

ORIGINAL ARTICLE

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

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ABSTRACT

**BACKGROUND**

Limited data are available to guide the choice of a target for the systolic blood-pressure level when treating acute hypertensive response in patients with intracerebral hemorrhage.

METHODS

We randomly assigned eligible participants with intracerebral hemorrhage (volume, <60 cm³) and a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating worse condition) to a systolic blood-pressure target of 110 to 139 mm Hg (intensive treatment) or a target of 140 to 179 mm Hg (standard treatment) in order to test the superiority of intensive reduction of systolic blood pressure to standard reduction. Intravenous nicardipine to lower blood pressure was administered within 4.5 hours after symptom onset. The primary outcome was death or disability (modified Rankin scale score of 4 to 6, on a scale ranging from 0 [no symptoms] to 6 [death]) at 3 months after randomization, as ascertained by an investigator who was unaware of the treatment assignments.

RESULTS

Among 1000 participants with a mean (\pm SD) systolic blood pressure of 200.6 \pm 27.0 mm Hg at baseline, 500 were assigned to intensive treatment and 500 to standard treatment. The mean age of the patients was 61.9 years, and 56.2% were Asian. Enrollment was stopped because of futility after a prespecified interim analysis. The primary outcome of death or disability was observed in 38.7% of the participants (186 of 481) in the intensive-treatment group and in 37.7% (181 of 480) in the standard-treatment group (relative risk, 1.04; 95% confidence interval, 0.85 to 1.27; analysis was adjusted for age, initial GCS score, and presence or absence of intraventricular hemorrhage). Serious adverse events occurring within 72 hours after randomization that were considered by the site investigator to be related to treatment were reported in 1.6% of the patients in the intensive-treatment group and in 1.2% of those in the standard-treatment group. The rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group (9.0% vs. 4.0%, $P=0.002$).

CONCLUSIONS

The treatment of participants with intracerebral hemorrhage to achieve a target systolic blood pressure of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg. (Funded by the National Institute of Neurological Disorders and Stroke and the National Cerebral and Cardiovascular Center; ATACH-2 ClinicalTrials.gov number, NCT01176565.)

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*A complete list of the investigators and sites participating in the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial is provided in the Supplementary Appendix, available at NEJM.org.

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AN ACUTE HYPERTENSIVE RESPONSE IN patients with intracerebral hemorrhage is common¹ and may be associated with hematoma expansion and increased mortality.^{2,3,4} The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial⁵ (INTERACT2) included patients with spontaneous intracerebral hemorrhage who had a systolic blood pressure of 150 to 220 mm Hg within 6 hours after symptom onset. The rate of death or disability among patients randomly assigned to intensive reduction in the systolic blood-pressure level, with a target systolic blood pressure of less than 140 mm Hg within 1 hour, was nonsignificantly lower than the rate among those assigned to guideline-recommended treatment, with a target systolic blood pressure of less than 180 mm Hg, with the use of a variety of antihypertensive medications (absolute difference, 3.6 percentage points; $P=0.06$).⁵

We designed the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial⁶ to determine the efficacy of rapidly lowering the systolic blood-pressure level in patients in an earlier time window after symptom onset than that evaluated in previous trials.^{4,5,7} The trial was based on evidence that hematoma expansion and the rate of subsequent death or disability might be reduced with very early and more aggressive reduction in the systolic blood-pressure level^{8,9} among persons at high risk owing to a high systolic blood-pressure level (≥ 170 mm Hg¹⁰ to ≥ 200 mm Hg¹¹) at presentation.

METHODS

TRIAL DESIGN

We designed this randomized, multicenter, two-group, open-label trial to determine the relative efficacy of intensive versus standard antihypertensive treatment that was initiated within 4.5 hours after symptom onset and continued for the next 24 hours in patients with spontaneous supratentorial intracerebral hemorrhage. At least one reading of systolic blood pressure of 180 mm Hg or more between symptom onset and the initiation of intravenous antihypertensive treatment was required for eligibility.⁶ Treatment could be initiated before randomization to lower the systolic blood pressure to less than 180 mm Hg, which is consistent with guidelines from the American Stroke Association Stroke Council,¹² but patients were not eligible if the systolic blood

pressure was reduced to less than 140 mm Hg before randomization. The initiation of intravenous antihypertensive treatment according to the trial protocol (available with the full text of this article at NEJM.org) and randomization had to occur within 4.5 hours after symptom onset.

The trial initially recruited patients within 3 hours after symptom onset, but the recruitment window was extended to 4.5 hours.¹³ The extension was based on new data suggesting that the occurrence of hematoma expansion, the primary target for reduction in the systolic blood-pressure level, was equally prevalent among patients who presented between 0 and 3 hours after symptom onset and those who presented between 3 and 4.5 hours after symptom onset.¹³ Data from the pilot study¹³ also supported the reductions in hematoma expansion and the rate of death or disability among participants whose systolic blood pressure was reduced within 4.5 hours after symptom onset. Patients 18 years of age or older with a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating a worse condition) at the time of arrival in the emergency department and with a measurement of the intraparenchymal hematoma of less than 60 cm³ on initial computed tomographic (CT) scan were eligible for inclusion in the trial if antihypertensive treatment could be initiated within 4.5 hours after symptom onset.

Randomization was performed centrally through the trial website with the use of a minimization algorithm combined with the biased-coin method to ensure a balance of treatment assignment within and across clinical sites, baseline GCS score, age (divided into seven strata), and presence or absence of intraventricular hemorrhage at baseline. An independent oversight committee adjudicated the trial safety outcomes and evaluated adherence to the protocol at participating sites by review of summary reports of collected data and deidentified medical records.¹⁴

TRIAL OVERSIGHT

The trial was monitored by an independent data and safety monitoring board whose members were appointed by the National Institute of Neurological Disorders and Stroke. The protocol and consent forms were approved by the institutional review board or equivalent ethics committee at each participating site, and all participants or their legally authorized representative provided

written informed consent before randomization. The members of the steering committee (see the Supplementary Appendix, available at NEJM.org) designed the trial and performed the analyses. The first author wrote the first draft of the manuscript, and the members of the steering committee contributed to revisions. All the investigators and coordinators who were provided access to the results were asked to sign a confidentiality agreement to ensure that the results were not disclosed to third parties before publication and presentation of primary results as determined by the steering committee. Chiesi USA and Astellas Pharma supplied intravenous nicardipine for use during the trial but had no other role in the design or conduct of the trial or in the review of the manuscript.

The statistical analysis plan was revised and finalized before data analysis. The investigators vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of this report to the trial protocol and statistical analysis plan.

TRIAL INTERVENTION

The goal of treatment was to reduce and maintain the hourly minimum systolic blood pressure in the range of 140 to 179 mm Hg in the standard-treatment group and in the range of 110 to 139 mm Hg in the intensive-treatment group throughout the period of 24 hours after randomization. Before randomization, intravenous antihypertensive medication, including nicardipine, could be administered to lower the systolic blood pressure to less than 180 mm Hg,¹² but patients were not eligible if the systolic blood pressure was lowered to less than 140 mm Hg. After randomization, nicardipine, administered by intravenous infusion, was the first-line antihypertensive agent and was initiated at a dose of 5 mg per hour, which was then increased by 2.5 mg per hour every 15 minutes as needed, up to a maximum dose of 15 mg per hour. If the systolic blood-pressure level was higher than the target, despite infusion of the maximum dose of nicardipine for 30 minutes, a prespecified second agent, intravenous labetalol, was used. In countries where labetalol was not available, intravenous diltiazem or urapidil was used. Additional care was based on the best available evidence¹⁵ and the guidelines from the American Stroke Association Stroke Council¹² and the European Stroke Initiative Writing Committee.¹⁶

We assessed the success, or lack thereof, of the reduction in the systolic blood-pressure level. Primary treatment failure was defined as not reaching the target systolic blood pressure of less than 140 mm Hg in the intensive-treatment group and less than 180 mm Hg in the standard-treatment group within 2 hours after randomization. Secondary treatment failure was defined as the hourly minimum systolic blood pressure remaining higher than the upper limit of the target range for 2 consecutive hours during the period of 2 to 24 hours after randomization. No effort was made to conceal the treatment assignment from the participants or treating physicians.

TRIAL ASSESSMENTS

A CT scan of the head without the use of contrast material was obtained at 24 hours after the initiation of treatment. Baseline and 24-hour CT scans were forwarded to the core image analysis center. The reader, who was unaware of the treatment assignments, clinical findings, and time points of image acquisition, determined the site of hemorrhage, the presence or absence of blood in the ventricles, and the volume of the parenchymal hematoma. The area of the hematoma was delineated by image analysis software with the use of density thresholds on each slice, followed by manual correction; those performing manual correction were unaware of the treatment assignments. The software provided total volume measurements by summing up volumes (product of area and slice thickness) from all the slices containing the hematoma. Serious adverse events were systematically reported up to 3 months after randomization. Nonserious adverse events were systematically reported up to day 7 or hospital discharge, whichever came first.

Follow-up after discharge included telephone contact at 1 month and in-person clinical evaluation at 3 months. During the telephone interview, the site staff obtained information regarding serious adverse events and deaths. The data collection at the 3-month visit consisted of the score on the modified Rankin scale (which assesses the degree of disability or dependence in daily activities, with scores ranging from 0 [no symptoms] to 6 [death]); quality of life as assessed by means of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire¹⁷; serious adverse events; and results of physical and neurologic examinations. The assessments were conducted by a qualified investigator who did not

participate in the randomization, treatment, or in-hospital clinical treatment of the patient.

OUTCOME MEASURES

The primary outcome was the proportion of patients who had moderately severe or severe disability or who had died (modified Rankin scale score, 4 to 6; hereafter referred to as “death or disability”) at 3 months. Secondary outcomes were the scores on the EQ-5D utility index and visual-analogue scale (VAS) at 3 months and the proportion of participants with expansion of 33% or more in the volume of the hematoma on the CT scan obtained at 24 hours after randomization, as compared with the entry scan. The 3-month EQ-5D utility index (on which scores range from -0.109 [least favorable health state] to 1 [most favorable health state], with 0 imputed for death) was derived by applying Shaw’s weight¹⁸ to the response patterns of the five questions regarding mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The EQ-5D VAS score was obtained by requesting that patients indicate their perception of their own health state on a scale of 0 (worst) to 100 (best), with a score of 0 assigned to those who died.¹⁷ Safety outcomes were neurologic deterioration, defined as a decrease from baseline of 2 or more points in the GCS score or an increase of 4 or more points in the score on the National Institutes of Health Stroke Scale (on which scores range from 0 to 42, with higher scores indicating more severe stroke) that was not related to sedation or hypnotic-agent use and was sustained for at least 8 hours within the 24 hours after randomization; serious adverse events occurring within 72 hours after randomization that were considered by the site investigator to be related to treatment; and death within 3 months after randomization.

STATISTICAL ANALYSIS

The primary hypothesis was that intensive treatment would be associated with a likelihood of death or disability at 3 months after intracerebral hemorrhage that was at least 10 percentage points lower than the likelihood associated with standard treatment. For an effect size of 10 percentage points (relative risk, 0.83), assuming a rate of death or disability of 60% in the standard-treatment group (derived from the literature), a type I error probability of 0.05, and a type II error probability of 0.10, we estimated that the

total sample should be 1042 participants; two interim analyses for overwhelming efficacy and for futility were to be performed (Section D1 in the Supplementary Appendix). A sample size of 1280 participants was calculated after inflation by a factor of 1.23 as derived from the following calculation: $1/(1-R)^2$, where R was the proportion of patients with anticipated nonadherence (e.g., treatment failure or loss to follow-up). Two prespecified interim analyses and one unplanned interim analysis of the primary outcome were conducted; the unplanned analysis was requested by the data and safety monitoring board. Enrollment was stopped because of futility after the prespecified second interim analysis.

The prespecified primary analysis was conducted under the intention-to-treat principle, with adjustment for the effects of age, GCS score, and presence or absence of intraventricular hemorrhage as determined by the central imaging evaluator. The analysis of the dichotomized 3-month modified Rankin scale score (4 to 6 vs. 0 to 3) was based on the generalized linear model with log-link function with Poisson distribution (rather than binomial distribution, because of convergence issues). The PROC GENMOD procedure of SAS software, version 9.4 (SAS Institute), was used for all the analyses.

Missing data were imputed with the use of the multiple-imputation method that generated and analyzed 100 samples (with the use of a computer simulation) of the trial data, each with a variable imputed value for the missing data, and results were subsequently compiled as described in the statistical analysis plan (Section D2 in the Supplementary Appendix). In the prespecified sensitivity analysis, we imputed missing data using the worst outcome (modified Rankin scale score, 4 to 6). To address multiple comparisons, we prespecified in our statistical analysis plan that for secondary outcomes, we considered test results with P values of less than 0.025 to indicate statistical significance.

Any adverse events and serious adverse events were classified with the use of terminology from the *Medical Dictionary for Regulatory Activities*. A post hoc analysis was performed after grouping the related events (events that represent the same condition of interest according to body system) so that the true occurrence rate of an event with relationship to blood-pressure lowering was not obscured. The unplanned analysis was performed because of a between-group difference in the

rates of serious adverse events within 3 months after randomization.

RESULTS

PARTICIPANT POPULATION

The trial enrolled the first patient in May 2011 and the last in September 2015. We conducted the trial at 110 sites in the United States, Japan, China, Taiwan, South Korea, and Germany. A total of 8532 patients were screened, of whom 1000 un-

derwent randomization; 500 patients were assigned to the intensive-treatment group and 500 to the standard-treatment group (Fig. S1 in the Supplementary Appendix). The mean age of the enrolled patients was 61.9 years. A total of 38.0% of the patients were women, and 56.2% of the patients were Asian. The mean (\pm SD) systolic blood pressure at baseline was 200.6 \pm 27.0 mm Hg. The demographic and clinical characteristics of the participants at baseline, which are shown in Table 1, were similar in the two treatment groups.

Table 1. Demographic and Clinical Characteristics of the Participants, According to Treatment Group.*

Characteristic	Intensive Treatment (N=500)	Standard Treatment (N=500)
Age — yr	62 \pm 13.1	61.9 \pm 13.1
Male sex — no. (%)	304 (60.8)	316 (63.2)
Race — no. (%) [†]		
Asian	277 (55.4)	285 (57.0)
Black	73 (14.6)	58 (11.6)
White	142 (28.4)	145 (29.0)
Other or unknown	8 (1.6)	12 (2.4)
Hispanic ethnic group — no. (%) [†]	38 (7.6)	41 (8.2)
Recruited at site in Asia — no. (%)	264 (52.8)	273 (54.6)
Glasgow Coma Scale score — no. (%) [‡]		
3–11	73 (14.6)	74 (14.8)
12–14	152 (30.4)	142 (28.4)
15	275 (55.0)	284 (56.8)
Systolic blood pressure at presentation in emergency department — mm Hg [§]	200 \pm 27.1	201.1 \pm 26.9
Median NIHSS score (range) [¶]	11 (0–40)	11 (0–40)
Intracerebral hematoma volume		
>30 cm ³ — no./total no. (%)	45/496 (9.1)	51/492 (10.4)
Median (range) — cm ³	10.3 (2.3–85.2)	10.2 (0.98–79.1)
Intraventricular hemorrhage — no./total no. (%)	122/496 (24.6)	142/492 (28.9)
Location of hemorrhage — no./total no. (%)		
Thalamus	193/496 (38.9)	180/492 (36.6)
Basal ganglia	255/496 (51.4)	251/492 (51.0)
Cerebral lobe	48/496 (9.7)	60/492 (12.2)
Cerebellum	0/496	1/492 (0.2)

* Plus–minus values are means \pm SD. There were no significant differences between the two groups at baseline.

[†] Race and ethnic group were self-reported. Asian race included patients enrolled in Asian countries and non-Asian countries.

[‡] The Glasgow Coma Scale score (range, 3 to 15), a measure of level of consciousness, is a scale that quantifies response in three components, with a score of 3 indicating deep unconsciousness and higher scores indicating milder impairment of consciousness.

[§] Data were missing for 1 patient in the standard-treatment group.

[¶] The National Institutes of Health Stroke Scale (NIHSS), a serial measure of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories, with a score of 0 indicating normal function without neurologic deficit and higher scores indicating greater severity of deficit. Data were missing or were obtained outside the specified time window for 30 patients in the intensive-treatment group and for 41 in the standard-treatment group.

^{||} Hematoma volume was measured by a central reader. The rapid assessment of the hematoma volume by the site investigator was used to determine eligibility.

INTERVENTION

The mean interval between symptom onset and randomization was 182.2 ± 57.2 minutes in the intensive-treatment group and 184.7 ± 56.7 minutes in the standard-treatment group (Table S1 in the Supplementary Appendix). The mean values of hourly minimum systolic blood pressure for the first 24 hours after randomization according to treatment group are shown in Figure 1. The mean minimum systolic blood pressure during the first 2 hours was 128.9 ± 16 mm Hg in the intensive-treatment group and 141.1 ± 14.8 mm Hg in the standard-treatment group.

Primary treatment failure occurred in 61 patients (12.2%) in the intensive-treatment group versus 4 (0.8%) in the standard-treatment group ($P < 0.001$); secondary treatment failure occurred in 78 patients (15.6%) in the intensive-treatment group versus 7 (1.4%) in the standard-treatment group ($P < 0.001$). Among patients who died, withdrawal of care was reported in 61% (20 of 33) of those in the intensive-treatment group and in 76% (26 of 34) in the standard-treatment group.

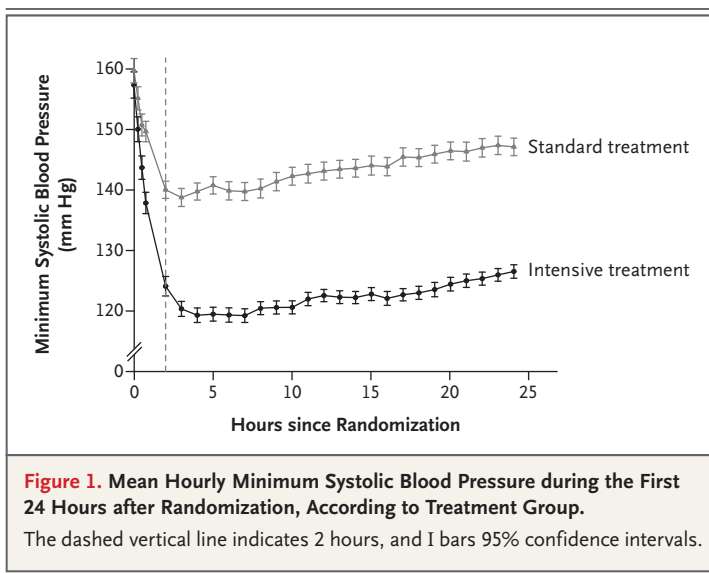
OUTCOMES

Among the 961 participants in whom the primary outcome was ascertained, death or disability was observed in 186 participants (38.7%) in the intensive-treatment group and in 181 (37.7%) in the standard-treatment group (Table 2). In the primary analysis that used the multiple-imputation method for the 39 participants with missing outcome data, the relative risk was 1.04 (95%

confidence interval [CI], 0.85 to 1.27), with adjustment for age, initial GCS score, and presence or absence of intraventricular hemorrhage. The prespecified sensitivity analysis that used the worst-case imputation yielded a relative risk of 1.04 (95% CI, 0.85 to 1.26). There was no significant between-group difference in the ordinal distribution of the modified Rankin scale score at 3 months (Fig. 2). The post hoc proportional-odds logistic-regression analysis yielded a common odds ratio of 1.07 ($P = 0.56$) without violation of assumption of proportionality of the odds. Analysis of the primary outcome according to prespecified subgroups showed no significant differences (Fig. 3). In addition, neither the EQ-5D measures nor the percentages of patients with hematoma expansion differed significantly between the treatment groups (Table 2).

There were no significant between-group differences in the rate of death at 3 months or in neurologic deterioration at 24 hours after randomization. The percentage of patients with treatment-related serious adverse events within 72 hours after randomization was 1.6% in the intensive-treatment group and 1.2% in the standard-treatment group. However, the percentage of patients with any serious adverse event during the 3 months after randomization was higher in the intensive-treatment group than in the standard-treatment group (25.6% vs. 20.0%; adjusted relative risk, 1.30; 95% CI, 1.00 to 1.69; $P = 0.05$) (Table 2). Lists of adverse events and serious adverse events, according to treatment group, are provided in Tables S2 and S3, respectively, in the Supplementary Appendix.

Table S4 in the Supplementary Appendix lists adverse events and serious adverse events that were related to renal function, cardiac function, brain hemorrhage, and brain infarction after randomization. The rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group (9.0% vs. 4.0%, $P = 0.002$). There was no significant difference in the rates in any of the other adverse-event groups.

**DISCUSSION**

The ATACH-2 trial was discontinued for futility before we reached the target enrollment of 1280 participants. The absolute difference between

Table 2. Primary, Secondary, and Safety Outcomes, According to Treatment Group.*

Outcome	Intensive Treatment (N = 500)		Standard Treatment (N = 500)		Unadjusted Analysis		Adjusted Analysis†	
	Relative Risk or Beta Estimate (95% CI)	P Value	Relative Risk or Beta Estimate (95% CI)	P Value	Relative Risk or Beta Estimate (95% CI)	P Value	Relative Risk or Beta Estimate (95% CI)	P Value
Primary outcome: death or disability — no./total no. (%)‡	186/481 (38.7)	0.84	181/480 (37.7)	0.84	1.02 (0.83 to 1.25)	0.84	1.04 (0.85 to 1.27)	0.72
Hematoma expansion — no./total no. (%)§	85/450 (18.9)	0.09	104/426 (24.4)	0.09	0.78 (0.59 to 1.04)	0.09	0.78 (0.58 to 1.03)	0.08
Neurologic deterioration within 24 hr — no. (%)¶	55 (11.0)	0.13	40 (8.0)	0.13	1.38 (0.92 to 2.07)	0.13	1.39 (0.92 to 2.09)	0.11
Treatment-related serious adverse event within 72 hr — no. (%)	8 (1.6)	0.59	6 (1.2)	0.59	1.33 (0.46 to 3.84)	0.59	1.37 (0.47 to 3.95)	0.56
Any serious adverse event within 3 mo — no. (%)	128 (25.6)	0.06	100 (20.0)	0.06	1.28 (0.99 to 1.66)	0.06	1.30 (1.00 to 1.69)	0.05
Hypotension within 72 hr — no. (%)	6 (1.2)	0.33	3 (0.6)	0.33	2.00 (0.50 to 8.00)	0.33	1.96 (0.49 to 7.87)	0.34
Death — no. (%)	33 (6.6)	0.90	34 (6.8)	0.90	0.97 (0.60 to 1.57)	0.90	0.99 (0.61 to 1.60)	0.97
EQ-5D utility index score***††	0.7	0.47	0.7	0.47	-0.01 (-0.05 to 0.02)	0.47	-0.02 (-0.05 to 0.02)	0.29
Median	0.7		0.7					
Range	-0.1 to 1.0		0 to 1.0					
EQ-5D visual-analogue scale score***‡‡	62.5	0.59	70	0.59	-1.14 (-5.28 to 2.99)	0.59	-1.32 (-5.25 to 2.60)	0.51
Median	62.5		70					
Range	0 to 100		0 to 100					

* The relative risk or beta estimate with 95% confidence intervals for the modified Rankin scale score, hematoma expansion, European Quality of Life-5 Dimensions (EQ-5D) utility index score, and EQ-5D visual-analogue scale score were based on analyses inclusive of missing data imputed by the multiple-imputation method.
 † The analysis was adjusted for age, baseline Glasgow Coma Scale (GCS) score, and the presence or absence of intraventricular hemorrhage at baseline.
 ‡ The modified Rankin scale grades the degree of disability or dependence in the daily activities using scores ranging from 0 (no symptoms) to 6 (death). The primary outcome was defined as a score of 4 to 6.
 § Hematoma expansion was defined as an increase of 33% or more in the hematoma volume from baseline to 24 hours.
 ¶ Neurologic deterioration was defined as decrease from baseline of 2 or more points on the GCS score or an increase from baseline of 4 or more points on the NIHSS score that was not related to sedation or hypnotic-agent use and that was sustained for at least 8 hours.
 || Treatment-related serious adverse events were assessed by the site investigator.
 ** Since the EQ-5D utility index and the visual-analogue scale scores are continuous variables, beta is the regression coefficient for the treatment effect (standard-treatment group divided by intensive-treatment group) in the generalized linear model. A beta of 0 indicates there was no effect of the treatment on the outcome.
 †† The EQ-5D utility index (with scores ranging from -0.109 [least favorable health state] to 1 [most favorable health state], with 0 imputed for death) was derived by applying Shaw's weight¹⁸ to the response combinations of five questions regarding mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Data were missing for 28 patients in the intensive-treatment group and for 27 in standard-treatment group.
 ‡‡ On the EQ-5D visual-analogue scale, patients were requested to indicate their perception of their own health state on a scale of 0 (worst) to 100 (best). Data were missing for 144 patients in the intensive-treatment group and for 146 in the standard-treatment group.

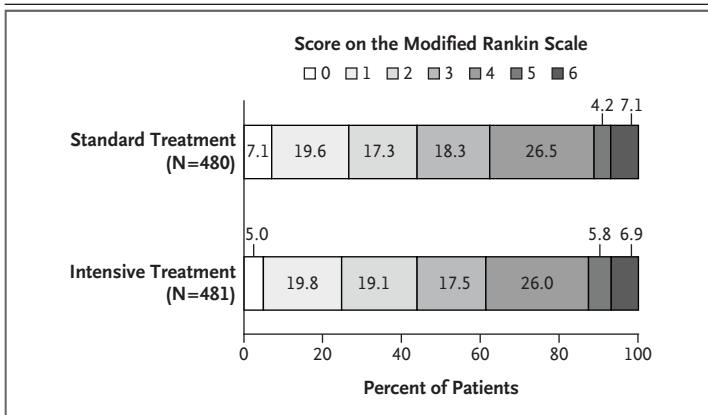


Figure 2. Distribution of Scores on the Modified Rankin Scale, According to Treatment Group.

The data are presented only for participants for whom a score on the modified Rankin scale score was obtained at 90 days. The percentage of participants with each score on the modified Rankin scale is shown in or above each cell. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Percentages may not sum to exactly 100.0 owing to rounding.

the two groups in the rate of death or disability was 1 percentage point. The trial was powered to identify a difference in risk of 10 percentage points or more with intensive treatment as compared with standard treatment, because a smaller difference in risk was expected to be viewed as insufficient for broad acceptance of a new intervention.⁵ A higher proportion of patients with primary treatment failure was observed in the intensive-treatment group than in the standard-treatment group, and perhaps the treatment effect would have been greater if the treatment goals had been met in a higher proportion of participants.

In the subgroup analysis (Fig. 3), the relative risk of death or disability with intensive treatment as compared with standard treatment was 1.02 among participants who met the specified target within 2 hours after randomization and 0.61 among those who did not meet the specified target. However, the test for interaction was not significant, and the precision of relative-risk estimates is too wide to make any definitive conclusions.

The recruitment window was extended dur-

ing the trial on the basis of evidence that an intensive reduction in the systolic blood-pressure level could benefit participants who were treated between 3 and 4.5 hours after symptom onset. A time-dependent loss of benefit of intensive reduction in the systolic blood-pressure level in participants who were recruited between 3 and 4.5 hours after symptom onset is possible, although it was not observed in the subgroup analysis of INTERACT2.⁵ A relatively high proportion of Asian participants were recruited in our trial, although the percentage was lower than that in INTERACT2. However, there was no significant difference in treatment effect between Asian patients and non-Asian patients in our trial or between participants recruited in China and those recruited in other countries in INTERACT2.⁵

Our trial incorporated the prerandomization use of intravenous antihypertensive agents to ensure timely compliance with existing guidelines,¹⁶ but this strategy may have obscured the effectiveness of the trial intervention. The observed rate of death or disability at 3 months in the standard-treatment group (37.7%) was lower than the rate that was anticipated in the trial design on the basis of previous literature (60%).^{6,19,20} A high percentage of patients with favorable characteristics at baseline (e.g., 56% of the patients had a baseline GCS score of 15) may have conferred a predisposition to a favorable outcome in our trial sample regardless of treatment (ceiling effect), making it difficult to discern the beneficial effect of an intensive reduction in the systolic blood-pressure level in this trial.⁶ The high proportion of favorable outcomes may also have resulted from the monitoring and standardizing intensity of medical care provided at each site and a low rate of withdrawal of care among participants recruited in the trial (as compared with a 34% rate outside clinical trials).²¹

There were several key differences between INTERACT2 and the ATACH-2 trial. An estimated 41% of the participants in INTERACT2 underwent randomization 4 or more hours after symptom onset, whereas all the participants in the ATACH-2 trial underwent randomization and were treated within 4.5 hours after symptom onset. In INTERACT2,⁵ only 48% of the 2839 participants underwent randomization with an initial systolic blood pressure of 180 mm Hg or more, whereas all the participants in the ATACH-2 trial had an initial systolic blood pressure of

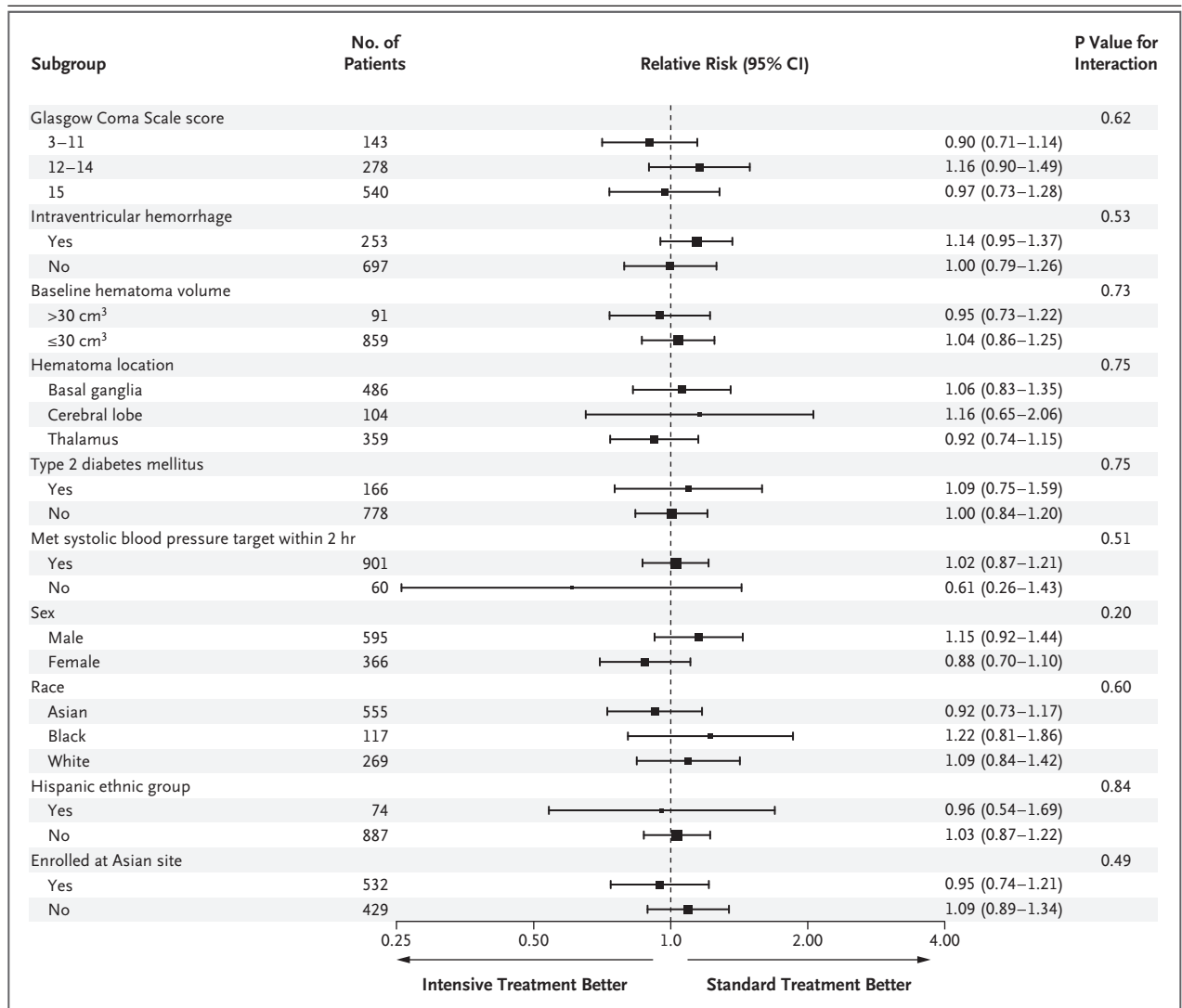


Figure 3. Unadjusted Relative Risk of Death or Disability at 3 Months, According to Subgroup.

The Glasgow Coma Scale is a measure of level of consciousness, with a score of 3 indicating deep unconsciousness and higher scores indicating milder impairment of consciousness; scores range from 3 to 15. The data are presented only for participants for whom a score on the modified Rankin scale score was obtained at 90 days. Data were missing on the following characteristics: on presence or absence of intraventricular hemorrhage for 4 patients in the intensive-treatment group and 7 in the standard-treatment group; on baseline hematoma volume for 4 in the intensive-treatment group and 7 in the standard-treatment group; on location of hematoma for 4 in the intensive-treatment group and 7 in the standard-treatment group; and on presence or absence of type 2 diabetes mellitus for 10 in the intensive-treatment group and 7 in the standard-treatment group. Data on location of hematoma are not shown for 1 patient in the intensive-treatment group whose hematoma was in the cerebellum (no patient in the standard-treatment group had a hematoma in this location). Data for patients with other or unknown race are not shown. The size of the squares is proportional to the precision of the estimates.

180 mm Hg or more. Primary treatment failure was seen in 66% of the participants within 1 hour after randomization in INTERACT2 and in 12.2% of those in the intensive-treatment group within 2 hours after randomization in the ATACH-2 trial.

In our trial, the mean minimum systolic blood

pressure in the first 2 hours after randomization was 128.9 mm Hg in the intensive-treatment group and 141.1 mm Hg in the standard-treatment group. In INTERACT2, the mean systolic blood pressure was 150 mm Hg in the first hour in the intensive-treatment group and 164 mm

Hg in the standard-treatment group. Thus, the early profile of the systolic blood-pressure level in the standard-treatment group in the ATACH-2 trial was similar to values observed early in the intensive-treatment group in INTERACT2. We had postulated that a more rapid intensive reduction in the systolic blood-pressure level than that used in INTERACT2 and the exclusion of patients with no requirement for intravenous antihypertensive medication would make it more likely to show a larger magnitude of therapeutic benefit, but our results did not confirm this hypothesis.

The results of our trial suggest that intensive reduction in the systolic blood-pressure level does not provide an incremental clinical benefit. It is also possible that the blunting of fluctuations in the systolic blood-pressure level in patients with intracerebral hemorrhage and an acute hypertensive response^{22,23} may exert a therapeutic benefit that is independent of the magnitude of lowering the systolic blood-pressure level. **We observed a higher occurrence of serious adverse events within 3 months after randomization** (but not a higher occurrence of serious adverse events that were considered by the investigator to be related to treatment within 72 hours after randomization) among participants who were randomly assigned to intensive treatment

than among those randomly assigned to standard treatment. A post hoc comparison after the grouping of related events identified a higher proportion of renal adverse events within 7 days after randomization among participants randomly assigned to intensive treatment than among those randomly assigned to standard treatment. It should be noted that the results of this trial cannot be generalized to patients with large intracerebral hemorrhage, intracranial pressure elevation, or compromised cerebral perfusion pressure. Therefore, the possibility of precipitating global or regional cerebral hypoperfusion with the intensive reduction of the systolic blood-pressure level in such patients may still be a concern.

In conclusion, our results do not support the notion that acute reduction to a target systolic blood pressure of 110 to 139 mm Hg in patients with intracerebral hemorrhage is more effective in improving functional outcome than a reduction to a target systolic blood pressure of 140 to 179 mm Hg.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med* 2007;25:32-8.
2. Qureshi AI. The importance of acute hypertensive response in ICH. *Stroke* 2013;44:Suppl 1:S67-9.
3. Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC. Relation between blood pressure and outcome in intracerebral hemorrhage. *Stroke* 1995;26:21-4.
4. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke* 2010;41:307-12.
5. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368:2355-65.
6. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. *Neurocrit Care* 2011;15:559-76.
7. Qureshi AI, Palesch YY, Martin R, et al. Interpretation and implementation of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT II). *J Vasc Interv Neurol* 2014;7:34-40.
8. Qureshi AI, Palesch YY, Martin R, et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the Antihypertensive Treatment of Acute Cerebral Hemorrhage study. *Arch Neurol* 2010;67:570-6.
9. Arima H, Anderson CS, Wang JG, et al.

- Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. *Hypertension* 2010;56:852-8.
10. Broderick JP, Diringer MN, Hill MD, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* 2007;38:1072-5.
 11. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: incidence and time course. *Stroke* 1996;27:1783-7.
 12. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007;38:2001-23.
 13. Qureshi A, Palesch Y, ATACH II Investigators. Expansion of recruitment time window in Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial. *J Vasc Interv Neurol* 2012;5:6-9.
 14. McBee N, Hanley D, Kase C, Lane K, Carhuapoma J. The importance of an independent oversight committee to preserve treatment fidelity, ensure protocol compliance, and adjudicate safety endpoints in the ATACH II trial. *J Vasc Interv Neurol* 2012;5:10-3.
 15. Qureshi AI. Intracerebral hemorrhage specific intensity of care quality metrics. *Neurocrit Care* 2011;14:291-317.
 16. The European Stroke Initiative Writing Committee, Writing Committee for the EUSI Executive Committee. Recommendations for the management of intracranial haemorrhage — part I: spontaneous intracerebral haemorrhage. *Cerebrovasc Dis* 2006;22:294-316.
 17. About EQ-5D. Rotterdam, the Netherlands: EuroQol (<http://www.euroqol.org/about-eq-5d.html>).
 18. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005;43:203-20.
 19. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777-85.
 20. Lyden PD, Shuaib A, Lees KR, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. *Stroke* 2007;38:2262-9.
 21. Zahuranec DB, Brown DL, Lisabeth LD, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology* 2007;68:1651-7.
 22. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Blood pressure variability and clinical outcome in patients with acute intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2015;24:1493-9.
 23. Sykora M, Diedler J, Turcani P, Rupp A, Steiner T. Subacute perihematomal edema in intracerebral hemorrhage is associated with impaired blood pressure regulation. *J Neurol Sci* 2009;284:108-12.

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