The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 20, 2013 VOL. 368 NO. 25

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

Craig S. Anderson, M.D., Ph.D., Emma Heeley, Ph.D., Yining Huang, M.D., Jiguang Wang, M.D., Christian Stapf, M.D., Candice Delcourt, M.D., Richard Lindley, M.D., Thompson Robinson, M.D., Pablo Lavados, M.D., M.P.H., Bruce Neal, M.D., Ph.D., Jun Hata, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Mark Parsons, M.D., Ph.D., Yuechun Li, M.D., Jinchao Wang, M.D., Stephane Heritier, Ph.D., Qiang Li, B.Sc., Mark Woodward, Ph.D., R. John Simes, M.D., Ph.D., Stephen M. Davis, M.D., and John Chalmers, M.D., Ph.D., for the INTERACT2 Investigators*

ABSTRACT

BACKGROUND

Whether rapid lowering of elevated blood pressure would improve the outcome in patients with intracerebral hemorrhage is not known.

METHODS

We randomly assigned 2839 patients who had had a spontaneous intracerebral hemorrhage within the previous 6 hours and who had elevated systolic blood pressure to receive intensive treatment to lower their blood pressure (with a target systolic level of <140 mm Hg within 1 hour) or guideline-recommended treatment (with a target systolic level of <180 mm Hg) with the use of agents of the physician's choosing. The primary outcome was death or major disability, which was defined as a score of 3 to 6 on the modified Rankin scale (in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death) at 90 days. A prespecified ordinal analysis of the modified Rankin score was also performed. The rate of serious adverse events was compared between the two groups.

RESULTS

Among the 2794 participants for whom the primary outcome could be determined, 719 of 1382 participants (52.0%) receiving intensive treatment, as compared with 785 of 1412 (55.6%) receiving guideline-recommended treatment, had a primary outcome event (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). The ordinal analysis showed significantly lower modified Rankin scores with intensive treatment (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04). Mortality was 11.9% in the group receiving intensive treatment and 12.0% in the group receiving guideline-recommended treatment. Nonfatal serious adverse events occurred in 23.3% and 23.6% of the patients in the two groups, respectively.

CONCLUSIONS

In patients with intracerebral hemorrhage, intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability. An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure. (Funded by the National Health and Medical Research Council of Australia; INTERACT2 ClinicalTrials.gov number, NCT00716079.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Anderson at the George Institute for Global Health, Royal Prince Alfred Hospital and the University of Sydney, P.O. Box M201, Missenden Rd., Sydney NSW 2050, Australia, or at canderson@georgeinstitute.org.au.

*Investigators in the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on May 29, 2013, at NEJM.org.

N Engl J Med 2013;368:2355-65.
DOI: 10.1056/NEJMoa1214609

Acute intracerebral hemorrhage, which is the least treatable form of stroke, affects more than 1 million people worldwide annually,[1,2] with the outcome determined by the volume and growth of the underlying hematoma.[3-5] Blood pressure often becomes elevated after intracerebral hemorrhage,[6] frequently reaching very high levels, and is a predictor of outcome.[7-11] On the basis of the results of the pilot-phase study, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 1 (INTERACT1),[12-14] we conducted the main-phase study, INTERACT2,[15] to determine the safety and effectiveness of early intensive lowering of blood pressure in patients with intracerebral hemorrhage.

Methods

Trial Design

INTERACT2 was an international, multicenter, prospective, randomized, open-treatment, blinded end-point trial. Details of the design have been published previously[15,16] and are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. In brief, we compared the effect of a management strategy targeting a lower systolic blood pressure within 1 hour with the current guideline-recommended strategy, which targets a higher systolic blood pressure, in patients who had a systolic blood pressure between 150 and 220 mm Hg and who did not have a definite indication for or contraindication to blood-pressure–lowering treatment that could be commenced within 6 hours after the onset of spontaneous intracranial hemorrhage; the diagnosis of intracranial hemorrhage was confirmed by means of computed tomography (CT) or magnetic resonance imaging (MRI). Patients were excluded if there was a structural cerebral cause for the intracerebral hemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale [GCS],[17] in which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned. Written informed consent was obtained from each patient or legal surrogate (before randomization or as soon as possible afterward) in accordance with national regulations.

Investigators entered baseline data into a database associated with a secure Web-based randomization system. The data were checked to confirm the eligibility of the patient, and several key clinical variables were recorded before the system assigned a participant to intensive or guideline-recommended management of blood pressure with the use of a minimization algorithm to ensure that the groups were balanced with respect to country, hospital, and time (≤4 hours vs. >4 hours) since the onset of the intracerebral hemorrhage. In participants who were assigned to receive intensive treatment to lower their blood pressure (intensive-treatment group), intravenous treatment and therapy with oral agents were to be initiated according to prespecified treatment protocols that were based on the local availability of agents, with the goal of achieving a systolic blood-pressure level of less than 140 mm Hg within 1 hour after randomization and of maintaining this level for the next 7 days. In participants who were assigned to receive guideline-recommended treatment (standard-treatment group), blood-pressure–lowering treatment was to be administered if their systolic blood pressure was higher than 180 mm Hg; no lower level was stipulated.[18-20] All participants were to receive oral antihypertensive agents (or topical nitrates) within 7 days (or at discharge from the hospital if that occurred before 7 days), even if the agents had to be administered through a nasogastric tube; combination treatment with an angiotensin-converting–enzyme inhibitor and a diuretic was recommended if that treatment was not contraindicated and if no different drugs were specifically required, with the goal of achieving a systolic blood pressure of less than 140 mm Hg during follow-up for the prevention of recurrent stroke.

Assessments

Demographic and clinical characteristics were recorded at the time of enrollment. The severity of the stroke was assessed with the use of the GCS[17] and the National Institutes of Health Stroke Scale[21] (NIHSS, on which scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit) at baseline, at 24 hours, and at 7 days (or at the time of discharge, if that occurred before 7 days). Brain CT (or MRI) was performed according to standard techniques at baseline (to confirm the diagnosis) in all patients, and at 24±3 hours in a subgroup of patients who were being treated at sites at which

repeat scanning was either part of routine practice or approved for research. Participants were followed up in person or by telephone at 28 days and at 90 days by trained local staff who were unaware of the group assignments. Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analyses according to the intention-to-treat principle.

OUTCOME MEASURES

The primary outcome measure was the proportion of participants with a poor outcome, defined as death or major disability. Major disability was defined as a score of 3 to 5 on the modified Rankin scale at 90 days after randomization. Scores on the modified Rankin scale range from 0 to 6, with a score of 0 indicating no symptoms; a score of 5 indicating severe disability, confinement to bed, or incontinence; and a score of 6 indicating death. The protocol specified "death or severe disability in patients treated within 4 hours of onset of intracranial hemorrhage" as the key secondary outcome.[15] However, during the course of the trial, ordinal approaches to the analysis of the modified Rankin scores gained acceptance in stroke trials. Therefore, in the final statistical analysis plan,[16] which was written before the initiation of data analysis, the key secondary outcome was redefined as physical function across all seven levels of the modified Rankin scale, as determined with the use of an ordinal analysis.[22]

Other secondary outcomes were all-cause mortality and cause-specific mortality (classified at a central location, according to the definitions provided in the Supplementary Appendix, by independent adjudication experts who reviewed submitted medical documents); five dimensions of health-related quality of life (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), as assessed with the use of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire,[23] with each dimension graded according to one of three levels of severity (no problems, moderate problems, or extreme problems); the duration of the initial hospitalization; residence in a residential care facility at 90 days; poor outcomes at 7 days and at 28 days; and serious adverse events. The health statuses from each subscale of the EQ-5D were transformed into a single utility value as a fraction of 1 (with 0 representing death and 1 representing perfect health), with the use of population-based preference weights for the United Kingdom.[24]

The safety outcomes of primary interest were early neurologic deterioration (defined as an increase from baseline to 24 hours of 4 or more points on the NIHSS or a decrease of 2 or more points on the GCS) and episodes of severe hypotension with clinical consequences that required corrective therapy with intravenous fluids or vasopressor agents. The difference in the volume of the hematoma from baseline to 24 hours was assessed in a prespecified subgroup of participants who underwent repeat brain imaging.

STUDY OVERSIGHT

The study was conceived and designed by the executive committee (see the Supplementary Appendix), whose members, along with selected principal investigators from various countries, developed the protocol (which is available at NEJM.org) and conducted the study. The study was approved by the ethics committee at each participating site. The corresponding author wrote the first draft of the manuscript, and other authors provided input. All the authors made the decision to submit the manuscript for publication. Experienced research staff monitored the study for quality and for the integrity of the accumulation of clinical data according to the study protocol. Monitoring for serious adverse events was performed routinely, and any events that occurred were confirmed according to regulatory and Good Clinical Practice requirements, as outlined in the Supplementary Appendix. There was no commercial support for the study. Study data were collected, monitored, and analyzed by the INTERACT2 Project Office and by statisticians at the George Institute for Global Health, who vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

We estimated that with a sample of 2800 participants, the study would have at least 90% power to detect a 14% relative reduction (a difference of 7 percentage points) in the primary outcome, from 50% in the standard-treatment group to 43% in the intensive-treatment group, assuming a between-group difference in systolic blood pressure of 13 mm Hg, a rate of nonadherence to treatment of 10%, and an overall loss to follow-up of 3%, with a type I error rate of 5% and with the use of a two-sided significance test. The data were ana-

lyzed with the use of SAS software, version 9.2, according to the intention-to-treat principle.[16]

The primary analysis of the effect of treatment on the primary outcome was unadjusted and is reported as an odds ratio with associated 95% confidence intervals. We tested for significance using a standard chi-square test of proportions (with a two-sided alpha level of 5%). The scores on the modified Rankin scale were also analyzed with the use of an unadjusted proportional-odds regression model across all levels of the scale, after we checked that the assumption of a common proportional odds was not violated.[25] For sensitivity purposes, the primary outcome was analyzed after adjustment for randomization strata and prognostic baseline variables (age, region, NIHSS score, time from onset of the intracranial hemorrhage to random-

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Intensive Blood-Pressure Lowering (N = 1399)	Guideline-Recommended Blood-Pressure Lowering (N = 1430)
Time from onset of ICH to randomization — hr		
Median	3.7	3.7
Interquartile range	2.8–4.8	2.9–4.7
Age — yr	63.0±13.1	64.1±12.6
Male sex — no. (%)	898 (64.2)	882 (61.7)
Recruited from China — no. (%)	947 (67.7)	973 (68.0)
Blood pressure — mm Hg		
Systolic	179±17	179±17
Diastolic	101±15	101±15
NIHSS score†		
Median	10	11
Interquartile range	6–15	6–16
GCS score‡		
Median	14	14
Interquartile range	12–15	12–15
History of hypertension — no./total no. (%)	1012/1398 (72.4)	1036/1428 (72.5)
Current use of antihypertensive drugs — no./total no. (%)	627/1398 (44.8)	647/1428 (45.3)
Prior intracerebral hemorrhage — no./total no. (%)	115/1398 (8.2)	114/1428 (8.0)
Prior ischemic or undifferentiated stroke — no./total no. (%)	157/1398 (11.2)	166/1428 (11.6)
Prior acute coronary event — no./total no. (%)	39/1398 (2.8)	42/1428 (2.9)
Diabetes mellitus — no./total no. (%)	155/1398 (11.1)	150/1428 (10.5)
Use of warfarin anticoagulation — no./total no. (%)	50/1398 (3.6)	31/1428 (2.2)
Use of aspirin or other antiplatelet agent — no./total no. (%)	123/1398 (8.8)	142/1428 (9.9)
Baseline hematoma volume — ml		
Median	11	11
Interquartile range	6–19	6–20
Deep location of hematoma — no./total no. (%)§	1084/1294 (83.8)	1098/1319 (83.2)
Left hemisphere site of hematoma — no./total no. (%)	644/1294 (49.8)	669/1319 (50.7)
Intraventricular extension of hemorrhage — no./total no. (%)	371/1294 (28.7)	369/1319 (28.0)

* There were no significant differences between the groups in any of the characteristics listed here. ICH denotes intracerebral hemorrhage.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).
‡ Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma).
§ Deep location refers to location in the basal ganglia or thalamus.

ization, volume and location of the hematoma, and presence or absence of intraventricular hemorrhage). The primary outcome was also analyzed according to various alternative cutoff points on the modified Rankin scale that have been used previously: a score of 0, 1, 2, or 3 as compared with scores of 4, 5, and 6 grouped together[26] and a score of 0 or 1 as compared with a score of 2, 3, 4, 5, or 6.[27]

We assessed the heterogeneity of the treatment effect on the primary outcome in eight prespecified subgroups by adding an interaction term in an unadjusted logistic-regression model. The effects of treatment on relative and absolute changes in hematoma volume were assessed by means of an analysis of covariance. The baseline volume of the hematoma and the time from the onset of the intracerebral hemorrhage to the CT were included as covariates, since both predict hematoma growth.[4] The relative change in hema-

Table 2. Treatment of Patients with Intracerebral Hemorrhage.

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	P Value
Time from ICH to start of treatment — hr			<0.001
Median	4.0	4.5	
Interquartile range	2.9–5.1	3.0–7.0	
Time from randomization to start of treatment — hr			<0.001
Median	0.1	0.3	
Interquartile range	0.0–0.39	0.0–2.8	
Blood-pressure–lowering treatment during first 24 hr — no. (%)			
Any intravenous treatment	1260 (90.1)	613 (42.9)	<0.001
Use of a single intravenous agent	849 (60.7)	421 (29.4)	<0.001
Type of intravenous agent used			
Alpha-adrenergic antagonist, such as urapidil	454 (32.5)	191 (13.4)	
Calcium-channel blocker, such as nicardipine or nimodipine	227 (16.2)	122 (8.5)	
Combined alpha- and beta-blocker, such as labetalol	202 (14.4)	83 (5.8)	
Nitroglycerin	209 (14.9)	59 (4.1)	
Diuretic, such as furosemide	174 (12.4)	94 (6.6)	
Nitroprusside	169 (12.1)	28 (2.0)	
Hydralazine	82 (5.9)	50 (3.5)	
Other	85 (6.1)	44 (3.1)	
Medical and surgical treatment during the first 7 days — no./total no. (%)			
Intubation	96/1379 (7.0)	93/1400 (6.6)	0.74
Admission to an intensive care unit	532/1379 (38.6)	529/1400 (37.8)	0.67
Prophylactic treatment for deep-vein thrombosis	306/1379 (22.2)	304/1400 (21.7)	0.76
Compression stockings	147/1379 (10.7)	146/1400 (10.4)	0.84
Subcutaneous heparin	248/1379 (18.0)	245/1400 (17.5)	0.74
Use of intravenous mannitol	855/1379 (62.0)	864/1400 (61.7)	0.88
Hemostatic therapy*	57/1379 (4.1)	40/1400 (2.9)	0.07
Any surgical intervention	77/1379 (5.6)	77/1400 (5.5)	0.92
Evacuation or decompression of the hematoma	43/1379 (3.1)	38/1400 (2.7)	0.53
Insertion of a ventricular drain	41/1379 (3.0)	44/1400 (3.1)	0.80
Decision to withdraw active treatment and care	75/1379 (5.4)	46/1400 (3.3)	0.005

* Hemostatic therapy included the use of fresh-frozen plasma, vitamin K, and recombinant tissue factor VIIa.

toma volume was log-transformed to remove skewness after the addition of the value 1.1 to eliminate negative values. The nominal level of significance for all analyses was P<0.048, since two interim analyses were performed in which the Haybittle–Peto efficacy stopping rule was used.[16]

RESULTS

STUDY POPULATION

From October 2008 through August 2012, a total of 2839 participants (mean age, 63.5 years; 62.9% men) were enrolled at 144 hospitals in 21 countries; 1403 participants were randomly assigned to receive early intensive treatment to lower their blood pressure, and 1436 were assigned to receive guideline-recommended treatment (Fig. S1 in the Supplementary Appendix). The baseline characteristics were balanced between the two groups (Table 1). The primary outcome was determined for 1382 of the participants (98.5%) in the intensive-treatment group and for 1412 (98.3%) in the standard-treatment group.

BLOOD-PRESSURE–LOWERING TREATMENT AND ACHIEVED BLOOD-PRESSURE LEVELS

As shown in Table 2, the median time from the onset of the intracerebral hemorrhage to the initiation of intravenous treatment was shorter in the intensive-treatment group than in the standard-therapy group (4.0 hours [interquartile range, 2.9 to 5.1] vs. 4.5 hours [interquartile range, 3.0 to 7.0], P<0.001); the median time from randomization to the initiation of treatment was also shorter in the intensive-treatment group (6 minutes [inter-

Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.*

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
Primary outcome: death or major disability — no./total no. (%)†	719/1382 (52.0)	785/1412 (55.6)	0.87 (0.75–1.01)	0.06
Secondary outcomes				
Score on the modified Rankin scale — no./total no. (%)‡			0.87 (0.77–1.00)	0.04
0: No symptoms at all	112/1382 (8.1)	107/1412 (7.6)		
1: No substantive disability despite symptoms	292/1382 (21.1)	254/1412 (18.0)		
2: Slight disability	259/1382 (18.7)	266/1412 (18.8)		
3: Moderate disability requiring some help	220/1382 (15.9)	234/1412 (16.6)		
4: Moderate–severe disability requiring assistance with daily living	250/1382 (18.1)	268/1412 (19.0)		
5: Severe disability, bed-bound and incontinent	83/1382 (6.0)	113/1412 (8.0)		
6: Death by 90 days	166/1382 (12.0)	170/1412 (12.0)		
Death — no./total no. (%)	166/1394 (11.9)	170/1421 (12.0)	0.99 (0.79–1.25)	0.96
Health-related quality of life§				
Problems with mobility — no./total no. (%)	767/1203 (63.8)	821/1231 (66.7)	0.88 (0.74–1.04)	0.13
Problems with self-care — no./total no. (%)	563/1202 (46.8)	635/1230 (51.6)	0.83 (0.70–0.97)	0.02
Problems with usual activities — no./total no. (%)	731/1203 (60.8)	814/1231 (66.1)	0.79 (0.67–0.94)	0.006
Problems with pain or discomfort — no./total no. (%)	477/1197 (39.8)	552/1227 (45.0)	0.81 (0.69–0.95)	0.01
Problems with anxiety or depression — no./total no. (%)	406/1192 (34.1)	463/1220 (38.0)	0.84 (0.72–1.00)	0.05
Overall health utility score	0.60±0.39	0.55±0.40		0.002
Living in residential care facility — no./total no. (%)	108/1222 (8.8)	114/1248 (9.1)	0.96 (0.73–1.27)	0.80
Duration of initial hospitalization — days				0.43
Median	20	19		
Interquartile range	12–35	11–33		

Table 3. (Continued.)

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
Safety outcomes — no./total no. (%)				
Neurologic deterioration in first 24 hr¶	198/1369 (14.5)	211/1395 (15.1)	0.95 (0.77–1.17)	0.62
Nonfatal serious adverse events‖	326/1399 (23.3)	338/1430 (23.6)		0.92
Any neurologic deterioration from intracerebral hemorrhage**	47/1399 (3.4)	55/1430 (3.8)		0.49
Recurrent intracerebral hemorrhage	4/1399 (0.3)	4/1430 (0.3)		
Ischemic or undifferentiated stroke	8/1399 (0.6)	8/1430 (0.6)		
Acute coronary event	5/1399 (0.4)	5/1430 (0.3)		
Other cardiovascular disease	22/1399 (1.6)	26/1430 (1.8)		
Noncardiovascular disease	160/1399 (11.4)	152/1430 (10.6)		0.49
Severe hypotension††	7/1399 (0.5)	8/1430 (0.6)		

* Plus–minus values are means ±SD. All odds ratios are unadjusted.
† The modified Rankin scale evaluates global disability and functioning; scores range from 0 (no symptoms) to 6 (death); the primary outcome of death or major disability was assessed as a score on the modified Rankin scale of 3 to 6 at 90 days.
‡ The difference between the groups in scores across all seven levels of the modified Rankin scale was determined with the use of a logistic-regression analysis of the ordinal data.
§ Possible responses in each domain were "no problems," "moderate problems," or "extreme problems"; for these analyses, the latter two levels were combined as "any problems." The overall health utility score was calculated with the use of population norms from the United Kingdom.
¶ Neurologic deterioration was defined as an increase from baseline to 24 hours of 4 or more points on the National Institutes of Health Stroke Scale or a decline of 2 or more points on the Glasgow Coma Scale.
‖ Nonfatal serious adverse events included those that were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, or resulted in disability or a medical or surgical intervention; a patient could have more than one event.
** This category includes clinician-reported neurologic deterioration in a patient with cerebral mass effect or extension of the hematoma.
†† Severe hypotension was defined as hypotension with clinical consequences (including acute renal failure) that required corrective therapy with intravenous fluids, vasopressors, or hemodialysis.

quartile range, 0 to 39] vs. 19 minutes [interquartile range, 0 to 167]). More patients in the intensive-treatment group than in the standard-treatment group received two or more intravenous agents to lower their blood pressure (26.6% vs. 8.1%, P<0.001). The mean systolic blood-pressure levels differed significantly between the two groups from 15 minutes to day 7 after randomization (Fig. S2 in the Supplementary Appendix); at 1 hour, the mean systolic blood pressure was 150 mm Hg in the intensive-treatment group (with 462 patients [33.4%] achieving the target blood pressure of <140 mm Hg) as compared with 164 mm Hg in the standard-treatment group (a difference of 14 mm Hg, P<0.001). As shown in Table 2, there were no significant differences between the two groups with respect to other aspects of medical care during the 7 days after randomization, except that a decision to withdraw active treatment and care was made in the case of more participants in the intensive-treatment group than in the standard-treatment group (75 participants [5.4%] vs. 46 participants [3.3%], P=0.005).

CLINICAL OUTCOMES AND SERIOUS ADVERSE EVENTS

At 90 days, 719 of the participants (52.0%) in the intensive-treatment group, as compared with 785 (55.6%) in the standard-treatment group, had a poor outcome (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06) (Table 3). The ordinal analysis showed a significant favorable shift in the distribution of scores on the modified Rankin scale with intensive blood-pressure–lowering treatment (pooled odds ratio for shift to higher modified Rankin score, 0.87; 95% CI, 0.77 to 1.00; P=0.04) (Table 3, and Fig. S3 in the Supplementary Appendix). Adjusted analyses showed consistency in the treatment effect with respect to the primary and key secondary outcomes in logistic-regression

models that included prognostic variables and various cutoff points on the modified Rankin scale (Table S1 in the Supplementary Appendix).

In the assessment of the five domains of the EQ-5D, participants in the intensive-treatment group reported fewer problems and had significantly better overall health-related quality of life at 90 days than did those in the standard-therapy group (mean [±SD] utility score, 0.60±0.39 vs. 0.55±0.40; P=0.002) (Table 3).

The rate of death from any cause was similar in the intensive-treatment group and the standard-treatment group (11.9% and 12.0%, respectively) (Table 3), as was the percentage of these deaths attributed to the direct effect of the intracerebral hemorrhage (61.4% and 65.3%, respectively). The effects of intensive lowering of blood pressure were consistent across all prespecified subgroups (Fig. 1). There were no significant differences between the two groups in any of the other outcomes studied. The numbers of serious adverse events, including episodes of severe hypotension (which occurred in <1% of the participants), were also balanced between the two groups (Table 3).

HEMATOMA OUTCOMES

The prespecified subgroup of participants who underwent repeat brain imaging for an assessment of the between-group difference in hema-

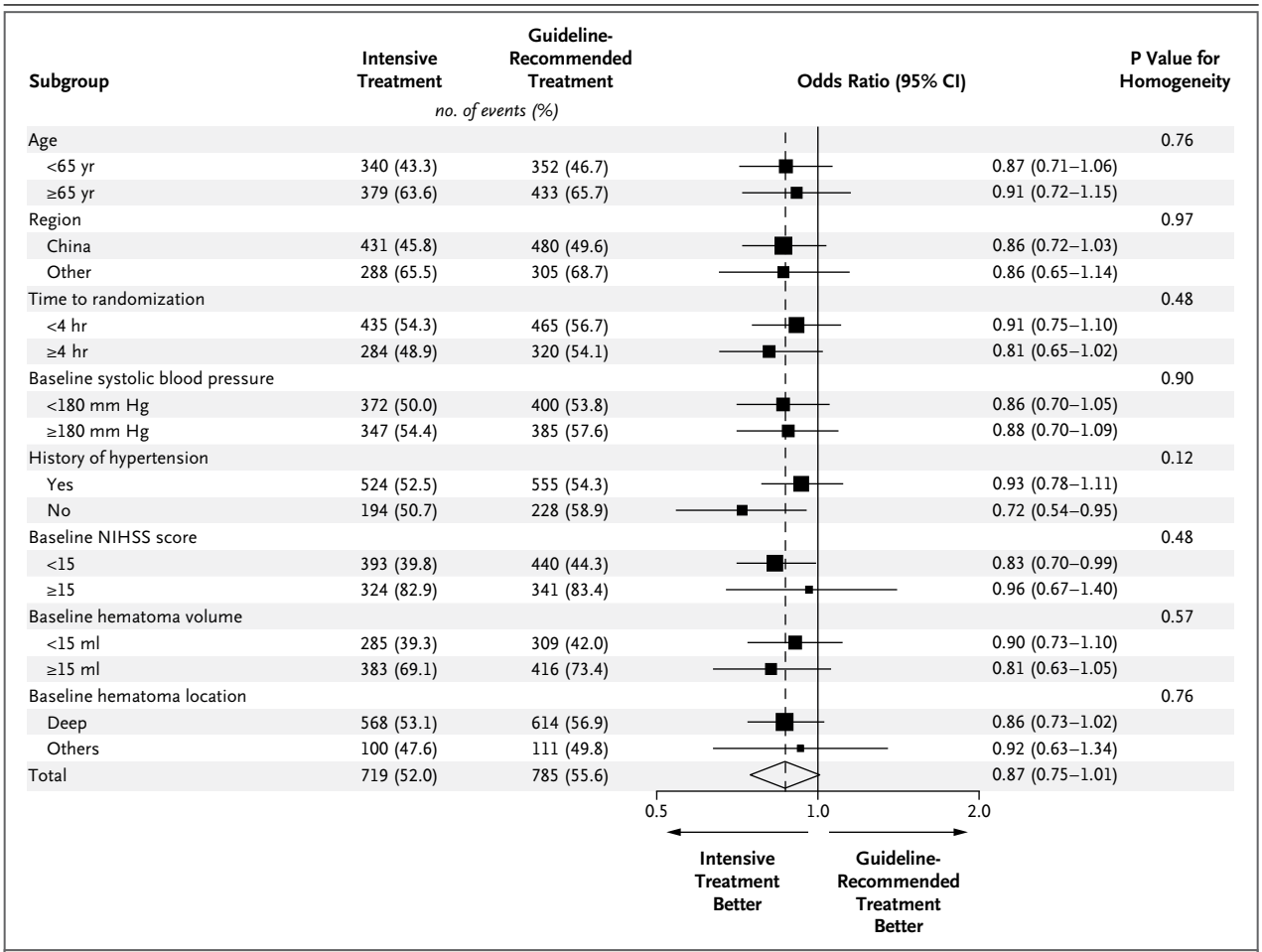

Figure 1. Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups.

The primary outcome of the study was death or major disability, defined as a score of 3 to 6 on the modified Rankin scale (in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death) at 90 days. Each percentage is based on the number of people in that subgroup. The black squares represent point estimates (with the area of the square proportional to the number of events), and the horizontal lines represent 95% confidence intervals. The diamond incorporates the point estimate, represented by the vertical dashed line, as well as the 95% confidence intervals, of the overall effects within categories. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

toma growth from baseline to 24 hours consisted of 491 of the 1399 participants with 90-day outcome data (35.1%) in the intensive-treatment group and 473 of the 1430 participants with 90-day outcome data (33.1%) in the standard-treatment group. The mean hematoma volumes were 15.7±15.7 ml and 15.1±14.9 ml in the two groups, respectively, at baseline and 18.2±19.1 ml and 20.6±24.9 ml, respectively, at 24 hours (Table S2 and Fig. S4 in the Supplementary Appendix). The difference in hematoma growth between the groups in the 24 hours after baseline was not significant (relative difference, 4.5% [95% CI, −3.1 to 12.7; P=0.27], and absolute difference, 1.4 ml [95% CI, −0.6 to 3.4; P=0.18], after adjustment for prognostic variables).

DISCUSSION

In this trial involving patients with intracranial hemorrhage, early intensive lowering of blood pressure, as compared with the more conservative level of blood-pressure control currently recommended in guidelines, did not result in a significant reduction in the rate of the primary outcome of death or major disability. However, in an ordinal analysis of the primary outcome, in which the statistical power for assessing physical functioning was enhanced, there were significantly better functional outcomes among patients assigned to intensive treatment to lower their blood pressure than among patients assigned to guideline-recommended treatment.[22,28] Furthermore, there was significantly better physical and psychological well-being among patients who received intensive treatment. These results are consistent with observational epidemiologic findings associating high blood-pressure levels with poor outcomes among patients with intracerebral hemorrhage[7-11] and indicate that early intensive lowering of blood pressure in this patient population is safe.

There was no clear evidence of heterogeneity in the effect of treatment in any prespecified subgroup — not even in the subgroup defined according to region (China vs. elsewhere). Moreover, there was no evidence of a significant effect modification according to a history or no history of hypertension — a finding that is relevant because it has been postulated that patients with hypertension have an upward shift in cerebral autoregulation and possibly an increased risk of cerebral ischemia related to intensive lowering of blood pressure.[8] However, given the critical nature and rapid evolution of bleeding in the brain, a somewhat surprising finding was the absence of a significant difference in the effect of treatment between patients who underwent randomization early (within 4 hours after the intracerebral hemorrhage) and those who underwent randomization later. This could reflect either the limited power of the subgroup analyses or true independence of the effect of the intervention from the time of initiation of treatment. Since early intensive lowering of blood pressure did not have a clear effect on reducing the growth of the hematoma, a key determinant of early death, there may be other mechanisms at play, such as neuroprotection or a reduction in edema, that result in the later positive clinical outcomes with this treatment. The ongoing Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial[29] is expected to provide additional information on the role of intensive lowering of blood pressure within 4.5 hours after the onset of a intracerebral hemorrhage, but future evaluations of the treatment in patients with intracerebral hemorrhage that are conducted in the prehospital setting or at more extended periods after onset than were tested in INTERACT2 may be warranted.

The current trial has several strengths, including the large sample size, central concealment of treatment assignments, and high rates of follow-up and adherence to treatment. Furthermore, the collection of data on serious adverse events, including hypotension, ensured that any potential harms were reliably detected and quantified. In addition, the range of drug therapies used and of outcomes assessed in participants from a variety of hospitals in different countries enhances the generalizability of the final results.

Some limitations should also be noted. First, although the option to use a range of available drug therapies rather than a single agent was a strength of the study, it introduced complexity in assessing the ways in which the effects may have varied across different agents. Moreover, in the open (unblinded) assignment of interventions that led to earlier and more intensive, as compared with less intensive, control of blood pressure, the outcomes may have been confounded by differences in the management strategies that were used for the two groups after randomization, other than those that were documented. Second, although we used established scales and

objective criteria, some bias may have been introduced in the assessment of key outcomes. Third, the difference in the blood-pressure levels achieved between the two groups may have been attenuated by the use of an active-comparator control group and the concomitant use of additional agents with blood-pressure–lowering properties (e.g., mannitol) or hemostatic properties (e.g., recombinant tissue factor VIIa); if this is so, however, the magnitude of the benefit of early intensive blood-pressure–lowering treatment could be greater in settings in which only the very highest levels of blood pressure are treated in the hyperacute phase of stroke.

In summary, early intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or major disability, but an ordinal analysis of scores on the modified Rankin scale did suggest that intensive treatment improved functional outcomes. Intensive lowering of blood pressure was not associated with an increase in the rates of death or serious adverse events.

Supported by a program grant (571281), project grants (512402 and 1004170), a Senior Principal Research Fellowship (to Dr. Anderson), and a Principal Research Fellowship (to Dr. Neal) from the National Health and Medical Research Council (NHMRC) of Australia. Drs. Neal, Arima, and Parsons are recipients of Future Fellowships from the Australian Research Council. Dr. Hata is a recipient of a Postgraduate Fellowship from the High Blood Pressure Research Council of Australia.

Dr. Huang reports receiving reimbursement for travel expenses from Osaka Pharmaceuticals; Dr. Jiguang Wang, receiving consulting fees from Novartis, Omron Healthcare, Pfizer, and Takeda, grant support from Novartis, Omron Healthcare, and Pfizer, lecture fees from A&D Pharma, Omron Healthcare, Novartis, Pfizer, and Servier, and reimbursement for travel expenses from Pfizer and Takeda; Dr. Lavados, receiving grant support from Lundbeck, payment for manuscript preparation from BMJ, and payment for advisory board membership from Bristol-Myers Squibb; and Dr. Davis, receiving lecture fees from Boehringer Ingelheim, Sanofi-Aventis, and EVER Neuro Pharma. No other potential conflict of interest relevant to this article was reported.

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

We thank the patients who participated in this trial and their relatives; the clinical and research teams of the various emergency departments, intensive care units, stroke units, and neurology departments; Vlado Perkovic, Stephen MacMahon, and Gary Ford for their support; the staff of Apollo Medical Imaging Technology in Melbourne, Australia, for their support of the MiStar software used in the CT analyses; and Beijing MedSept Consulting for developing the interactive voice-activated system that was used for the randomization process in China.

APPENDIX

The authors' affiliations are as follows: George Institute for Global Health (C.S.A., E.H., C.D., R.L., B.N., J.H., H.A., S.H., Q.L., M.W., J.C.) and National Health and Medical Research Council Clinical Trials Centre (R.J.S.), University of Sydney, and the Neurology Department, Royal Prince Alfred Hospital (C.S.A., C.D.), Sydney, the Department of Neurology, John Hunter Hospital, University of Newcastle, Newcastle, NSW (M.P.), and Melbourne Brain Centre, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC (S.M.D.) — all in Australia; the Department of Neurology, Peking University First Hospital, Beijing (Y.H.), the Shanghai Institute of Hypertension, Rui Jin Hospital, Shanghai Jiaotong University, Shanghai (Jiguang Wang), the Department of Neurology, Baotou Central Hospital, Baotou (Y.L.), and the Department of Neurology, Yutian County Hospital, Tangshan, Hebei Province (Jinchao Wang) — all in China; the Department of Neurology, Assistance Publique–Hôpitaux de Paris–Hôpital Lariboisière and DHU NeuroVasc Paris–Sorbonne, Université Paris Diderot–Sorbonne Paris Cité, Paris (C.S.); the Department of Cardiovascular Sciences and NIHR Biomedical Research Unit for Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom (T.R.); Servicio de Neurología, Departamento de Medicina, Clínica Alemana, Universidad del Desarrollo, and Universidad de Chile, Santiago (P.L.) — both in Chile; the Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan (J.H.); and the Department of Epidemiology, Johns Hopkins University, Baltimore (M.W.).

REFERENCES

1. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med 2001;344:1450-60.
2. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH, Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. Lancet Neurol 2007;6:456-64.
3. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28:1-5.
4. Broderick JP, Diringer MH, Hill MD, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. Stroke 2007;38:1072-5.
5. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987-93.
6. 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.
7. Zhang Y, Reilly KH, Tong W, et al. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. J Hypertens 2008;26:1446-52.
8. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. J Hypertens 2005;23:1217-23.
9. Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004;255:257-65.
10. Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. Stroke 1997;28:1396-400.
11. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 2004;35:1364-7.
12. Anderson CS, Huang Y, Wang JG, et al. Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT): a randomised pilot trial. Lancet Neurol 2008;7:391-9.

13. 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.
14. 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.
15. Delcourt C, Huang Y, Wang J, et al. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT2). Int J Stroke 2010;5:110-6.
16. Anderson C, Heeley E, Heritier S, et al. Statistical analysis plan for the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2): a large-scale investigation to solve longstanding controversy over the most appropriate management of elevated blood pressure in the hyperacute phase of intracerebral hemorrhage. Int J Stroke 2013 January 7 (Epub ahead of print).
17. Teasdale G, Jannett B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974;2:81-4.
18. 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.
19. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108-29.
20. Steiner T, Kaste M, Forsting M, et al. Recommendations for the management of intracranial haemorrhage. I. Spontaneous intracerebral haemorrhage. Cerebrovasc Dis 2006;22:294-316. [Erratum, Cerebrovasc Dis 2006;22:461.]
21. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-70.
22. Bath PMW, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials. Stroke 2012;43:1171-8. [Erratum, Stroke 2012;43(9):e100.]
23. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
24. Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: results from a UK general population survey. Discussion paper 138. York, United Kingdom: University of York Centre for Health Economics, September 1995.
25. Woodward M. Epidemiology: study design and data analysis. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC, 2005: 587-91.
26. IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial. Lancet 2012;379:2352-63. [Erratum, Lancet 2012:380:730.]
27. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245-51.
28. Howard G, Waller JL, Voeks JH, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. Stroke 2012; 43:664-9.
29. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. Neurocrit Care 2011;15:559-76.