Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

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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.)
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.\(^3\) Blood pressure often becomes elevated after intracerebral hemorrhage,\(^4\) frequently reaching very high levels, and is a predictor of outcome.\(^7\) On the basis of the results of the pilot-phase study, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 1 (INTERACT1),\(^12\) 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.\(^10\) 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 prac-
tice 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 analy-
theses according to the intention-to-treat principle.

**OUTCOME MEASURES**
The primary outcome measure was the propor-
tion 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, confine-
ment 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. 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 fi-
nal statistical analysis plan, which was written
before the initiation of data analysis, the key sec-
ondary outcome was redefined as physical func-
tion across all seven levels of the modified
Rankin scale, as determined with the use of an
ordinal analysis.

Other secondary outcomes were all-cause mor-
tality and cause-specific mortality (classified at
a central location, according to the definitions
provided in the Supplementary Appendix, by in-
dependent 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, with each dimension
graded according to one of three levels of sever-
ity (no problems, moderate problems, or extreme
problems); the duration of the initial hospital-
ization; 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 trans-
formed 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.

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 hypo-
tension with clinical consequences that required
corrective therapy with intravenous fluids or
vasopressor agents. The difference in the vol-
ume of the hematoma from baseline to 24 hours
was assessed in a prespecified subgroup of par-
ticipants who underwent repeat brain imaging.

**STUDY OVERSIGHT**
The study was conceived and designed by the ex-
cutive committee (see the Supplementary Appen-
dix), 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 re-
search 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 routine-
ly, and any events that occurred were confirmed
according to regulatory and Good Clinical Prac-
tice requirements, as outlined in the Supplemen-
tary Appendix. There was no commercial support
for the study. Study data were collected, moni-
tored, 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 partici-
pants, 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.\textsuperscript{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.\textsuperscript{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-
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 and a score of 0 or 1 as compared with a score of 2, 3, 4, 5, or 6.

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. The relative change in hema-

Table 2. Treatment of Patients with Intracerebral Hemorrhage.

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

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

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 hemorrhage7-11 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 initiations 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 trial29 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.

APPENDIX

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