Significance of Intraventricular Hemorrhage in Acute Intracerebral Hemorrhage

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Results

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Background and Purpose—Intraventricular hemorrhage (IVH) with spontaneous intracerebral hemorrhage indicates a poor prognosis but uncertainty exists over the pattern of association. We aimed to elucidate risk associations of IVH and outcome in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) data set.

Methods—INTERACT2 was an international prospective, open-blinded end point, randomized controlled trial in 2839 patients with intracerebral hemorrhage (<6 hours) with elevated systolic blood pressure randomly assigned to intensive (target systolic blood pressure <140 mm Hg) or guideline-based (systolic blood pressure <180 mm Hg) blood pressure management. Associations of baseline IVH in 740 of 2613 (28%) patients and poor outcomes (death and major disability defined on the modified Rankin Scale) at 90 days were determined in linear and logistic regression models.

Results—Patients with IVH were significantly older and with greater neurological impairment, history of ischemic stroke, and larger hematomas more often deep hemisphere located at presentation, after adjustment for other baseline variables. Death or major disability occurred in 66% with IVH versus 49% in intracerebral hemorrhage–alone patients (adjusted odds ratio, 1.68; 95% confidence interval, 1.38–2.06; $P<0.01$). Associations of IVH volume and clinical outcomes were strong and near continuous. Adjusted analyses by thirds of IVH volume indicate thresholds of ≈5 and 10 mL for significantly increased odds of death and death or major disability, respectively.

Conclusions—A strong association exists between the amount of IVH and poor outcome in intracerebral hemorrhage. An IVH volume of 5 to 10 mL emerges as a significant threshold for decision making on prognosis in these patients.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00716079.

(*Stroke*. 2015;46:653-658. DOI: 10.1161/STROKEAHA.114.008470.)

Key Words: cerebral hemorrhage ■ cerebral ventricles ■ clinical trial ■ mortality ■ outcome measures

Acute spontaneous intracerebral hemorrhage (ICH) is the least treatable and most serious form of stroke.[1] When ICH spills into the ventricular system, which occurs in about one third of cases,[2] the risk of death increases 5-fold and survivors are left with greater long-term disability.[3–5] However, the pattern of association between intraventricular hemorrhage (IVH) volume and adverse outcomes in ICH remains unclear, and the amount of IVH that is clinically relevant for patient care has not been clearly defined. Such data are important for planning inclusion criteria and outcomes in clinical trials and in decisions about patient management, such as the use of drainage and fibrinolysis of IVH.[3,6,7] We aimed to elucidate risk associations of IVH and outcomes among participants of the main phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) study.

Received December 15, 2014; final revision received December 31, 2014; accepted January 2, 2015.

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Presented in part at the International Stroke Conference of the American Heart Association, Nashville, TN, February 11–13, 2015.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.008470/-/DC1.

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Methods

The INTERACT2 study was an international, multicenter, open-blinded end point, randomized controlled trial, the details of which are outlined elsewhere.[8] In brief, 2839 patients with computed tomographic–confirmed spontaneous ICH within 6 hours of onset and elevated systolic blood pressure (systolic BP, 150–220 mm Hg) were randomly assigned to receive intensive (target systolic BP, <140 mm Hg within 1 hour) or guideline-recommended (target systolic BP, <180 mm Hg) BP-lowering therapy using locally available agents according to standardized protocols. The study protocol was approved by the appropriate ethics committee at each participating site, and written informed consent was obtained from the patient or an appropriate surrogate.

Demographic and clinical characteristics were recorded at the time of enrollment. Stroke severity was measured using the Glasgow Coma Scale and National Institutes of Health Stroke Scale at baseline, 24 hours, and at day 7 (or earlier on discharge from hospital). Uncompressed digital images of all baseline and follow-up CT scans were collected in DICOM format, identified only with the patient's unique study number, for central analysis of ICH and IVH volumes blind to clinical data, treatment, and date and sequence of scan, using computer-assisted multislice planimetric and voxel threshold techniques in MIStar version 3.2 (Apollo Medical Imaging Technology). Inter-reader reliability was checked by periodic reanalysis of 15% of the scans reviewed by each imaging scientist against a gold standard single neurologist to avoid drift (intraclass correlation coefficient, 0.92 for total hematoma volume and 0.96 after removing outlier data with total volumes >50 mL).

The primary clinical outcome was death or major disability, defined by scores 3 to 6 on the modified Rankin Scale[9] at 90 days. Secondary outcomes were death and major disability (modified Rankin Scale score of 6 and 3–5, respectively), as well as serious adverse events and length of initial hospital stay.

Independent associations between various defined baseline characteristics and the presence of IVH at baseline were examined in a multivariable logistic regression model with all significant baseline characteristics as well as sex. Multivariable logistic regression models were also used to evaluate associations of baseline IVH volume, either as a continuous or categorical (thirds and fourths) variable, and clinical outcomes. These models included (1) initial adjustment for significant baseline univariates (including ICH volume, time to initial CT, randomized treatment, age, sex, China region, baseline systolic BP, location of ICH location [deep hemisphere versus other], history of heart disease, history of ischemic or undifferentiated stroke, and prior use of antithrombotic treatment [anticoagulation or antiplatelet agents]) and then with (2) further adjustment for significant differences in management variables >7 days postrandomization,[8] including the use of intubation (and ventilation), admission to an intensive care unit, prophylactic treatment for venous thromboembolism, use of any hemostatic therapy, any specific neurosurgical intervention, and a decision to withdraw active treatment/care. The predicted probabilities for outcomes were evaluated in univariate logistic regression models using IVH volume as a continuous variable. Collinearity and interaction between variables were checked. Data are presented with odds ratios (ORs) and 95% confidence intervals (CIs). Adjusted survival curves were used to assess survival in patients with and without IVH. A 2-sided P value <0.05 was set for statistical significance. All analyses were performed using SAS version 9.3 (SAS institute, Cary, NC).

Results

There were 2613 patients with ICH from the INTERACT2 trial with available CT data, of whom 740 (28%) had associated IVH at entry. Table 1 shows the characteristics of patients with and without IVH. In multivariable analysis, those with IVH were significantly older, more clinically severe (ie, higher National Institutes of Health Stroke Scale scores), having a slightly longer delay to initial (diagnostic) CT, higher heart rate, greater frequency of prior ischemic stroke, and larger volume of hematoma more often deeply located in the cerebral hemisphere.

As there was a strong correlation between China region and prophylactic treatment for venous thromboembolism (r=−0.74) among patients, the latter variable was excluded in further multivariable analysis. Four significant variable interactions were found which were also adjusted in the multivariable analysis: baseline hematoma volume and location, baseline hematoma volume and intubation, baseline hematoma volume and any neurosurgical intervention, and intubation and any neurosurgical intervention. Table 2 shows that IVH was significantly associated with poorer 90-day clinical outcomes: ORs were 1.68 (95% CI, 1.38–2.06; P<0.01), 1.76 (95% CI, 1.34–2.31; P<0.01), and 1.56 (95% CI, 1.26–1.93; P<0.01), for the outcomes of death or major disability, death, and major disability alone, respectively. Other serious adverse outcomes were more frequent in patients with IVH, including any serious adverse event, clinical reported neurological deterioration, and specific noncardiovascular serious adverse events. Despite the differential prognosis between patients with and without IVH, there was no difference in their length of initial hospital stay. There were, however, significant differences in aspects of their medical and surgical management in the 7-day postrandomization, as outlined in Table 3. In particular, patients with IVH received more intravenous BP-lowering treatment in the first 24 hours, any hemostatic therapy and ventricular drain insertion. Survival curves adjusted for imbalances in baseline characteristics show that the greatest probability of death from IVH occurred in the first 30 days after ICH onset and most apparent within the first several days (Figure I in the online-only Data Supplement). After adjustment for differences in management, the survival curves were no longer significant (Figure II in the online-only Data Supplement).

There was a strong and near continuous relationship between IVH volume and death (OR, 1.04; 95% CI, 1.02–1.06; P<0.01) as well as death or major disability (OR, 1.03; 95% CI, 1.01–1.05; P<0.01) at 90 days, in adjusted models according to increasing IVH volume (Figures 1 and 2). In Table 4 and the Table in the online-only Data Supplement, with baseline IVH volume divided into thirds and fourths categories, respectively, the threshold for significantly increased OR seemed lower for mortality (≈5 mL) than for the combined poor outcome of death or major disability (≈10 mL) with adjustment for baseline variables. The strength of these associations diminished after further adjustment for differences in management. There was no such trend in OR across similar categories of IVH volume and major disability alone.

Discussion

Our post hoc analysis of the INTERACT2 data set confirms that IVH denotes a worse outcome in patients with acute ICH. As well as showing a strong and near continuous relationship between IVH volume and the odds of death, and of death or major disability, logistic regression analysis identified volume of between 5 and 10 mL as being a statistically significant threshold for increased odds of poor clinical outcomes, whether defined by death or death and major disability, after

Table 1. Baseline Characteristics of Patients With and Without Intraventricular Hemorrhage

	All (n=2613)	ICH With IVH (n=740)	ICH Without IVH (n=1873)	*P* Value	Adjusted OR* (95% CI)	*P* Value
Age, median (IQR), y	63 (54–74)	66 (58–76)	62 (53–73)	<0.01	1.02 (1.01–1.03)	<0.01
Men	1631/2613 (62)	457/740 (62)	1174/1873 (63)	0.66	0.96 (0.80–1.16)	0.69
Chinese region	1737 (67)	467/740 (63)	1270/1873 (68)	0.02	1.01 (0.82–1.25)	0.90
GCS, median (IQR)	14 (13–15)	14 (12–15)	14 (13–15)	<0.01	…	…
Time to CT scan, h	1.8 (1.2–2.7)	1.8 (1.3–2.8)	1.8 (1.2–2.6)	0.05	1.10 (1.02–1.20)	0.02
NIHSS score, median (IQR)	11 (6–16)	13 (7–17)	10 (6–15)	<0.01	1.03 (1.02–1.05)	<0.01
Systolic BP, mean (SD), mm Hg	179 (17)	180 (17)	179 (17)	0.07	…	…
Diastolic BP, mean (SD), mm Hg	101 (115)	100 (14)	101 (15)	0.28	…	…
History of hypertension	1890/2611 (72)	550/739 (74)	1340/1872 (72)	0.14	…	…
Use of antihypertensive therapy	1174/2611 (45)	346/739 (47)	828/1872 (44)	0.23	…	…
History of heart disease	285/2613 (11)	105/740 (14)	180/1873 (10)	<0.01	1.21 (0.91–1.61)	0.19
Diabetes mellitus	286/2611 (11)	92/739 (13)	194/1872 (10)	0.12	…	…
Prior ICH	209/2611 (8)	61/739 (8)	148/1872 (8)	0.77	…	…
Prior ischemic or undifferentiated stroke	298/2613 (11)	125/740 (17)	173/1873 (9)	<0.01	2.04 (1.57–2.67)	<0.01
Prior warfarin anticoagulation	80/2611 (3)	32/739 (4)	48/1872 (3)	0.02	1.11 (0.67–1.81)	0.71
Prior aspirin or other antiplatelet agent	251/2613 (10)	87/740 (12)	164/1873 (9)	0.02	0.98 (0.72–1.35)	0.91
Deep location of hematoma†	2182/2613 (84)	645/740 (87)	1537/1873 (82)	<0.01	1.74 (1.34–2.28)	<0.01
Left hemisphere site of hematoma	1313/2613 (50)	366/740 (47)	947/1873 (51)	0.61	…	…
Hematoma volume, median (IQR), mL						
ICH	11.0 (5.8–19.5)	11.0 (6.7–21.3)	10.9 (5.3–18.8)	<0.01	1.01 (1.01–1.02)	<0.01
IVH	…	5.9 (2.1–13.8)	…	…	…	…
ICH+IVH	13.1 (6.5–23.8)	20.8 (11.5–37.0)	10.9 (5.3–18.8)	<0.01	…	…
Randomized treatment	1294/2613 (50)	371/740 (50)	923/1873 (49)	0.69	1.05 (0.88–1.25)	0.59

Data are n (%) unless otherwise stated. *P* values are based on χ^2, *t* test, or Wilcoxon rank-sum test. BP indicates blood pressure; CI, confidence intervals; CT, computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratios.

*Adjusted for all other variables.

†Deep location refers to location in the basal ganglia or thalamus.

adjustment for baseline imbalances. This volume of IVH seems meaningful for clinical decision making on prognosis and as a therapeutic target for residual IVH in those patients who have a ventricular drain inserted. When the model includes adjustment for ventricular drain and other management imbalances, more modest associations of IVH and these outcomes were evident.

Although the literature is consistent for IVH being a predictor of poor outcome in ICH,[10–15] there is uncertainty on the strength and pattern of association. One study suggests a curvilinear relationship between IVH volume and 30-day mortality, with 10 to 15 mL of IVH proposed as an appropriate threshold for predicting poor outcome in patients with comatose state (Glasgow Coma Scale scores <8),[5] whereas another study indicates IVH volumes >20 mL as being relevant for survival.[13] Our analyses indicate a near linear relationship between the amount of IVH and adverse outcomes in ICH, with a much lower volume threshold than previously considered for increased odds of death (≈5 mL) and the combined poor outcome of death or major disability (or dependency, ≈10 mL).

The pathophysiological mechanisms underlying the independent prognostic significance of IVH are relatively well understood. Obstructive hydrocephalus and meningeal irritation from blood and its breakdown products obstruct arachnoid granulations, which are key to draining cerebrospinal fluid into dural venous sinuses, although intracranial pressure may not necessarily be increased.[16] Ependymal inflammation and fibrosis also contribute to delayed clearance of cerebrospinal fluid, which may further contribute to tissue damage caused from the primary parenchymal ICH.[10,17] The weaker association of IVH with major disability is likely explained by residual disability in survivors being more strongly related to neuronal injury resulting from the underlying intraparenchymal hematoma. Furthermore, the weaker association of IVH and the primary outcome and mortality after adjustment for differences in management between randomized groups suggests potential beneficial effects of some interventions, in particular, the insertion of a ventricular drain.

Major strengths of this study are that it was undertaken on a large heterogeneous sample of patients recruited from a diverse range of hospitals and healthcare settings, who were assessed according to a standardized protocol and objective measures. This approach allowed adjustment for multiple confounding variables and provides some reassurance over both the reliability and the validity of the results.

Table 2. Clinical Outcomes Associated With Intraventricular Hemorrhage

	ICH With IVH (n=730)	ICH Without IVH (n=1852)	OR (95% CI)	*P* Value	AOR* (95% CI)	*P* Value
Day 90						
Death or major disability	481/730 (66)	912/1852 (49)	1.99 (1.67–2.38)	<0.01	1.68 (1.38–2.06)	<0.01
Death	143/730 (20)	170/1852 (9)	2.41 (1.89–3.07)	<0.01	1.76 (1.34–2.31)	<0.01
Major disability	338/587 (58)	742/1682 (44)	1.72 (1.42–2.08)	<0.01	1.56 (1.26–1.93)	<0.01
Days of hospitalization (median)	21 (11–39)	20 (12–33)	…	0.35	…	…
Serious adverse events						
Any†	382/730 (52)	591/1852 (32)	2.00 (1.70–2.36)	<0.01	…	…
Neurological deterioration‡						
Nonfatal	28/730(3.8)	27/1852(1.5)	…	…	…	…
Fatal	86/730(11.8)	87/1852(4.7)	…	…	…	…
Recurrent cardiovascular event‡						
Nonfatal	6/730 (1)	16/1852 (1)	…	…	…	…
Fatal	3/730 (0)	2/1852 (0)	…	…	…	…
Noncardiovascular event‡						
Nonfatal	75/730 (10)	138/1852 (8)	…	…	…	…
Renal failure	3/730 (3)	5/1852 (1)	…	…	…	…
Respiratory infections	25/730 (3)	26/1852 (1)	…	…	…	…
Sepsis	2/730 (0)	4/1852 (0)	…	…	…	…
Fatal	26/730 (4)	50/1852 (3)	…	…	…	…

Data are n (%) unless otherwise stated. AOR indicates adjusted odds ratio; CI, confidence intervals; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and OR, odds ratios.

*Adjusted for age, sex, China region, time to computed tomographic scan, baseline blood pressure, history of heart disease, history of ischemic stroke or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment, and interaction between baseline hematoma volume and location.

†Number of events.

‡Counts correspond to the number of subjects who experienced a specific serious adverse event at least once; 1 subject may be counted in >1 category.

Even so, we recognize several limitations, in particular that some patients such as those with large hematomas and who required early neurosurgery were excluded, leading to the influence of selection bias on a clinical trial population. However, this is likely to have led to an underestimation rather than overestimation of the prognostic significance of IVH. Another issue is that although our results are based on prospectively collected data, this is a retrospective study and thus prone to random error and incomplete adjustment for potential confounding including decisions on the

Table 3. Treatment of Patients With and Without Intraventricular Hemorrhage

Parameter	ICH Without IVH (n=1873)	ICH With IVH (n=740)	*P* Value
Time from ICH to start of treatment, median (IQR), h	4.0 (2.9–5.3)	4.3 (3.0–5.5)	0.03
Any intravenous BP-lowering treatment	1195/1873 (64)	541/740 (73)	<0.01
Use of a single intravenous BP-lowering agent	823/1873 (44)	351/740 (47)	0.11
Intubation	96/1852 (5)	83/718 (12)	<0.01
Admission to an intensive care unit	659/1852 (36)	315/718 (44)	<0.01
Prophylactic treatment for deep venous thrombosis	405/1852 (22)	185/718 (26)	0.04
Compression stockings used	182/1852 (10)	99/718 (14)	<0.01
Subcutaneous heparin administered	337/1852 (18)	142/718 (20)	0.36
Use of intravenous mannitol	1117/1852 (60)	438/718 (61)	0.75
Hemostatic therapy*	55/1852 (3)	33/718 (5)	0.04
Any surgical intervention	86/1852 (5)	58/718 (8)	<0.01
Evacuation or decompression of the hematoma	60/1852 (3)	17/718 (2)	0.24
Insertion of a ventricular drain	32/1852 (2)	47/718 (7)	<0.01
Decision to withdraw active treatment and care	54/1852 (3)	58/718 (8)	<0.01

Data are n (%) unless otherwise stated. BP indicates blood pressure; ICH, intracerebral hemorrhage; IQR, interquartile range; and IVH, intraventricular hemorrhage.

*Includes the use of fresh frozen plasma, vitamin K, and recombinant tissue factor VIIa.

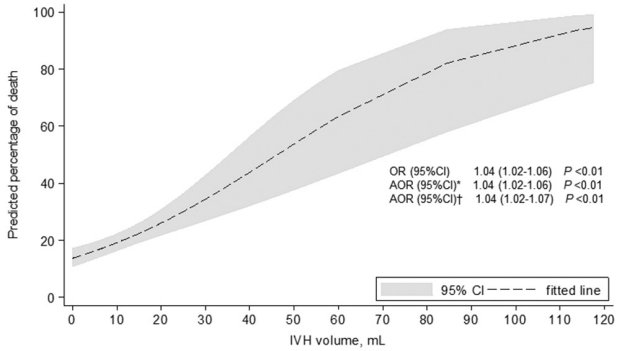

Figure 1. Predicted probabilities for death by baseline intraventricular volume. *Adjusted factors are age, sex, China region, time to computed tomographic scan, baseline blood pressure, history of heart disease, history of ischemic stroke or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment. †Additional adjustment for all baseline characteristics in model 1 together with the use of intubation, intensive care unit admission, any hemostatic therapy, any surgical intervention, decision to withdraw active treatment and care, and interactions of baseline hematoma volume and location, baseline hematoma volume and intubation, baseline hematoma volume and any neurosurgical intervention, and intubation and any neurosurgical intervention. AOR indicates adjusted odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; and OR, odds ratio.

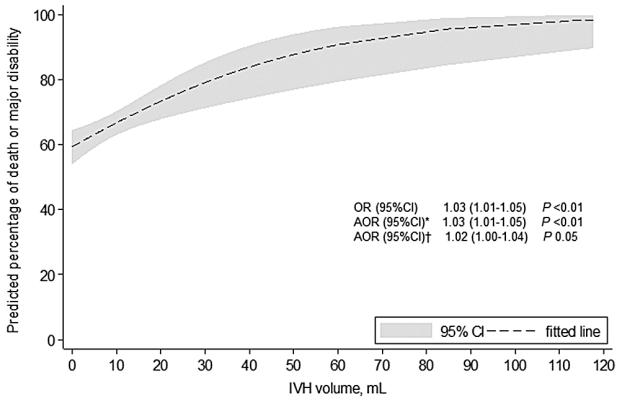

Figure 2. Predicted probabilities for death or major disability by baseline intraventricular volume. *Adjusted factors are age, sex, China region, time to computed tomographic scan, baseline blood pressure, history of heart disease, history of ischemic stroke or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment, and baseline hematoma volume and location. †Additional adjustment for all baseline characteristics in model 1 together with the use of intubation, intensive care unit admission, any hemostatic therapy, any surgical intervention, and decision to withdraw active treatment and care. AOR indicates adjusted odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; and OR, odds ratio.

management of patients. Finally, as two thirds of participants were from China, differences in the patterns of ICH and background care from other regions may raise concerns over the robustness of these results.

In summary, this study reaffirms the importance of IVH as a major independent prognostic factor in patients with acute spontaneous ICH, in particular for predicting early mortality. Our approach defined not only a strong near linear association between IVH volume and poor outcome but also a statistically significant, and potentially clinically important, categorical threshold of 5 to 10 mL. This threshold may be useful for informing clinical-decision pathways and to indicate the need to consider early neurosurgical intervention, for example, external ventricular drainage. The results of ongoing studies such as the Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) trial[18] are eagerly awaited to provide a basis for further validation of these results and advance the treatment of IVH.

Table 4. Relationship of Baseline Intraventricular Hemorrhage Volume and Outcome

Outcome/IVH Volume	n (%)	OR (95% CI)	*P* Trend	AOR (95% CI)*	*P* Trend	AOR (95% CI)†	*P* Trend
Death or major disability	…	…	<0.01	…	0.03	…	0.16
0–2.99	144 (59)	1.0	…	1.0	…	1.0	…
3.01–10.14	159 (65)	1.29 (0.89–1.86)	…	1.32 (0.86–2.02)	…	1.24 (0.80–1.93)	…
10.15–117.55	178 (73)	1.88 (1.28–2.76)	…	1.62 (1.04–2.53)	…	1.40 (0.88–2.23)	…
Death		…	<0.01	…	<0.01	…	0.02
0–2.99	31 (13)	1.0	…	1.0	…	1.0	…
3.01–10.14	49 (20)	1.72 (1.05–2.81)	…	1.84 (1.06–3.22)	…	1.62 (0.83–3.17)	…
10.15–117.55	63 (26)	2.39 (1.49–3.84)	…	2.46 (1.44–4.22)	…	2.13 (1.10–4.10)	…
Major disability	…	…	0.04	…	0.07	…	0.21
0–2.99	113 (53)	1.0	…	1.0	…	1.0	…
3.01–10.14	110 (56)	1.13 (0.77–1.68)	…	1.22 (0.79–1.91)	…	1.23 (0.78–1.94)	…
10.15–117.55	115 (64)	1.55 (1.03–2.33)	…	1.52 (0.96–2.42)	…	1.35 (0.84–2.18)	…

Data are n (%) unless otherwise stated.

AOR indicates adjusted odds ratio; CI, confidence intervals; IVH, intraventricular hemorrhage; and OR, odds ratio.

*Adjusted factors are age, sex, China region, time to computed tomographic scan, baseline blood pressure, history of heart disease, history of ischemic stroke or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment, and interaction between baseline hematoma volume and location.

†Additional adjustment for all baseline characteristics in model 1 together with and significant management variables including the use of intubation, admission to an intensive care unit, use of any hemostatic therapy, any neurosurgical intervention, a decision to withdraw active treatment and care and interactions of baseline hematoma volume and location, baseline hematoma volume and intubation, baseline hematoma volume and any neurosurgical intervention, and intubation and any neurosurgical intervention.

Sources of Funding

The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial study was supported by Program (571281) and Project (512402 and 1004170) grants from the National Health and Medical Research Council of Australia. The study was designed, conducted, analyzed, and interpreted by the investigators independent of sponsors.

Disclosures

Dr Anderson reports membership of Advisory Boards for Pfizer and The Medicines Company, and receiving travel reimbursement and honorarium from Takeda China and Covidien. The other authors report no conflicts.

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Stroke
Journal of the American Heart Association

Significance of Intraventricular Hemorrhage in Acute Intracerebral Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Results

Edward Chan, Craig S. Anderson, Xia Wang, Hisatomi Arima, Anubhav Saxena, Tom J. Moullaali, Emma Heeley, Candice Delcourt, Guojun Wu, Jinchao Wang, Guofang Chen, Pablo M. Lavados, Christian Stapf, Thompson Robinson, John Chalmers and Yining Huang
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Stroke. 2015;46:653-658; originally published online February 12, 2015;
doi: 10.1161/STROKEAHA.114.008470
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Supplemental Material: Table and Figures I and I

Significance of intraventricular hemorrhage in acute intracerebral hemorrhage: INTERACT2 results

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Supplemental Table. Baseline intraventricular hemorrhage volume (fourths) and outcome (N=730)

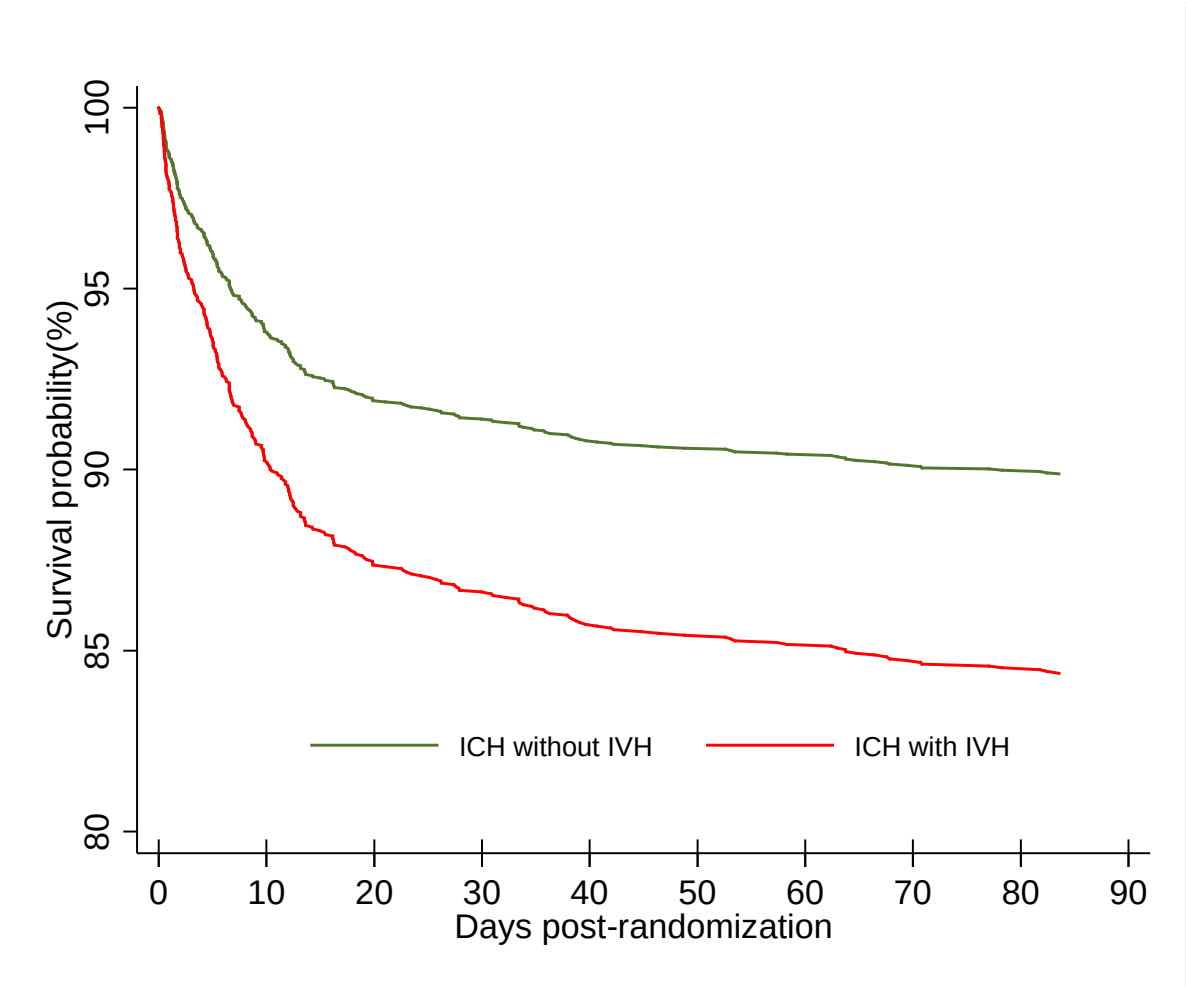
Outcome/IVH volume	n (%)	OR (95% CI)	*P* trend	AOR (95% CI)*	*P* trend	AOR (95% CI)[†]	*P* trend
Death or major disability							
0-2.07	114 (63)	1.0	<0.01	1.0	0.03	1.0	0.17
2.08-5.84	101 (55)	0.74 (0.48-1.12)		0.71 (0.43-1.14)		0.64 (0.39-1.06)	
5.97-13.84	129 (72)	1.50 (0.97-2.33)		1.41 (0.85-2.34)		1.24 (0.74-2.09)	
13.86-117.55	137 (74)	1.71 (1.10-2.68)		1.44 (0.85-2.44)		1.21 (0.70-2.08)	
Death							
0-2.07	23 (13)	1.0	<0.01	1.0	<0.01	1.0	<0.01
2.08-5.84	25 (14)	1.09 (0.60-2.01)		1.09 (0.55-2.19)		1.04 (0.46-2.37)	
5.97-13.84	43 (24)	2.12 (1.22-3.70)		2.46 (1.31-4.62)		1.86 (0.86-4.03)	
13.86-117.55	52 (29)	2.77 (1.61-4.76)		3.11 (1.67-5.81)		3.00 (1.41-6.38)	
Major disability							
0-2.07	91 (57)	1.0	0.07	1.0	0.11	1.0	0.28
2.08-5.84	76 (48)	0.69 (0.45-1.08)		0.70 (0.42-1.15)		0.65 (0.39-1.09)	
5.97-13.84	88 (63)	1.27 (0.79-2.01)		1.29 (0.76-2.19)		1.20 (0.70-2.06)	
13.86-117.55	83 (64)	1.32 (0.82-2.12)		1.30 (0.75-2.25)		1.13 (0.64-1.99)	

IVH denotes intraventricular hemorrhage; ICH, intracerebral hemorrhage; OR, odds ratio; AOR, adjusted odds ratio; and CI, confidence intervals.

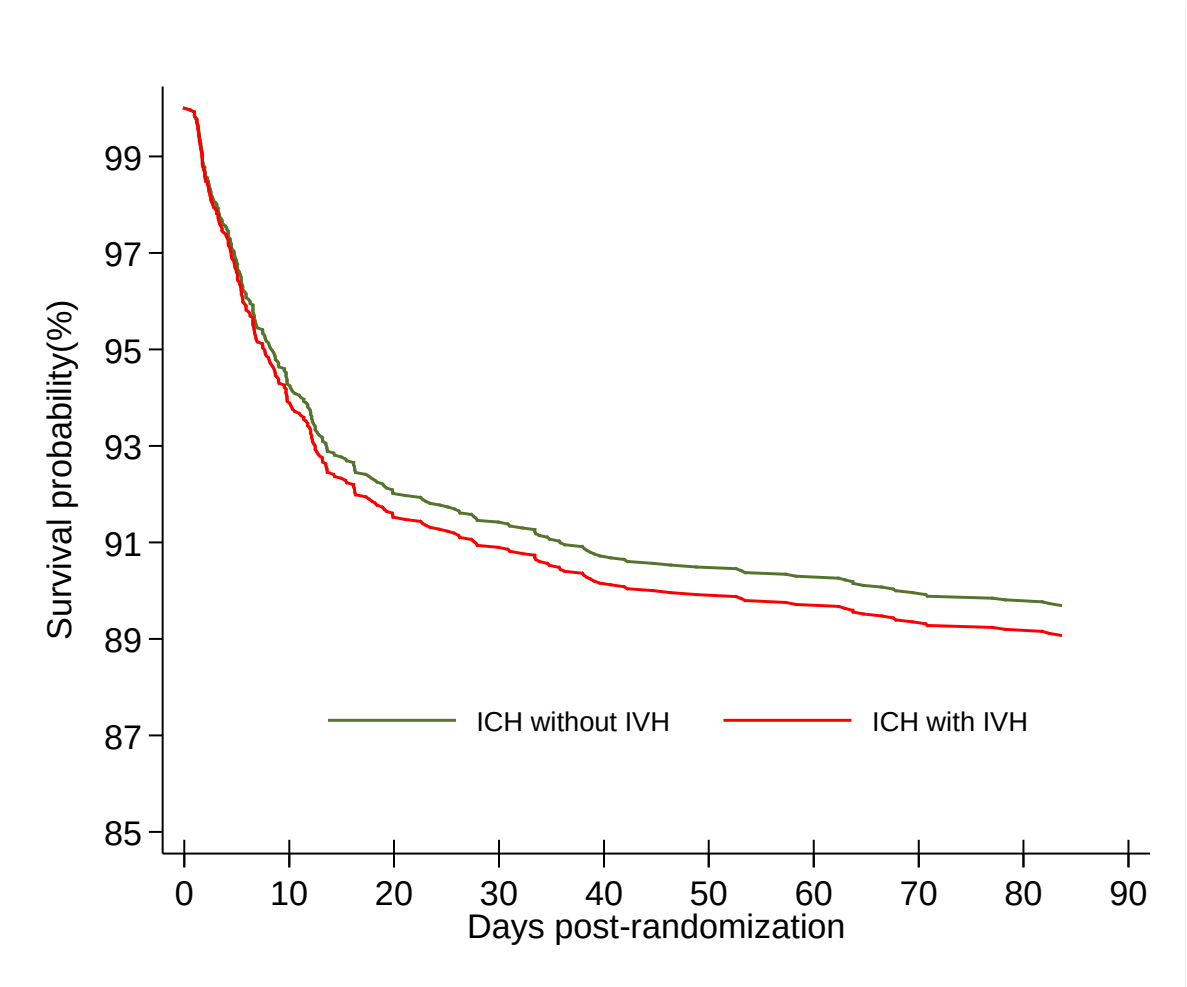
*Adjusted factors are: age, sex, China region, time to CT scan, baseline blood pressure, history of heart disease, history of ischemic or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment, and interaction between baseline hematoma volume and location.

[†]Additional adjustment for all baseline characteristics in model 1 together with significant management variables including use of intubation, admission to an intensive care unit, use of any hemostatic therapy, any neurosurgical intervention, a decision to withdraw active treatment and care, and 4 interactions: baseline hematoma volume and location; baseline hematoma volume and intubation; baseline hematoma volume and any neurosurgical intervention; intubation and any neurosurgical intervention.

Supplemental Figure I. Adjusted survival curves by baseline characteristics



Supplemental Figure II. Adjusted survival curves by baseline characteristics and management factors



Abstract

急性脳内出血における脳室内出血の重要性

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage 試験の結果

Significance of Intraventricular Hemorrhage in Acute Intracerebral Hemorrhage

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Results

Edward Chan, BSc (Adv)[1,2]; Craig S. Anderson, MD, PhD[1,2]; Xia Wang, MMed[1,2], et al.

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背景および目的：特発性脳内出血に伴う脳室内出血（IVH）は予後不良を示唆するが，その関連性パターンについては不明なところがある。本研究では，Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial（INTERACT2）のデータセットにおいて，IVH のリスクと転帰の関連性について究明した。

方法：INTERACT2 は，収縮期血圧上昇を呈した脳内出血（< 6 時間）患者 2,839 例を集中血圧管理群（目標収縮期血圧 < 140 mmHg），またはガイドラインに基づいた血圧管理群（目標収縮期血圧 < 180 mmHg）に無作為に割り付けた国際前向き非盲検エンドポイント無作為化対照試験である。線形回帰モデルおよびロジスティック回帰モデルを用いて，2,613 例中 740 例（28%）におけるベースライン時の IVH と 90 日時点の転帰不良（死亡および修正 Rankin スケール 3-6 で定義された重度の障害）の関連性を評価した。

結果：ベースライン時のその他の変数で補正したところ，IVH を伴う患者は著しく高齢で，より重度の神経学的障害があり，虚血性脳卒中の病歴を有する頻度が高く，登録時の診察で大脳半球深部に大きな血腫を有する頻度が高かった。死亡または重度障害は IVH を伴う患者の 66% で発生したが，脳内出血のみの患者では 49% であった（補正オッズ比 = 1.68, 95% 信頼区間（CI）:1.38 ～ 2.06, $P < 0.01$）。IVH 容積と臨床転帰の関連性は強く，ほぼ一貫していた。IVH 容積の 3 分の 1 を用いた補正後の解析では，オッズが有意に上昇する閾値として，死亡については約 5 mL，死亡または重度障害については約10 mL であることが示された。

結論：脳内出血患者において IVH 容積と転帰不良の間には強い関連性がみられた。IVH を伴う脳内出血患者の予後に関わる意思決定に関して，IVH 容積 5 mL ～ 10 mL が有意な閾値として示された。

臨床試験登録情報：URL: http://www.clinicaltrials.gov。固有の識別番号：NCT00716079。

Stroke 2015; 46: 653-658. DOI: 10.1161/STROKEAHA.114.008470.

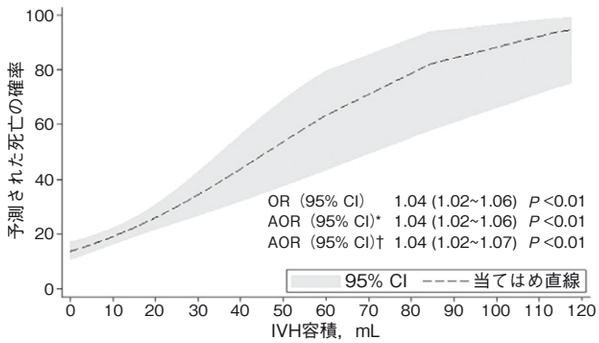

図 1 ベースライン時の脳室内出血容積により予測した死亡の確率。* 年齢，性別，中国内の地域，CT 施行までの時間，ベースライン時の血圧，心疾患の病歴，虚血性脳卒中または識別不能の脳卒中の病歴，ワルファリン／アスピリンの使用歴，ベースライン時の血腫容積および発生部位，割付けられた治療によって補正した。† さらに，モデル 1 のすべてのベースライン時の特性とともに，挿管の使用，集中治療室の滞在，止血治療，外科的介入，積極的治療およびケアからの撤退の決定，ベースライン時の血腫容積と発生部位との相互関係，ベースライン時の血腫容積と挿管の相互関係，ベースライン時の血腫容積と脳外科的治療の相互関係，および挿管と脳外科的治療の相互関係で補正した。AOR：補正オッズ比，CI：信頼区間，IVH：脳室内出血，OR：オッズ比。

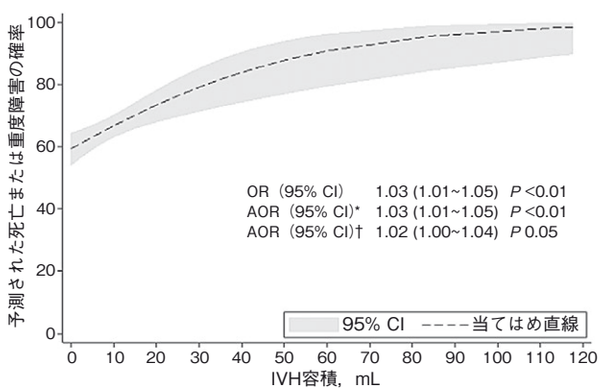

図 2 ベースライン時の脳室内出血容積により予測した死亡または重度障害の確率。* 年齢，性別，中国内の地域，CT 施行までの時間，ベースライン時の血圧，心疾患の病歴，虚血性脳卒中または識別不能の脳卒中の病歴，ワルファリン／アスピリンの使用歴，ベースライン時の血腫容積および発生部位，割付けられた治療，ベースライン時の血腫容積および発生部位によって補正した。† さらに，モデル 1 のすべてのベースライン時の特性とともに，挿管の使用，集中治療室の滞在，止血治療，外科的治療，積極的治療およびケアからの撤退の決定で補正した。AOR：補正オッズ比，CI：信頼区間，IVH：脳室内出血，OR：オッズ比。