The same analysis also showed that the greater the reduction in SBP from initial SBP, the greater the frequency of cardiorenal adverse events.[10] A hospital-based cohort study suggested that intensive SBP reduction of >90 mm Hg is an independent predictor of acute kidney injury.[11] The notable difference in SBP trajectories between the high-to-low SBP and moderate-to-low SBP groups was that SBP at hospital arrival was >210 mm Hg in the former group but was slightly lower at ≈190 mm Hg in the latter group. These results and our own suggest the importance of the range of BP reduction from initial SBP in determining the optimal target SBP level. In particular, if a sufficiently low SBP is achieved in patients with high initial SBP, monitoring the cardiorenal systems and reconsidering target SBP levels will be important. Another analysis

Table 3. Treatment Characteristics

	Group 1: Moderate SBP (n=298)	Group 2: Moderate-to-low SBP (n=395)	Group 3: High-to-low SBP (n=134)	Group 4: High SBP (n=173)
Randomized to intensive treatment	33 (11.1%)	350 (88.6%)	114 (85.1%)	3 (1.7%)
Nicardipine infusion before randomization	284 (95.3%)	388 (98.2%)	133 (99.3%)	172 (99.4%)
Time from onset to randomization, min, mean (SD)	189.3 (58.3)	177.7 (57.1)	179.3 (55.4)	189.8 (54.1)
SBP at hospital arrival, mm Hg, mean (SD)	194.3 (23.1)	194.6 (24.3)	215.8 (29.0)	213.2 (28.5)
SBP at randomization, mm Hg, mean (SD)	169.9 (21.1)	167.6 (21.2)	196.0 (27.0)	184.2 (26.0)
Maximum dosage of nicardipine, mg/h, mean (SD)	7.0 (4.2)	10.1 (4.2)	12.7 (3.8)	8.5 (4.1)
Use of secondary antihypertensive agents	38 (12.8%)	82 (20.8%)	66 (49.3%)	31 (17.9%)
Received intraventricular catheter	17 (5.8%)	23 (5.8%)	15 (11.5%)	15 (8.7%)
Received mechanical ventilation	35 (11.9%)	44 (11.2%)	31 (23.7%)	27 (15.7%)

SBP indicates systolic blood pressure.

of ATACH-2 demonstrated a higher rate of neurological deterioration associated with intensive SBP lowering in patients with an initial SBP ≥220 mm Hg.[12] Both death or disability (48.0% versus 34.7%) and mortality (9.0% versus 6.1%) were more frequent in the high-to-low SBP group than in the moderate-to-low SBP group, but the OR for death in the high-to-low SBP group became lower than 1 after adjustment for mechanical ventilation. Initial SBP, target SBP level, range of SBP reduction, and prognosis of intracerebral hemorrhage may be intricately related to protection of the brain and cardiovascular and renal systems.

Another feature of the high-to-low SBP group was the highest dose of intravenous nicardipine and the highest rate of secondary antihypertensive agent use among the 4 SBP trajectory groups. In a comparison of the high-to-low SBP group and the moderate-to-low SBP group, the former also had a higher nicardipine dose and a higher rate of secondary agent use. Given that ≥85% of patients in both groups were assigned to receive intensive treatment, patients with strong acute hypertensive response might constitute the high-to-low SBP group. The SBP reduction effect from nicardipine results largely from peripheral vasodilatation.[13] In a subanalysis of ATACH-2, a higher dose of intravenous nicardipine was associated with acute kidney injury and renal adverse events.[14] In a study of hypertensive patients in which SBP was reduced by infusion of the vasodilator sodium nitroprusside, glomerular filtration rate, and effective renal plasma flow were well-maintained across the range of SBP of 170 to 130 mm Hg in moderate hypertensives, but both fell progressively in the range of 200 to 135 mm Hg in patients with severe hypertension.[15] This suggests a breakdown in renal autoregulation in those with severe hypertension.[16] The occurrence of cardiac adverse events may have been related to reflex tachycardia induced by nicardipine or the negative inotropic effects of other agents, including labetalol. Although the severity of cardiac adverse events in the high-to-low SBP group does not seem to be particularly high compared with the moderate-to-low SBP group, the incidence of serious cardiac adverse events was not lower in the high-to-low SBP group than in the moderate-to-low SBP group. Cardiovascular events were the most frequent cause of death in the high-to-low SBP group.

A key strength of this study is the comprehensive demonstration of relevant relationships between clinical outcomes of acute intracerebral hemorrhage and SBP trajectories identified by the GBTM approach, which has less arbitrariness in the grouping of SBP.

It should be noted that the fitted model used for analyses may not appear when using other data sets because the trajectory grouping depends on the data. Thus, the present results are only hypothesis generating. The fact that the majority of patients in the high-to-low and moderate-to-low SBP groups were assigned to intensive SBP lowering may be a major limitation. The causal relationship between outcomes and treatment assignment, SBP trajectory grouping, and other prognostic factors needs to be further investigated. In addition, model selection on the number and shapes of SBP trajectories could affect the results of this study. To secure the reproducibility of the model selection process, candidate models in this study were mechanically selected using BIC through brute-force search, and similar relationships between SBP trajectories and outcomes were observed in both the 4-group main analysis model and the 5-group sensitivity analysis model. In the present analysis, maximum SBP within each of the total 29 measurement intervals was used for GBTM. Minimum SBP per measurement interval was not suitable for a GBTM approach due to its small heterogeneity within each treatment group.[5] The sample analyzed in this study was from a randomized controlled trial with potential issues with generalizability; the results might not be totally applicable to lobar ICH patients because of the low proportion of lobar ICH in ATACH-2. Lobar ICH patients presumably had a less chance to be registered in ATACH-2 partly because of their less frequency of hypertension than the other patients with ICH.[17] Cerebral small vessel disease may be an important factor in considering BP lowering for intracerebral hemorrhage, but it was not available in the

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Table 4. Outcomes

	Group 1: Moderate SBP (n=298)	Group 2: Moderate-to-low SBP (n=395)	Group 3: High-to-low SBP (n=134)	Group 4: High SBP (n=173)	*P* value*
Death or disability at 3 mo	104 (36.2%, n=287)	132 (34.7%, n=380)	61 (48.0%, n=127)	70 (41.9%, n=167)	0.04
Crude OR (95% CI)	1.07 (0.78–1.47); *P*=0.68	1 [Reference]	1.74 (1.16–2.61); *P*<0.01	1.36 (0.93–1.97); *P*=0.11	
Adjusted OR (95% CI)†	1.42 (0.73–2.77); *P*=0.29 (n=259)	1 [Reference] (n=353)	2.29 (1.24–4.26); *P*<0.01 (n=118)	1.69 (0.78–3.69); *P*=0.18 (n=150)	
Death within 3 mo	17 (5.7%, n=298)	24 (6.1%, n=395)	12 (9.0%, n=134)	14 (8.1%, n=173)	0.50
Crude OR (95% CI)	0.94 (0.49–1.77); *P*=0.83	1 [Reference]	1.52 (0.74–3.13); *P*=0.25	1.36 (0.69–2.69); *P*=0.37	
Adjusted OR (95% CI)†	0.83 (0.27–2.53); *P*=0.74 (n=269)	1 [Reference] (n=367)	0.67 (0.19–2.33); *P*=0.52 (n=123)	0.89 (0.25–3.22); *P*=0.86 (n=154)	
Hematoma expansion within 24 h	63 (21.1%, n=298)	76 (19.2%, n=395)	15 (11.2%, n=134)	35 (20.2%, n=173)	0.09
Crude OR (95% CI)	1.13 (0.77–1.64); *P*=0.53	1 [Reference]	0.53 (0.29–0.96); *P*=0.03	1.06 (0.68–1.67); *P*=0.78	
Adjusted OR (95% CI)†	1.03 (0.56–1.89); *P*=0.93 (n=269)	1 [Reference] (n=367)	0.51 (0.25–1.04); *P*=0.06 (n=123)	1.09 (0.53–2.26); *P*=0.80 (n=154)	
Neurological deterioration within 24 h	25 (8.4%, n=298)	39 (9.9%, n=395)	18 (13.4%, n=134)	11 (6.4%, n=173)	0.18
Crude OR (95% CI)	0.84 (0.49–1.41); *P*=0.50	1 [Reference]	1.42 (0.78–2.57); *P*=0.25	0.62 (0.31–1.24); *P*=0.17	
Adjusted OR (95% CI)†	0.78 (0.33–1.85); *P*=0.57 (n=269)	1 [Reference] (n=367)	0.48 (0.20–1.13); *P*=0.09 (n=123)	0.39 (0.13–1.25); *P*=0.11 (n=154)	
Acute kidney injury within 7 d	34 (11.4%, n=298)	31 (7.8%, n=395)	37 (27.6%, n=134)	24 (13.9%, n=173)	<0.01
Crude OR (95% CI)	1.51 (0.91–2.52); *P*=0.11	1 [Reference]	4.48 (2.64–7.59); *P*<0.01	1.89 (1.07–3.33); *P*=0.02	
Adjusted OR (95% CI)†	1.32 (0.59–2.93); *P*=0.49 (n=269)	1 [Reference] (n=367)	3.50 (1.83–6.69); *P*<0.01 (n=123)	1.42 (0.56–3.64); *P*=0.46 (n=154)	
Renal adverse events within 7 d	10 (3.4%, n=298)	17 (4.3%, n=395)	20 (14.9%, n=134)	8 (4.6%, n=173)	<0.01
Crude OR (95% CI)	0.77 (0.35–1.71); *P*=0.52	1 [Reference]	3.90 (1.98–7.69); *P*<0.01	1.08 (0.46–2.55); *P*=0.86	
Adjusted OR (95% CI)†	1.84 (0.60–5.61); *P*=0.28 (n=269)	1 [Reference] (n=367)	2.84 (1.22–6.62); *P*=0.01 (n=123)	1.39 (0.30–6.44); *P*=0.66 (n=154)	
Serious renal adverse events within 7 d	0 (0.0%, n=298)	1 (0.3%, n=395)	3 (2.2%, n=134)	2 (1.2%, n=173)	0.02
Cardiac adverse events within 7 d	22 (7.4%, n=298)	36 (9.1%, n=395)	23 (17.2%, n=134)	18 (10.4%, n=173)	0.02
Crude OR (95% CI)	0.79 (0.46–1.38); *P*=0.41	1 [Reference]	2.07 (1.17–3.63); *P*=0.01	1.16 (0.64–2.10); *P*=0.63	
Adjusted OR (95% CI)†	0.88 (0.38–2.02); *P*=0.75 (n=269)	1 [Reference] (n=367)	2.26 (1.10–4.64); *P*=0.02 (n=123)	1.11 (0.41–2.95); *P*=0.84 (n=154)	
Serious cardiac adverse events within 7 d	0 (0.0%, n=298)	14 (3.5%, n=395)	5 (3.7%, n=134)	3 (1.7%, n=173)	<0.01
Brain infarction adverse events within 7 d	3 (1.0%, n=298)	2 (0.5%, n=395)	1 (0.7%, n=134)	0 (0.0%, n=173)	0.58

OR indicates odds ratio; and SBP, systolic blood pressure.

*Pearson χ^2 test.

†Adjusting covariates are sex, age, recruited sites (Asia or non-Asia), prescribed antihypertensive medication, baseline National Institutes of Health Stroke Scale score, white blood cell count, serum creatinine, baseline hematoma volume, time from onset to randomization, treatment assignment (intensive or standard SBP lowering), SBP at randomization, maximum dosage of nicardipine, use of secondary antihypertensive agents, and mechanical ventilation.

ATACH-2 data set. In the present study, missing data in the statistical analysis after GBTM was handled using pairwise-deletion method; it is necessary to pay attention to the bias associated with this mising data handling process when interpreting the results. Last, this is a set of post hoc analyses compounded by multiple tests, which can inflate the probability of type I error.

In conclusion, this analysis suggested the presence of distinct SBP trajectories during the first 24 hours in ATACH-2 data. A group of patients with severe hypertension who were treated with high-dose nicardipine and additional antihypertensive agents was identified, and this group showed higher risks of death or disability and cardiorenal complications. Requirements for setting more tailored target SBP levels for such patients are suggested. Data-driven observation through GBTM approaches may be useful to clarify the relationships between antihypertensive treatment, temporal SBP changes, and outcomes for acute intracerebral hemorrhage.

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Supplemental Material

Supplemental Methods
Tables S1–S8
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STROBE Checklist

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