

Rapid blood-pressure lowering in patients
with acute intracerebral hemorrhage

急性期脳内出血患者に対する急速降圧治療

N Engl J Med. 2013 Jun 20;368(25):2355-65. doi: 10.

Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J; INTERACT2 Investigators.

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

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

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

N Engl J Med 2013;368:2355-65.

DOI: 10.1056/NEJMoa1214609

Copyright © 2013 Massachusetts Medical Society.

【方法】

2008年10月～2012年8月にかけて、特発性脳出血患者のうち、発症後6時間以内に収縮期血圧が上昇していた2839例を無作為に割り付け

①積極的に降圧した群（1時間以内に収縮期血圧140mmHg未満を目標）→1403例

②ガイドラインで推奨されている治療群（収縮期血圧180mmHg未満を目標）→1436例

<降圧剤の選択は現場医師の裁量による>

*主要転帰：死亡、重症の障害(90日目)

*EQ-5D(Euro Quality of life 5-Dimension)

健康水準の変化を数値化した評価尺度

①移動の程度, ②身の回りの管理, ③普段の活動,

④痛み/不快感, ⑤不安/ふさぎ込みの5項目

→1～3点で評価

・modified Rankin score

modified Rankin Scale	
0	まったく症状がない
1	症状はあっても明らかな障害はない： 日常の動機や活動は行える
2	軽度の障害： 発症以前の活動がすべて行えるわけではないが、自分の身の回りのことは介助なしに行える
3	中程度の障害： 何らかの介助を必要とするが、歩行は介助なしに行える
4	中程度から重度の障害： 歩行や身体的要求には介助が必要である
5	重度の障害： 寝たきり、失禁状態、常に介護と見守りを必要とする
6	死亡

*入院期間、介護施設入所(90日目)、重篤な有害事象の発生

【結果】

主要転帰を判定できた2794例

*主要イベントが発生した割合

①積極的治療群：1382例中719例(52.0%)

②ガイドラインで推奨されている治療群：1412例中785例(55.6%)

P=0.06

*modified Rankin score

①積極的治療群

②ガイドラインで推奨されている治療群

P=0.04→積極的治療群のほうが有意に低下

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

Table 3. (Continued.)

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

* Plus-minus values are means \pm SD. All odds ratios are unadjusted.

† The modified Rankin scale evaluates global disability and functioning; scores range from 0 (no symptoms) to 6 (death); the primary outcome of death or major disability was assessed as a score on the modified Rankin scale of 3 to 6 at 90 days.

‡ The difference between the groups in scores across all seven levels of the modified Rankin scale was determined with the use of a logistic-regression analysis of the ordinal data.

§ Possible responses in each domain were "no problems," "moderate problems," or "extreme problems"; for these analyses, the latter two levels were combined as "any problems." The overall health utility score was calculated with the use of population norms from the United Kingdom.

¶ Neurologic deterioration was defined as an increase from baseline to 24 hours of 4 or more points on the National Institutes of Health Stroke Scale or a decline of 2 or more points on the Glasgow Coma Scale.

‡ Nonfatal serious adverse events included those that were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, or resulted in disability or a medical or surgical intervention; a patient could have more than one event.

** This category includes clinician-reported neurologic deterioration in a patient with cerebral mass effect or extension of the hematoma.

†† Severe hypotension was defined as hypotension with clinical consequences (including acute renal failure) that required corrective therapy with intravenous fluids, vasopressors, or hemodialysis.

* EQ-5D : 多くの項目で積極的治療群のほうが有意に改善

* 死亡率や重篤な有害事象→有意差なし

【結論】

・脳内出血患者に対し、積極的な降圧治療を行っても、死亡や重篤な障害の発生率に有意な低下はなかった。

・modified Rankin score の解析では、積極的な降圧治療により機能的転帰の改善が示唆された。