Subarachnoid Extension of Intracerebral Hemorrhage and 90-Day Outcomes in INTERACT2

Guofang Chen, MD; Hisatomi Arima, MD; Guojun Wu, MD; Emma Heeley, PhD; Candice Delcourt, MD; Peiying Zhang, MD; Alejandro A. Rabinstein, MD; Thompson Robinson, MD; Christian Stapf, MD; Yining Huang, MD; Lili Song, MD; Jie Yang, MD; Xia Wang, MMed; Qiang Li, BSc; Xiaoying Chen, BM; John Chalmers, MD; Craig Anderson, MD; for the INTERACT2 Investigators*

Background and Purpose—The prognostic significance of subarachnoid extension of intracerebral hemorrhage was determined in the INTensive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2) study.

Methods—INTERACT2 was an open randomized controlled trial of early intensive compared with guideline-recommended blood pressure lowering in patients with elevated systolic blood pressure within 6 hours of intracerebral hemorrhage. Independent predictors of death or major disability (scores 3–6 on the modified Rankin Scale) at 90 days were analyzed in logistic regression models.

Results—Of 2582 participants, 192 (7%) had subarachnoid extension, which was associated with larger hematoma volumes (P<0.0001) and higher National Institute of Health Stroke Scale score (P<0.0001). Subarachnoid extension predicted death or major disability at 90 days (71% versus 53%; unadjusted odds ratio, 2.25; 95% confidence interval, 1.63–3.10; P<0.0001). The association remained significant after adjusting for age, region, lipid-lowering therapy, systolic blood pressure, glucose, location of hematoma, intraventricular extension, and randomized treatment (odds ratio, 2.17; 95% confidence interval, 1.50–3.14; P<0.0001), but not after further adjustment for baseline hematoma volume (P=0.62).

Conclusions—Subarachnoid extension of intracerebral hemorrhage is associated with poor prognosis, which is determined by a larger volume of the underlying intraparenchymal hematoma.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00716079. (Stroke. 2013;45:00-00.)

Key Words: assessment, outcomes □ cerebral hemorrhage □ clinical trial

A
cute intracerebral hemorrhage (ICH) is the least treatable form of stroke affecting more than a million people in the world each year. Effective management requires better understanding of pathophysiology and prognostic factors. Recently, a hospital-based observational study found that subarachnoid extension of ICH was significantly associated with increased 14-day mortality and 28-day disability in 234 patients with acute ICH. The authors proposed that subarachnoid extension could produce cortical dysfunction and injury from mechanisms akin to those observed in aneurysmal subarachnoid hemorrhage (SAH). In comparison with subarachnoid hemorrhage, however, only a small amount of blood usually reaches the subarachnoid space in ICH. The clinical significance of subarachnoid extension and clinical outcome in ICH was examined in the INTERACT2 study, where rigorous evaluations were undertaken in a large number of participants with 90 days of follow-up.

Methods
The design and main results of the INTERACT2 trial are outlined elsewhere. Briefly, 2829 patients with spontaneous ICH within 6 hours of onset and elevated systolic blood pressure were assigned to receive intensive (target systolic level <140 mm Hg within 1 hour) or guideline-recommended (<180 mm Hg) blood pressure–lowering treatment.

Received September 12, 2013; accepted September 19, 2013.

From the Department of Neurology (G.C.) and Department of Cardiology (P.Z.), Xuzhou Central Hospital, Jiangsu, China; The George Institute for Global Health, University of Sydney, Sydney, Australia (G.C., H.A., G.W., E.H., C.D., L.S., J.Y., W.Q., L.C., J.C., C.A.); Department of Neurology, Hebei Yutian Hospital, Tang Shan, China (G.W.); Department of Neurology, Mayo Clinic, Rochester, MN (A.A.R.); Department of Cardiovascular Sciences and NIHR Biomedical Research Unit for Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom (T.R.); Department of Neurology, Université Paris Diderot–Sorbonne Paris Cité, Paris, France (C.S.); Department of Neurology, Peking University First Hospital, Beijing, China (Y.H.); Department of Neurology, Shanghai 85th Hospital of PLA, Shanghai, China (L.S.); and Department of Neurology, Nanjing Hospital Affiliated to Nanjing Medical University, Nanjing, China (J.Y.).

*For a full list of investigators, see Ref. 4.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/supp/doi:10.1161/STROKEAHA.113.003524./DC1.

Correspondence to Craig Anderson, MD, The George Institute for Global Health, University of Sydney, PO Box M201, Missenden Rd, Sydney, NSW 2050, Australia. E-mail canderson@georgeinstitute.org.au

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.113.003524
The study was approved by the ethics committees for each site and informed consent was obtained from all patients or relevant surrogates.

Brain imaging was performed according to standardized techniques. Digital computed tomographic images were collected in uncompressed DICOM format and analyzed centrally for the presence of bleeding into the subarachnoid space, location and volume of hematoma, and any intraventricular extension. Subarachnoid extension of ICH was classified into sulcal and generalized patterns, the latter was further classified according to the modified Fisher scale.1

Outcomes were death or major disability, defined as a modified Rankin Scale (mRS) score2 of 3 to 6, death, major disability (mRS, 3–5), and an ordinal analysis of mRS scores at 7, 28, and 90 days.

Results

Overall, 2582 participants with information on baseline computed tomography and 90-day mRS were included in analyses. There were 192 (7%) patients with subarachnoid extension of ICH at baseline, who had significantly higher National Institute of Health Stroke Scale scores and larger hematoma volumes (all \(P<0.0001\); Table I in the online-only Data Supplement).

The Table shows that subarachnoid extension was associated with increased risk of death or major disability at 90 days (71% versus 53%; \(P<0.0001\)). Likewise, patients with subarachnoid extension had higher risks of poorer function on ordinal analysis of mRS scores \(P<0.0001\); Figure). The association between subarachnoid extension and death or major disability remained significant in multivariable-adjusted model 1 \(\left(P<0.0001\right);\) Table). However, there was no longer any independent significance after further adjustment for baseline hematoma volume (model 2; \(P=0.62\)). Additional adjustment of seizures during follow-up did not change the findings (Table II in the online-only Data Supplement).

Table III in the online-only Data Supplement shows baseline characteristics by distribution of subarachnoid extension of ICH. There were no clear differences in baseline hematoma volume between sulcal (median, 28.9 mL) and generalized patterns (28.5 mL; \(P=0.49\)). Patients with generalized pattern had significantly higher 90-day mortality than those with sulcal subarachnoid extension \(\left(\text{odds ratio, 2.54; 95\% confidence interval, 1.32–4.90; } P=0.005\right)\) but not after adjustment for other covariates including baseline hematoma volume \(\left(\text{model 2; } P=0.12\right)\).

Among 964 patients in the computed tomographic sub-study, 952 with information on 90-day mRS were included in further analysis. There were 73 (8%) patients with baseline and 36 (4%) with delayed subarachnoid extension. Increased risks of death or major disability at 90 days were observed for both baseline \(\left(\text{odds ratio, 1.98; 95\% confidence interval, 1.04–3.80; } P=0.008\right)\) and delayed subarachnoid extension \(\left(\text{odds ratio, 4.01; 95\% confidence interval, 1.27–12.61; } P=0.02\right)\) even after adjustment for other covariates \(\text{(model 1)},\) but not after further adjustment for baseline hematoma volume \(\left(\text{model 2; } P=0.96\right)\) for baseline and \(0.19\) for delayed subarachnoid extension.

Discussion

In INTERACT2, which included >2500 patients, subarachnoid extension of ICH was associated with increased risks of death or major disability, but not after adjustment for baseline hematoma volume. These findings suggest that hematoma volume is the primary determinant of poor prognosis in patients with subarachnoid extension of ICH.

Our results differ from those of a previous hospital-based observational study of acute ICH, where a strong independent association was evident between subarachnoid extension and 14-day mortality and 28-day disability. However, that study reported a much higher rate of subarachnoid extension (40%), possibly because of differences in hematoma location and use of antithrombotics and was based on relatively small numbers (234) of patients. The greater sample size in INTERACT2 allowed us to undertake more precise adjustment for prognostic variables and as the data came from multiple centers, the results have strong external validity.

### Table. Effects of Subarachnoid Extension on Death and Major Disability

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subarachnoid Extension (n=192)</th>
<th>No Subarachnoid Extension (n=2390)</th>
<th>Crude OR (95% CI)</th>
<th>(P) Value</th>
<th>Multivariable Adjusted Model 1 OR (95% CI)</th>
<th>(P) Value</th>
<th>Multivariable Adjusted Model 2 OR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death/major disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>170 (89%)</td>
<td>1795 (75%)</td>
<td>2.41 (1.53–3.80)</td>
<td>0.0001</td>
<td>2.85 (1.74–4.68)</td>
<td>&lt;0.0001</td>
<td>1.31 (0.76–2.25)</td>
<td>0.33</td>
</tr>
<tr>
<td>Day 28</td>
<td>157 (82%)</td>
<td>1562 (65%)</td>
<td>2.35 (1.61–3.42)</td>
<td>&lt;0.0001</td>
<td>2.29 (1.51–3.48)</td>
<td>&lt;0.0001</td>
<td>1.06 (0.67–1.68)</td>
<td>0.81</td>
</tr>
<tr>
<td>Day 90</td>
<td>137 (71%)</td>
<td>1256 (53%)</td>
<td>2.25 (1.63–3.10)</td>
<td>&lt;0.0001</td>
<td>2.17 (1.50–3.14)</td>
<td>&lt;0.0001</td>
<td>1.11 (0.74–1.67)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>34 (18%)</td>
<td>132 (6%)</td>
<td>3.68 (2.44–5.55)</td>
<td>&lt;0.0001</td>
<td>3.47 (2.09–5.75)</td>
<td>&lt;0.0001</td>
<td>1.42 (0.81–2.49)</td>
<td>0.22</td>
</tr>
<tr>
<td>Day 28</td>
<td>51 (27%)</td>
<td>217 (9%)</td>
<td>3.62 (2.55–5.14)</td>
<td>&lt;0.0001</td>
<td>3.15 (2.05–4.84)</td>
<td>&lt;0.0001</td>
<td>1.34 (0.83–2.17)</td>
<td>0.23</td>
</tr>
<tr>
<td>Day 90</td>
<td>54 (28%)</td>
<td>259 (11%)</td>
<td>3.22 (2.29–4.52)</td>
<td>&lt;0.0001</td>
<td>2.64 (1.74–4.00)</td>
<td>&lt;0.0001</td>
<td>1.14 (0.71–1.83)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Major disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>136 (71%)</td>
<td>1663 (70%)</td>
<td>1.01 (0.73–1.40)</td>
<td>0.95</td>
<td>1.21 (0.84–1.74)</td>
<td>0.31</td>
<td>0.76 (0.51–1.12)</td>
<td>0.16</td>
</tr>
<tr>
<td>Day 28</td>
<td>106 (55%)</td>
<td>1345 (56%)</td>
<td>0.95 (0.70–1.27)</td>
<td>0.72</td>
<td>0.98 (0.70–1.37)</td>
<td>0.90</td>
<td>0.66 (0.46–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Day 90</td>
<td>83 (43%)</td>
<td>997 (42%)</td>
<td>1.06 (0.79–1.43)</td>
<td>0.68</td>
<td>1.09 (0.77–1.53)</td>
<td>0.64</td>
<td>0.78 (0.54–1.12)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Model 1: adjustment for age, region, lipid-lowering therapy, systolic blood pressure, glucose, hematoma location, intraventricular extension, and randomized treatment; model 2: model 1 variables+baseline hematoma volume. CI indicates confidence interval; and OR, odds ratio.
Our findings suggest that subarachnoid extension in ICH is often restricted to a few sulci of the ipsilateral convexity. Given the strong association between the amount of subarachnoid hemorrhage and the risk of delayed cerebral ischemia in patients with ruptured intracranial aneurysms,\textsuperscript{7,8} it is unlikely that the small amounts of sulcal hemorrhage often observed in ICH would be a major determinant of outcome. Although a generalized pattern of subarachnoid extension was associated with greater mortality in univariable analysis, this association was no longer significant after adjustment for other covariates.

Our study is limited in being subsidiary to the overall design of the trial and for the number of patients with each type of subarachnoid extension being insufficient to allow detailed multivariable analyses.

In summary, subarachnoid extension is associated with more severe clinical grade at presentation and poorer 90-day prognosis in acute ICH. The prognostic significance of subarachnoid extension of ICH on clinical outcome can be explained by its association with larger hematoma volumes.
Subarachnoid Extension of Intracerebral Hemorrhage and 90-Day Outcomes in INTERACT2
Guofang Chen, Hisatomi Arima, Guojun Wu, Emma Heeley, Candice Delcourt, Peiying Zhang, Alejandro A. Rabinstein, Thompson Robinson, Christian Stapf, Yining Huang, Lili Song, Jie Yang, Xia Wang, Qiang Li, Xiaoying Chen, John Chalmers and Craig Anderson

Stroke. published online October 22, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2013/10/22/STROKEAHA.113.003524

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/22/STROKEAHA.113.003524.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Subarachnoid extension of intracerebral hemorrhage and 90-day outcomes in INTERACT2

Guofang Chen MD, Hisatomi Arima MD PhD, Guojun Wu MD, Emma Heeley PhD, Candice Delcourt MD, Peiying Zhang MD, Alejandro A Rabinstein MD, Thompson Robinson MD, Christian Stapf MD, Yining Huang MD, Lili Song MD, Jie Yang MD, Xia Wang MMed, Qiang Li BSc, Xiaoying Chen BM, BS, John Chalmers MD PhD, Craig S Anderson MD PhD, for the INTERACT2 Investigators*

Department of Neurology (G.C.) and Department of Cardiology (P.Z.), Xuzhou Central Hospital, Jiangsu, China; The George Institute for Global Health (G.C., H.A., G.W., E.H., C.D., L.S., J.Y., X.W., Q.L., X.C., J.C., C.S.A.), University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia; Department of Neurology (A.A.R.), Mayo Clinic, Rochester, MN; Department of Cardiovascular Sciences and NIHR Biomedical Research Unit for Cardiovascular Sciences (T.R.), University of Leicester, Leicester, United Kingdom; Department of Neurology (C.S), Assistance Publique–Hôpitaux de Paris–Hôpital Lariboisière and DHU NeuroVasc Paris–Sorbonne, Université Paris Diderot–Sorbonne Paris Cité, Paris, France; Department of Neurology (Y.H.), Peking University First Hospital, Beijing, China; Department of Neurology (L.S.), Shanghai 85th Hospital of PLA, Shanghai, China; Department of Neurology (J.Y.), Nanjing Hospital affiliated to Nanjing Medical University, Nanjing, China; Department of Neurology (G.W.), Hebei Yutian Hospital, Tang Shan, China.
*for a full list of INTERACT2 Investigators, see reference 4.

Author for correspondence:
Professor Craig Anderson
The George Institute for Global Health
PO Box M201, Missenden Road, NSW 2050, AUSTRALIA
T: +61-2-9993-4500
F: +61-2-9993-4502
Email: canderson@georgeinstitute.org.au
Supplemental Methods

CT substudy
In a predefined CT substudy of the INTERACT2 trial, 964 selected patients underwent a repeat CT at 24 hours using the same procedure as the baseline CT with digital images analyzed centrally. Delayed subarachnoid extension of intracerebral hemorrhage (ICH) was defined as new-onset subarachnoid extension on the repeat CT scan alone.

Statistical analysis
The effects of subarachnoid extension on death/major disability, death and major disability were ascertained by logistic regression models. Association of subarachnoid extension on the modified Rankin Scale (mRS) score was also calculated using an ordinal logistic regression model. In multivariable analyses, age, region, lipid lowering therapy, systolic BP, glucose, location of hematoma, intraventricular extension, and randomized treatment at baseline were included into the model 1, while baseline hematoma volume was also included into the model 2. As a sensitivity analysis, additional adjustment for seizures during follow-up was conducted (model 3: variables in model 1 + seizures; model 4: variables in model 2 + seizures). Baseline scores on the Glasgow Coma Scale (GCS) and National Institute of Health Stroke Scale (NIHSS) were not included in the models to avoid over-adjustment. The data were reported with 95% confidence intervals (CI). Analyses were performed using SAS statistical software (version 9.3).
### Supplemental Table I. Baseline characteristics of participants with and without subarachnoid extension of intracerebral hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Subarachnoid extension (n=192)</th>
<th>No subarachnoid extension (n=2390)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 (14)</td>
<td>63 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>77 (40%)</td>
<td>898 (38%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Chinese region</td>
<td>116 (60%)</td>
<td>1614 (68%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>16 (8%)</td>
<td>191 (8%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>25 (13%)</td>
<td>233 (10%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>7 (4%)</td>
<td>70 (3%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130 (68%)</td>
<td>1735 (73%)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Medication history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>85 (44%)</td>
<td>1071 (45%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>9 (5%)</td>
<td>71 (3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>25 (13%)</td>
<td>222 (9%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>22 (11%)</td>
<td>168 (7%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Clinic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time from onset to</td>
<td>3.79 (2.92-4.89)</td>
<td>3.70 (2.79-4.70)</td>
<td>0.12</td>
</tr>
<tr>
<td>randomization (hour)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>178 (17)</td>
<td>179 (17)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>99 (15)</td>
<td>101 (15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Temperature</td>
<td>36.5 (0.6)</td>
<td>36.4 (0.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Median GCS score*</td>
<td>14 (10-15)</td>
<td>14 (13-15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GCS score ≤8</td>
<td>24 (13%)</td>
<td>122 (5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median NIHSS score†</td>
<td>14 (8-19)</td>
<td>10 (6-15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS score ≥14</td>
<td>97 (51%)</td>
<td>766 (32%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.7 (2.6)</td>
<td>7.1 (2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CT findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma volume (ml)</td>
<td>28.4 (15.7-43.5)</td>
<td>10.3 (5.5-17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hematoma location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>88 (46%)</td>
<td>165 (7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basal ganglia or thalamus</td>
<td>87 (45%)</td>
<td>2062 (86%)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar</td>
<td>13 (7%)</td>
<td>75 (3%)</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>1 (1%)</td>
<td>78 (3%)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>77 (40%)</td>
<td>653 (27%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Randomized intensive BP lowering</td>
<td>98 (51%)</td>
<td>1181 (49%)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or median (IQR).
P values are based on chi-squared or Wilcoxon test.
BP indicates blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; mRS, the modified Rankin Scale; CT, Computed tomography.

*GCS scores can range from 3 (deep coma) to 15 (normal, alert).
†NIHSS scores can range from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia).
Supplemental Table II. The effects of subarachnoid extension in intracerebral hemorrhage on death and major disability after additional adjustment of seizures during follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Death/major disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>2.86 (1.74-4.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 28</td>
<td>2.30 (1.52-3.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 90</td>
<td>2.17 (1.50-3.15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>3.46 (2.09-5.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 28</td>
<td>3.14 (2.05-4.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 90</td>
<td>2.63 (1.73-4.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>1.21 (0.84-1.75)</td>
<td>0.30</td>
</tr>
<tr>
<td>Day 28</td>
<td>0.98 (0.70-1.37)</td>
<td>0.91</td>
</tr>
<tr>
<td>Day 90</td>
<td>1.09 (0.77-1.53)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.
Model 3: adjusted for age, region, lipid lowering therapy, systolic blood pressure, glucose, location of hematoma, intraventricular extension, randomized treatment at baseline and seizures during follow-up; Model 4: model 3 variables + baseline hematoma volume.
Supplemental Table III. Baseline characteristics of participants by distribution of subarachnoid extension of intracerebral hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Sulcal (n=100)</th>
<th>Modified Fisher scale 1 (n=13)</th>
<th>Modified Fisher scale 2 (n=11)</th>
<th>Modified Fisher scale 3 (n=40)</th>
<th>Modified Fisher scale 4 (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (14)</td>
<td>69 (15)</td>
<td>76 (10)</td>
<td>69 (12)</td>
<td>67 (14)</td>
<td>0.28</td>
</tr>
<tr>
<td>Female</td>
<td>36 (36%)</td>
<td>3 (23%)</td>
<td>5 (45%)</td>
<td>21 (53%)</td>
<td>11 (41%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Chinese region</td>
<td>62 (62%)</td>
<td>5 (38%)</td>
<td>2 (18%)</td>
<td>29 (73%)</td>
<td>18 (67%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>6 (6%)</td>
<td>4 (31%)</td>
<td>0 (0%)</td>
<td>4 (10%)</td>
<td>1 (4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>9 (9%)</td>
<td>3 (23%)</td>
<td>2 (18%)</td>
<td>4 (10%)</td>
<td>7 (26%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2 (2%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>4 (10%)</td>
<td>0 (0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 (70%)</td>
<td>8 (62%)</td>
<td>7 (64%)</td>
<td>26 (65%)</td>
<td>18 (67%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>42 (42%)</td>
<td>7 (54%)</td>
<td>5 (45%)</td>
<td>20 (50%)</td>
<td>10 (37%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>4 (4%)</td>
<td>0 (0%)</td>
<td>2 (18%)</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>15 (15%)</td>
<td>2 (15%)</td>
<td>3 (27%)</td>
<td>3 (8%)</td>
<td>2 (7%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>12 (12%)</td>
<td>1 (8%)</td>
<td>4 (36%)</td>
<td>3 (8%)</td>
<td>2 (7%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Clinic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time from onset to randomization (hour)</td>
<td>4.17 (3.00-4.94)</td>
<td>3.25 (2.80-4.38)</td>
<td>3.72 (3.05-5.46)</td>
<td>3.71 (2.99-4.71)</td>
<td>3.5 (2.42-4.65)</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>178 (16)</td>
<td>183 (16)</td>
<td>168 (17)</td>
<td>177 (16)</td>
<td>178 (20)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>99 (17)</td>
<td>101 (17)</td>
<td>90 (15)</td>
<td>99 (13)</td>
<td>100 (11)</td>
<td>0.43</td>
</tr>
<tr>
<td>Temperature</td>
<td>36.5 (0.5)</td>
<td>36.2 (0.4)</td>
<td>36.7 (0.7)</td>
<td>36.4 (0.7)</td>
<td>36.5 (0.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Median GCS score*</td>
<td>14 (12-15)</td>
<td>14 (12-15)</td>
<td>11 (9-15)</td>
<td>13 (10-15)</td>
<td>12 (8-14)</td>
<td>0.01</td>
</tr>
<tr>
<td>GCS score ≤8</td>
<td>6 (6%)</td>
<td>2 (15%)</td>
<td>2 (18%)</td>
<td>6 (15%)</td>
<td>7 (26%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median NIHSS score†</td>
<td>13 (8-18)</td>
<td>15 (12-17)</td>
<td>18 (12-24)</td>
<td>14 (5-20)</td>
<td>17 (9-21)</td>
<td>0.12</td>
</tr>
<tr>
<td>NIHSS score ≥14</td>
<td>43 (43%)</td>
<td>7 (54%)</td>
<td>8 (73%)</td>
<td>20 (50%)</td>
<td>18 (67%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.4 (2.7)</td>
<td>7.5 (1.5)</td>
<td>7.7 (2.2)</td>
<td>8.3 (2.8)</td>
<td>8.3 (2.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>CT findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma volume (ml)</td>
<td>28.9 (15.9-38.8)</td>
<td>56.1 (45.6-72.1)</td>
<td>49 (18.7-71.6)</td>
<td>26.4 (15.7-44.3)</td>
<td>17.8 (5.3-34.4)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hematoma location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>55 (55%)</td>
<td>6 (46%)</td>
<td>5 (45%)</td>
<td>16 (40%)</td>
<td>6 (22%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basal ganglia or thalamus</td>
<td>43 (43%)</td>
<td>7 (54%)</td>
<td>6 (55%)</td>
<td>14 (35%)</td>
<td>16 (59%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (25%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>11 (11%)</td>
<td>12 (92%)</td>
<td>10 (91%)</td>
<td>17 (43%)</td>
<td>26 (96%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Randomized intensive BP lowering</td>
<td>52 (52%)</td>
<td>8 (62%)</td>
<td>6 (55%)</td>
<td>16 (40%)</td>
<td>15 (56%)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or median (IQR). P values are based on chi-squared or Kruskal-Wallis test. BP indicates blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; mRS, the modified Rankin Scale; CT, Computed tomography. *GCS scores can range from 3 (deep coma) to 15 (normal, alert). †NIHSS scores can range from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia).
Supplemental Table IV. Death and major disability by distribution of subarachnoid extension of intracerebral hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Sulcal</th>
<th>Generalized pattern</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n=100)</td>
<td>(n=13)</td>
<td>(n=11)</td>
<td>(n=40)</td>
<td>(n=27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/major disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>86 (86%)</td>
<td>13 (100%)</td>
<td>11 (100%)</td>
<td>34 (85%)</td>
<td>25 (93%)</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>81 (81%)</td>
<td>12 (92%)</td>
<td>11 (100%)</td>
<td>29 (73%)</td>
<td>23 (85%)</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 90</td>
<td>70 (70%)</td>
<td>10 (77%)</td>
<td>11 (100%)</td>
<td>25 (63%)</td>
<td>20 (74%)</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>8 (8%)</td>
<td>3 (23%)</td>
<td>4 (36%)</td>
<td>8 (20%)</td>
<td>10 (37%)</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>17 (17%)</td>
<td>4 (31%)</td>
<td>7 (64%)</td>
<td>10 (25%)</td>
<td>12 (44%)</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 90</td>
<td>19 (19%)</td>
<td>4 (31%)</td>
<td>7 (64%)</td>
<td>11 (28%)</td>
<td>12 (44%)</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>78 (78%)</td>
<td>10 (77%)</td>
<td>7 (64%)</td>
<td>26 (65%)</td>
<td>15 (56%)</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>64 (64%)</td>
<td>8 (62%)</td>
<td>4 (36%)</td>
<td>19 (48%)</td>
<td>11 (41%)</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 90</td>
<td>51 (51%)</td>
<td>6 (46%)</td>
<td>4 (36%)</td>
<td>14 (35%)</td>
<td>8 (30%)</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%).
P values are based on chi-squared test.