Table 1 Clinical characteristics of patients with different early outcomes

mRS at 3 weeks	mRS ≤1 ($n=66$)	mRS ≥2 ($n=178$)	*P* value
Baseline characteristics			
Age (year)	60.8 ± 10.6	66.0 ± 12.6	0.003
Male gender	41 (62%)	99 (56%)	0.362
Alcohol consumption (>2 drinks/day)	16 (24%)	23 (13%)	0.032
Physiological and clinical status on admission			
SBP_i (mmHg)	194.0 ± 19.0	204.1 ± 23.2	0.002
DBP_i (mmHg)	104.0 ± 18.4	105.1 ± 14.9	0.646
Blood glucose (mg/dl)	128.3 ± 49.6	154.6 ± 65.7	0.003
Activated partial thromboplastin time (s)	30.5 ± 4.3	29.2 ± 3.8	0.021
Onset-to-arrival time (h)	5.9 ± 5.9	2.8 ± 3.6	<0.001
NIHSS score, median (range)	4 (0–17)	14 (1–36)	<0.001
Hematoma volume (ml)	6.0 ± 6.3	19.9 ± 24.4	<0.001
Mortality at 3 weeks	**Dead ($n=12$)**	**Survived ($n=232$)**	***P* value**
Age (year)	64.2 ± 13.8	64.6 ± 12.2	0.907
Male gender	8 (67%)	132 (57%)	0.505
Symptomatic ischemic stroke	6 (50%)	29 (13%)	<0.001
Antithrombotic therapy	5 (42%)	32 (14%)	0.009
SBP_i (mmHg)	225.3 ± 29.3	200.1 ± 21.5	<0.001
DBP_i (mmHg)	113.7 ± 18.5	104.3 ± 15.6	0.047
Blood glucose (mg/dl)	246.7 ± 134.5	142.3 ± 52.3	<0.001
NIHSS score, median (range)	28 (9–36)	11 (1–36)	<0.001
Hematoma volume (ml)	59.6 ± 53.9	13.9 ± 16.4	<0.001
Deep ganglionic hematoma	5 (42%)	183 (79%)	0.011
Hematoma enlargement within 24 h	**Present ($n=32$)**	**Absent ($n=204$)**	***P* value**
Age (year)	68.6 ± 14.2	64.0 ± 12.0	0.049
Male gender	17 (53%)	118 (58%)	0.616
Heart disease	9 (28%)	26 (13%)	0.023
SBP_i (mmHg)	203.8 ± 22.7	199.7 ± 21.3	0.318
DBP_i (mmHg)	104.9 ± 17.4	104.3 ± 15.6	0.852
NIHSS score, median (range)	14 (3–36)	10 (0–31)	<0.001
Hematoma volume (ml)	21.8 ± 28.8	13.8 ± 16.8	0.028

Age, gender, SBP_i, DBP_i, and clinical characteristics that were statistically significantly different among the groups ($P<0.05$) are listed. Hypertension, diabetes mellitus, hypercholesterolemia, hypocholesterolemia, smoking habit, symptomatic hemorrhagic stroke, and liver disease were not significantly different for any of the three outcomes. DBP, diastolic blood pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

hazards model, multivariate-adjusted odds ratio (OR) and 95% confidence interval (CI) compared with the quartile with the most modest BP lowering in each item were calculated after adjustment for age, gender, blood glucose, onset-to-arrival time, NIHSS score, and hematoma volume; they were known predictors for ICH outcome and showed the significant association with an mRS score of 1 or less in the present study (Table 1). Finally, the clinical characteristics were compared among the patients in the quartiles using one-way factorial analysis of variance, the chi-squared test, and the Kruskal–Wallis test, as appropriate. Continuous values are expressed as mean ± SD. *P* value less than 0.05 was considered statistically significant.

Results

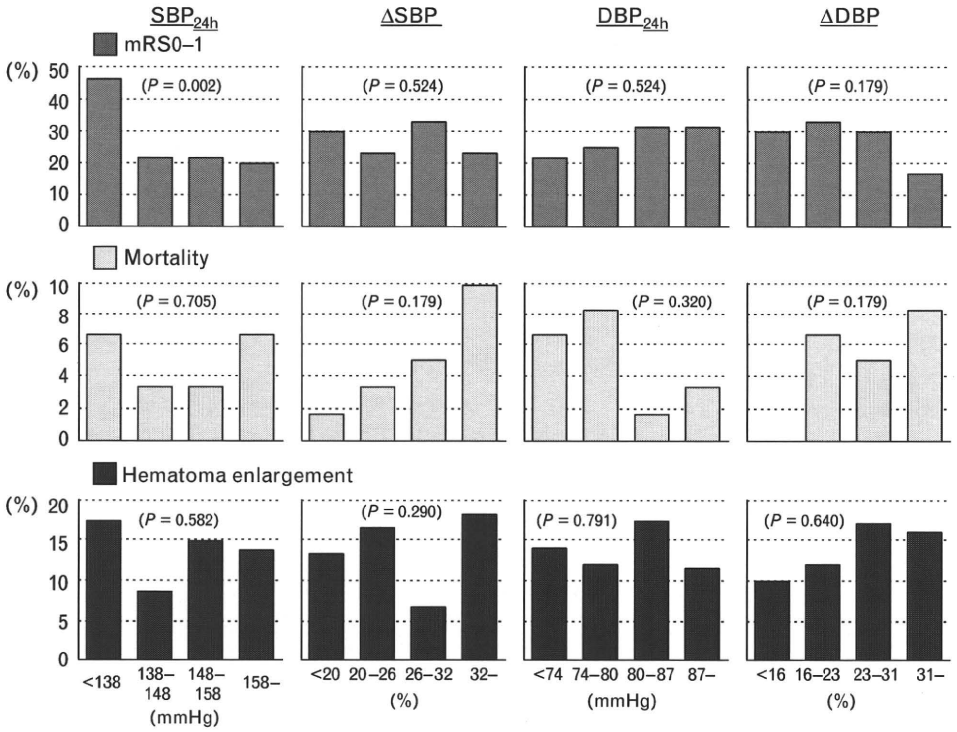
Overall, 244 patients (140 men, 65 ± 12 years old) were assessed; 229 (94%) had SBP_i at least 180 mmHg, 123 (50%) had DBP_i at least 105 mmHg, and 168 (69%) had MBP_i at least 130 mmHg. The median SBP_{24h} was 148 mmHg (interquartile range 138–158 mmHg), median ΔSBP was 26%, (20–32%), median DBP_{24h} was 80 mmHg (74–87 mmHg), and median ΔDBP was 23% (16–31%).

At 3 weeks, 66 patients (27%) had independent ADL (an mRS score of ≤1). Compared with patients with an mRS score of at least 2, these patients were younger, more frequently consumed alcohol, and had a lower SBP_i, a lower blood glucose level, a longer APTT, a lower NIHSS score, a longer onset-to-arrival time, and a smaller hematoma volume (Table 1). A higher proportion of patients with SBP_{24h} less than 138 mmHg had an mRS score of at least 1 (46%) than patients in the other three quartiles (top graphs of Fig. 1).

At 3 weeks, 12 patients (5%) had died. Compared with survivors, the patients who had died more frequently had a history of ischemic stroke, a higher rate of antithrombotic use, a higher SBP_i, a higher DBP_i, a higher blood glucose level, a higher NIHSS score, a larger hematoma volume, and a lower rate of deep ganglionic hematoma (Table 1). SBP_{24h}, ΔSBP, DBP_{24h}, and ΔDBP were not significantly associated with a fatal outcome, although the mortality rate had a nonsignificant tendency to increase as SBP reduction increased (middle graphs of Fig. 1).

Early hematoma enlargement was present in 32 of 236 patients (14%) who had a follow-up CT at approximately

Fig. 1



The relationship between primary and secondary outcomes and blood pressure in the initial 24 h. SBP_{24h}: the mean of the three SBP values at 6, 12, and 24 h; ΔSBP: $100 - SBP_{24h} \times 100/SBP_i$; DBP_{24h}: the mean of the three DBP values at 6, 12, and 24 h; ΔDBP: $100 - DBP_{24h} \times 100/DBP_i$. DBP, diastolic blood pressure; mRS, modified Rankin Scale; SBP, systolic blood pressure.

24 h. Compared with patients without enlargement, patients with early hematoma enlargement were older, and more frequently had heart disease, a higher NIHSS score, and a larger hematoma volume on CT (Table 1). Onset-to-arrival time was not associated with hematoma enlargement. SBP_{24h}, ΔSBP, DBP_{24h}, and ΔDBP were not significantly associated with hematoma enlargement (bottom graphs of Fig. 1).

Compared with patients with SBP_{24h} at least 158 mmHg, patients with SBP_{24h} less than 138 mmHg more frequently had an independent ADL at 3 weeks after adjustment for age and gender (OR 4.46, 95% CI 1.89–10.53) and for age, gender, blood glucose, onset-to-arrival time, NIHSS score, and hematoma volume (OR 4.36, 95% CI 1.10–17.22, Table 2). However, the frequency of independent ADL did not differ between the other two SBP_{24h} quartiles (148–158 mmHg, 138–148 mmHg) and the SBP_{24h} at least 158 mmHg quartile. After multivariate adjustment, the frequency of independent ADL did not differ among the patient quartiles based on ΔSBP, DBP_{24h}, or ΔDBP. After multivariate adjustment, the frequency of a fatal outcome or early hematoma enlargement did not differ

Table 2 Odds ratios for independent activity of daily living at 3 weeks (corresponding to mRS score ≤ 1)

	Age and gender adjusted			Multivariate adjusted*		
	OR	95% CI	*P* value	OR	95% CI	*P* value
SBP_{24h} (mmHg)						
158–	1.00	(Reference)		1.00	(Reference)	
148–158	1.26	0.51–3.12	0.618	1.72	0.45–6.62	0.433
138–148	1.26	0.51–3.14	0.614	1.34	0.33–5.48	0.680
<138	4.46	1.89–10.53	<0.001	4.36	1.10–17.22	0.036
ΔSBP (%)						
<20	1.00	(Reference)		1.00	(Reference)	
20–26	0.73	0.32–1.68	0.462	0.82	0.23–2.97	0.766
26–32	1.19	0.55–2.62	0.658	1.31	0.37–4.67	0.679
32–	0.73	0.32–1.67	0.453	1.04	0.28–3.86	0.952
DBP_{24h} (mmHg)						
87–	1.00	(Reference)		1.00	(Reference)	
80–87	1.13	0.51–2.48	0.766	3.16	0.92–10.94	0.069
74–80	0.89	0.39–2.03	0.779	1.65	0.47–5.79	0.437
<74	0.84	0.35–2.01	0.697	2.84	0.70–11.44	0.143
ΔDBP (%)						
<16	1.00	(Reference)		1.00	(Reference)	
16–23	1.11	0.50–2.42	0.803	1.13	0.34–3.76	0.848
23–31	0.97	0.44–2.15	0.935	1.96	0.57–6.74	0.285
31–	0.42	0.17–1.04	0.060	1.43	0.35–5.88	0.618

SBP_{24h}: the mean of the three SBP values at 6, 12, and 24 h; ΔSBP: $100 - SBP_{24h} \times 100/SBP_i$; DBP_{24h}: the mean of the three DBP values at 6, 12, and 24 h; ΔDBP: $100 - DBP_{24h} \times 100/DBP_i$. CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure. *Adjusted for age, gender, blood glucose, onset-to-arrival time, NIHSS score, and hematoma volume.

among the patient quartiles based on SBP_{24h}, ΔSBP, DBP_{24h}, or ΔDBP.

Discussion

The association that hyperacute BP lowering has to the early clinical outcome of ICH patients was assessed in this study. The present study's major finding was that, in ICH patients having an initial BP at least 180/105 mmHg, lowering SBP to less than 138 mmHg during the initial 24 h of hospitalization was related to independent ADL (corresponding to an mRS score $\leq$1) at 3 weeks after multivariate adjustment including the known determinants of patient outcomes such as the advanced age, the initial hematoma volume, and the initial severity of neurological deficits.

Hematoma growth is a predictor of mortality and poor functional outcome in acute ICH patients [20], and many [6,14,21], but not all [22,23], studies have reported that it is associated with high BP on admission. This association may be due to the enhancement of ongoing bleeding and rebleeding from ruptured small arteries and arterioles caused by high BP. However, after adjustment for time after onset, no relationship between admission BP and hematoma growth has been found [14,21]. This suggests that both the BP and the risk of hematoma growth are highest soon after ICH onset [2]. Growth of perihematomal edema also affects functional outcome [24]. Thus, appropriate control of hyperacute BP may prevent growth of hematoma and edema and improve patient outcome.

On the contrary, there is a concern that lowering BP reduces global cerebral blood flow (CBF) and exacerbates perihematomal ischemia. Most ICH patients have chronic hypertension, which increases the lower limit of CBF autoregulation. A rapid BP decline within 24 h after ICH was reported to be associated with increased mortality [25]. Thus, aggressive hyperacute BP lowering may worsen brain injury, particularly in patients with increased intracranial pressure. However, a small randomized study using positron emission tomography showed that i.v. antihypertensive therapy that reduced MBP by 15% did not alter global or perihematomal CBF [26]. On the basis of these findings, BP lowering appears to be more beneficial than harmful for hyperacute ICH patients.

The present results indicate that acute SBP lowering to less than 138 mmHg was statistically associated with independent ADL at 3 weeks. The result could be used to explain the SBP goal (<140 mmHg) that is being used in INTERACT [12] and ATACH [13]. However, on the basis of the present study design, it is difficult to conclude whether strict SBP lowering directly causes a good functional outcome or whether patients who are expected to have a good outcome tend to respond well to the antihypertensive therapy. The BP goal identified in the present study was relatively low compared with the BP goals identified in previous studies. Ohwaki *et al.* [10] assessed 76 patients and reported that an SBP target of 150 mmHg or less was less significantly associated with hematoma growth than that of an SBP at least 160 mmHg. Qureshi *et al.* [11] gave i.v. antihypertensive medication to 27 patients to maintain their BP less than 160/100 mmHg; most of the patients did not develop neurological deterioration or hematoma growth.

In the present study, the percentage reduction of the SBP was not found to be a good indicator for functional outcome, presumably because the patient group with the greatest SBP reduction included both patients in whom strict BP lowering was successful and was associated with a good outcome, and patients who had a very high admission SBP, which was associated with a poor outcome. Similarly, DBP was not a good indicator of outcome.

Limitations of the present study include: the study was not a randomized controlled study, and the antihypertensive agent doses were chosen by each physician; BP values after the initial 24 h were not assessed; chronic outcome at 3 months was not assessed; and the rates of hematoma enlargement and mortality in our population were too low to assess these outcomes appropriately.

As the incidence of ICH is known to be higher in Japan and many Asian countries than in Western countries [27–30], a different BP lowering goal from that in Western guidelines may be necessary in Asian countries. Appropriate BP management should be an established part of the medical therapy given to acute ICH patients.

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References

1 Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001; **344**:1450–1460.

2 Bath P, Chalmers J, Powers W, Beilin L, Davis S, Lenfant C, *et al.* International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. *J Hypertens* 2003; **21**:665–672.

3 Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004; **43**:18–24.

4 Carlberg B, Asplund K, Hagg E. The prognostic value of admission blood pressure in patients with acute stroke. *Stroke* 1993; **24**:1372–1375.

5 Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC. Relation between blood pressure and outcome in intracerebral hemorrhage. *Stroke* 1995; **26**:21–24.

6 Terayama Y, Tanahashi N, Fukuuchi Y, Gotoh F. Prognostic value of admission blood pressure in patients with intracerebral hemorrhage: Keio Cooperative Stroke Study. *Stroke* 1997; **28**:1185–1188.
7 Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J, Stroke Project, Cerebrovascular Disease Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology* 2004; **63**:461–467.
8 Broderick JP, Adams HP, Barsan W, Feinberg W, Feldmann E, Grotta J, *et al.* Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke* 1999; **30**:905–915.
9 Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, *et al.* Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/ American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007; **38**:2001–2023.
10 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004; **35**:1364–1367.
11 Qureshi AI, Mohammad YM, Yahia AM, Suarez JI, Siddiqui AM, Kirimani JF, *et al.* A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. *J Intensive Care Med* 2005; **20**:34–42.
12 Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, *et al.* Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008; **7**:391–399.
13 Qureshi AI. Antihypertensive treatment of acute cerebral hemorrhage (ATACH): rationale and design. *Neurocrit Care* 2007; **6**:56–66.
14 Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: incidence and time course. *Stroke* 1996; **27**:1783–1787.
15 Qureshi AI, Harris-Lane P, Kirmani JF, Ahmed S, Jacob M, Zada Y, Divani AA. Treatment of acute hypertension in patients with intracerebral hemorrhage using American Heart Association guidelines. *Crit Care Med* 2006; **34**:1975–1980.
16 Kothari RU, Brott TG, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996; **27**:1304–1305.
17 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke* 1997; **28**:2370–2375.
18 Toyoda K, Okada Y, Minematsu K, Kamouchi M, Fujimoto S, Ibayashi S, Inoue T. Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. *Neurology* 2005; **65**:1000–1004.
19 European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.
20 Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, *et al.* Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006; **66**:1175–1181.
21 Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke* 1998; **29**:1160–1166.
22 Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, *et al.* Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997; **28**:1–5.
23 Jauch EC, Lindsell CJ, Adeoye O, Khoury J, Barsan W, Broderick J, *et al.* Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. *Stroke* 2006; **37**:2061–2065.
24 Gebel JM Jr, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, *et al.* Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 2002; **33**:2636–2641.
25 Qureshi AI, Biliwise DL, Biliwise NG, Akbar MS, Uzen G, Frankel MR. Rate of 24-h blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. *Crit Care Med* 1999; **27**:480–485.
26 Powers WJ, Zazulia AR, Videen TO, Adams RE, Yundt KD, Aiyagari V, *et al.* Autoregulation of cerebral blood flow surrounding acute (6 to 22 h) intracerebral hemorrhage. *Neurology* 2001; **57**:18–24.
27 Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, *et al.* Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. *Stroke* 2003; **34**:2349–2354.
28 Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M, *et al.* Incidence of stroke in Shibata, Japan: 1976–1978. *Stroke* 1981; **12**:460–466.
29 Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, *et al.* Incidence and trends of stroke and its subtypes in China: results from three large cities. *Stroke* 2006; **37**:63–68.
30 Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007; **50**:309–315.

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ORIGINAL ARTICLE

Nationwide survey of antihypertensive treatment for acute intracerebral hemorrhage in Japan

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Acute hypertension is associated with hematoma enlargement and poor clinical outcomes in patients with intracerebral hemorrhage (ICH). However, the method of controlling blood pressure (BP) during the acute phase of ICH remains unknown. The aim of this study is to show current strategies about this issue in Japan. Questionnaires regarding antihypertensive treatment (AHT) strategies were sent to neurosurgeons, neurologists and others responsible for ICH management in 1424 hospitals. Of 600 respondents, 550 (92%) worked at hospitals wherein acute ICH patients are managed and 548 (99.6%) of them agreed with the application of AHT within 24 h of ICH onset. Most answered that the systolic BP threshold for starting AHT was 180 mm Hg (36%) or 160 mm Hg (31%), which differed significantly between neurosurgeons (median, 160 mm Hg) and neurologists/others (180 mm Hg, $P<0.001$). The goal of lowering systolic BP was to reach a maximum of 140, 150 or 160 mm Hg according to 448 respondents (82%) and 209 (38%) intensively lowered systolic BP to $\leqslant$140 mm Hg. Nicardipine was the first choice of intravenous drug for 313 (57%) and the second choice for 146 respondents (27%). However, 141 (26%) thought that nicardipine is inappropriate mainly because of a conflict with a description of contraindications on the official Japanese label for this drug. In conclusion, the present Japanese respondents, especially neurosurgeons, lower BP more aggressively than recommended in domestic and Western guidelines for managing acute ICH patients. Nicardipine was the most frequent choice of antihypertensive agent.
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Keywords: acute stroke; antihypertensive therapy; intracerebral hemorrhage; web questionnaire

INTRODUCTION

Intracerebral hemorrhage (ICH) is not only life threatening but also causes major disability. The annual incidence of ICH in Japan is several-fold higher than that in Caucasian populations.[1–5] Chronic hypertension is a leading risk factor for ICH[2,6,7] and such patients often have high blood pressure (BP) on admission. Acute high BP might enhance active intracranial bleeding and hematoma growth, which could be a determinant of poor clinical outcome.[8–12] In contrast, some investigators insist that high BP might work to maintain normal cerebral blood flow and prevent peri-hematomal ischemic damage.[13,14] However, pharmacologically mediated BP reduction apparently has no adverse effects on cerebral blood flow in humans or other animals.[15,16] Control of BP for acute ICH remains controversial.

American Heart Association/American Stroke Association (AHA/ASA) guidelines[17] and the Japanese Guidelines for the Management of Stroke 2004[18] both recommend lowering of BP for ICH patients with systolic blood pressure (SBP) of >180 mm Hg or mean arterial pressure of >130 mm Hg. The target BP level has not been defined. The European Stroke Initiative (EUSI) advocates an upper recommended limit of 180/105 mm Hg and a target BP of 160/100 mm Hg for acute ICH patients with known earlier hypertension or signs of chronic hypertension.[19] However, these recommendations are based on limited information and neither their usefulness nor their effects are well established.

Another concern regarding the lowering of BP in acute ICH patients is of the differences in recommendations for intravenous (i.v.) antihypertensive drugs among guidelines. Both the AHA/ASA and the EUSI guidelines recommend i.v. administration of the adrenergic inhibitors, labetalol and esmolol, and of the calcium channel blocker, nicardipine. In Japan, labetalol is not approved for commercial use, esmolol is used only for antiarrhythmia, and nicardipine

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administration for hyperacute ICH patients is limited by the description on the official label.

To conform to worldwide trends, BP control in ICH patients in Japan should be standardized, domestic recommendations that differ from others should be reconsidered, and an active role in international trials should be taken. Therefore, we conducted a nationwide web survey as the first step toward defining current standard strategies of BP control in Japanese patients with acute ICH.

METHODS

We surveyed 1424 certified training institutes recommended by the Japan Stroke Society, the Japan Neurosurgical Society and the Societas Neurologica Japonica. Web questionnaires (https://ssl.e-ult.jp/ICH/, for limited members) regarding acute ICH management and antihypertensive treatment (AHT) strategies were sent to hospital directors in July 2008 with a request that they encourage responsible physicians involved in stroke management to reply by September 2008.

The inquiry started by questioning whether acute ICH patients are usually treated in the respondents' hospitals. Those who responded affirmatively were required to answer seven questions about conditions surrounding acute ICH management and 14 questions about AHT for acute ICH (Table 1). When respondents disagreed with AHT for acute ICH patients in Question 10 (Q10), responses to subsequent questions were not required. All answers were multiple choice, except for Questions 2, 5 and 9, which required integral numbers.

At the end of the survey, we asked if the respondents were interested in further inquiries. Those who answered in the affirmative received a supplementary questionnaire in October 2008 to determine whether their patients experienced side effects of i.v. antihypertensive drugs during acute ICH management. Respondents were only required to e-mail a reply to this simple question if they recognized possible side effects.

Table 1 The web questionnaire in this study

Conditions for acute ICH management

Q1. What is your specialty?
Q2. How long is your career in clinical medicine?
Q3. How many acute ICH patients (hospitalized within 7 days of onset) are treated in your hospital per year?
Q4. Who mainly treats acute ICH patients at your hospital?
Q5. How many medical physicians attend patients with acute ICH at your hospital?
Q6. Where do you treat acute ICH patients?
Q7. Is your medical staff for acute ICH available during the nighttime and on weekends?

Antihypertensive therapy (AHT) for acute ICH

Q8. How do you measure BP in acute ICH patients?
Q9. How many times do you measure BP during the initial 24 h?
Q10. Do you agree with AHT within 24 h after ICH onset?
Q11. When do you start AHT?
Q12. At which SBP level or more do you initiate AHT?
Q13. At which level or less do you lower SBP during the hyperacute stage?
Q14. Which i.v. antihypertensive agent do you primarily choose?
Q15. Why do you choose the agent in Q14?
Q16. Which is your second choice of i.v. antihypertensive agent?
Q17. Do you think the listed i.v. agent is inappropriate for acute ICH patients?
Q18. Why do you choose the agent in Q17?
Q19. When do you think active intracranial bleeding ceases?
Q20. Which oral antihypertensive agent do you administer after acute i.v. AHT?
Q21. To which level or less do you lower SBP during the chronic stage?

Abbreviations: AHT, antihypertensive treatment; BP, blood pressure; ICH, intracerebral hemorrhage.

Statistics

The BP thresholds in Questions 12, 13 and 21 were compared between neurosurgeons and respondents from other specialties using the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2 test. A *P*-value of <0.05 was considered to represent a significant difference.

RESULTS

Among a total of 602 collected responses, two were excluded from the analyses because the same respondents answered twice, leaving 600 responses remaining from 1424 (42.1%) hospitals. Of these, 50 replied that they did not usually treat patients with acute ICH at their hospitals. Finally, 550 responses (38.6% of 1424 hospitals) were analyzed.

Conditions for acute ICH management

Of the 550 respondents, 457 (83.1%) were neurosurgeons (Q1; Table 2). Overall, the respondents had spent a median of 23 years in clinical medicine (Q2). The median number of ICH patients treated annually ranged between 41 and 60 (Q3). The main department for ICH management was neurosurgery (79.5%), whereas 10.5% of respondents replied that a mixed team from neurosurgery and neurology treated patients with acute ICH (Q4). The median number of ICH attending physicians was three per hospital (Q5). An ICU (intensive care unit) was the main ward (34.5%), and a SCU (stroke care unit) was used in only 12.7% of the respondent hospitals (Q6). The availability of doctors responsible for initial management of emergency ICH patients in the respondent hospitals or on call 24/7 was 61.6% (Q7).

Antihypertensive treatment for acute ICH

Blood pressure was measured during acute ICH mainly using automated equipment (81.3%, Q8; Table 2). The median number of BP measurements was 24 during the initial 24 h (Q9). Two respondents (0.4%) replied that AHT should not be performed within 24 h of ICH onset and the other 548 agreed with AHT (Q10). Thus, we analyzed the following results from these 548 respondents.

Antihypertensive treatment was started mostly in the emergency room or in the CT/MRI room immediately after a diagnosis of ICH was confirmed (85.0%, Q11). The threshold median SBP level for AHT initiation was 160 mm Hg (interquartile range: (IQR) 150–180 mm Hg), with biphasic peaks at 180 mm Hg (35.6%) and 160 mm Hg (30.8%, Q12; Figure 1, top). The median levels differed between neurosurgeons (160 mm Hg (IQR: 150–180)) and other physicians (180 mm Hg (160–180), $P<0.001$). Guideline-based initiation for patients with SBP $\geqslant$180 mm Hg was approved by 40.0% of the overall respondents, 35.3% of neurosurgeons and 63.0% of the remainder.

The target of lowering the SBP was also biphasic at 160 mm Hg (29.4%) and 140 mm Hg (29.7%); 448 respondents (81.8%) approved 140, 150 or 160 mm Hg as the target (Q13; Figure 1, middle). The median (IQR) target levels of neurosurgeons were 150 (140–160) mm Hg and those of others were 160 (150–170) mm Hg ($P<0.001$). Intensive lowering to $\leqslant$140 mm Hg was approved by 38.1% of the overall respondents, 41.0% of neurosurgeons and 23.9% of the remainder.

The most frequent first choice of i.v. drug was nicardipine (57.1%), followed by diltiazem (34.9%, Q14). The main reason for administering nicardipine was its ability to lower BP (96.2%, Q15). The second choice of respondents (26.5%) was nicardipine (Q16). Thus, nicardipine was used for acute ICH patients as the first or second choice by 83.5% of respondents, and by 396 (86.8%) neurosurgeons

Table 2 Answers to the web questionnaire

Question	*Multiple choice answers*	*Respondents*	*%*
Q1. Specialty	Neurosurgery	457	83.1
	Neurology	63	11.5
	Vascular neurology	12	2.2
	Emergency	2	0.4
	Other	16	2.9
Q2. Length of career[a]		23 (18–28) years	
Q3. Number of ICH patients	⩽20	88	16.0
	21–40	118	21.5
	41–60	113	20.5
	61–80	85	15.5
	81–100	63	11.5
	⩾101	83	15.1
Q4. Department for ICH care	Neurosurgery	437	79.5
	(Vascular) Neurology	44	8.0
	Mixed team composed of neurosurgery and neurology	58	10.5
	Emergency	2	0.4
	Other	9	1.6
Q5. Number of physicians for acute stroke care[a]		3 (2–5)	
Q6. Ward for ICH care	Stroke care unit	70	12.7
	Intensive care unit	190	34.5
	Emergency	110	20.0
	General	153	27.8
	Other	27	4.9
Q7. Nighttime/weekend availability of stroke team	Always available in hospital	182	33.1
	Always on call	157	28.5
	Occasionally	206	37.5
	Not available	5	0.9
Q8. Method of BP measurement	Manual sphygmomanometer	71	12.9
	Automated equipment	447	81.3
	Direct arterial monitor	32	5.8
Q9. Frequency of BP measurements[a]		24 (12–48)	
Q10. AHT for acute ICH	Agree	548	99.6
	Disagree	2	0.4
Q11. Timing to initiate AHT	Immediately after diagnosis	466	85.0
	Immediately after admission to ward	60	10.9
	After observation for several hours	22	4.0
Q12. Threshold SBP to initiate AHT		See Figure 1 (top)	
Q13. Target SBP during hyperacute stage		See Figure 1 (middle)	

Table 2 Continued

Question	*Multiple choice answers*	*Respondents*	*%*
Q14. First choice of i.v. drug	Nicardipine	313	57.1
	Nitroglycerin	38	6.9
	Diltiazem	191	34.9
	Nitroprusside	0	0.0
	Other i.v. drug	1	0.2
	Oral or transdermal drug	5	0.9
Q15-1. Reasons for choosing nicardipine in Q14[b]	Effectively reduces BP	301	96.2
	Safety	85	27.2
	Other	20	6.4
Q15-2. Reasons for choosing nitroglycerin in Q14[b]	Effectively reduces BP	19	50.0
	Safety	28	73.7
	Other	4	10.5
Q15-3. Reasons for choice of diltiazem in Q14[b]	Effectively reduces BP	72	37.7
	Safety	95	49.7
	Others	70	36.6
Q16. Second choice of i.v. drug	Nicardipine	146	26.5
	Nitroglycerin	132	24.0
	Diltiazem	159	28.9
	Nitroprusside	5	0.9
	Other i.v. drug	13	2.4
	Oral or transdermal drug	93	16.9
Q17. Inappropriate i.v. drug[b]	Nicardipine	141	25.6
	Nitroglycerin	123	22.4
	Diltiazem	55	10.0
	Nitroprusside	83	15.1
	Any drug is appropriate.	266	48.4
Q18-1. Reasons for choice of nicardipine in Q17[b]	Ineffective BP reduction	0	0.0
	Safety problems	14	9.9
	Limitations on official label	127	90.1
	Other	10	7.1
Q18-2. Reasons for choice of nitroglycerin in Q17[b]	Ineffective BP reduction	30	24.4
	Safety issues	23	18.7
	Limitation on official label	65	52.8
	Other	22	17.9
Q18-3. Reasons for choice of diltiazem in Q17[b]	Ineffective BP reduction	16	29.1
	Safety issues	19	34.5
	Limitations on official label	8	14.5
	Other	19	34.5
Q18-4. Reasons for choice of nitroprusside in Q17[b]	Less BP lowering power	10	12.0
	Safety issues	18	21.7
	Limitations on official label	44	53.0
	Other	16	19.3

Table 2 Continued

Question	*Multiple choice answers*	*Respondents*	*%*
Q19. Timing of end of active bleeding	⩽1 h after ICH onset	48	8.7
	1–3 h	74	13.5
	3–6 h	156	28.4
	6–12 h	121	22.0
	12–24 h	90	16.4
	⩾24 h	47	8.5
	Other	14	2.5
Q20. First choice of oral antihypertensive drug	Calcium channel blocker	360	65.5
	ARB	165	30.0
	ACE inhibitor	25	4.5
	β-Blocker	0	0.0
	Diuretic	0	0.0
Q21. Target SBP during chronic stage		See Figure 1 (bottom)	

Abbreviations: ACE, angiotensin-converting enzyme; AHT, antihypertensive therapy; ARB, angiotensin II receptor blocker; BP, blood pressure; ICH, intracerebral hemorrhage; SBP, systolic blood pressure.
[a]Data are expressed as medians (interquartile range).
[b]Multiple answers possible where applicable.

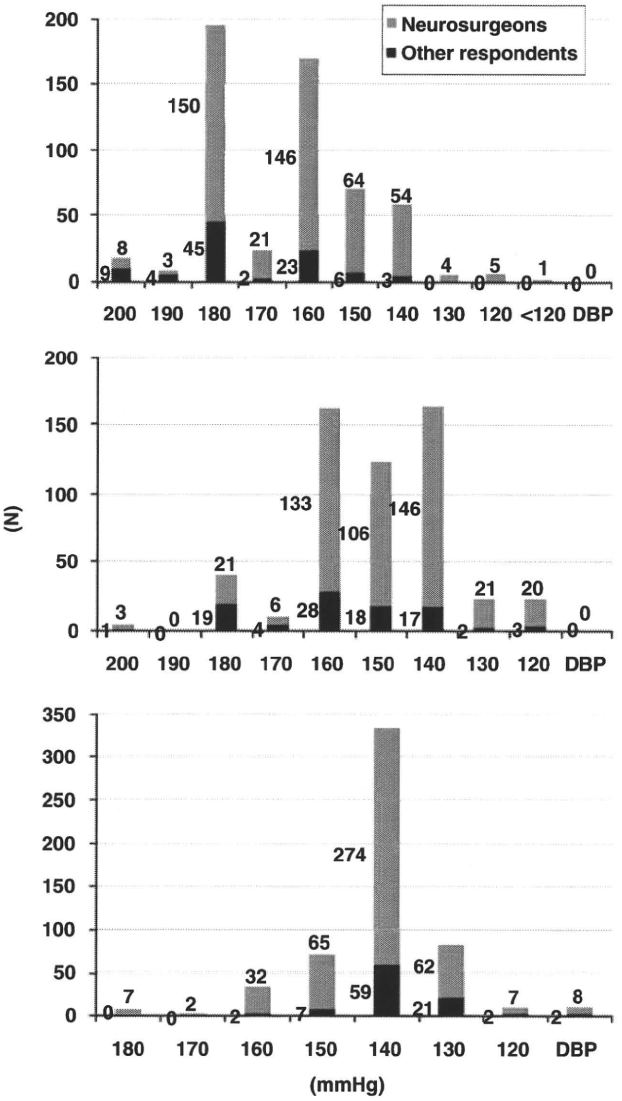

Figure 1 Answers to Questions 12, 13 and 21. Top: Threshold systolic blood pressure (SBP) required to start antihypertensive treatment (AHT). Middle: SBP during hyperacute stage by intravenous AHT. Bottom: SBP during chronic stage targeted by oral AHT. DBP: diastolic blood pressure (mm Hg) used by respondents rather than SBP as threshold or target value.

and 63 (68.5%) other respondents (P=0.14). Although 266 (48.4%) respondents answered that any i.v. drugs that lower BP are appropriate for patients with acute ICH, 141 (25.6%) replied that nicardipine is inappropriate, mainly because of the contraindications described on the label (90.1%, Q17, Q18). Around half of the respondents replied that active intracranial bleeding ceases within 6 h (50.5%, Q19).

After i.v. AHT, 360 respondents (65.5%) administer oral AHT using a calcium channel blocker, followed by an angiotensin II receptor blocker (30.0%, Q20). The target SBP value of 333 respondents (60.5%) was ⩽140 mm Hg (Q21). The median (IQR) target values of neurosurgeons were 140 (140–140) mm Hg and those of other physicians were 140 (130–140) mm Hg (P=0.001).

Supplementary inquiry

Among the respondents to the initial web questionnaire, 414 (75.3%) expressed an interest in further inquiries. We sent them another questionnaire to determine whether their patients experienced any possible side effects of i.v. antihypertensive drugs. A total of 32 physicians responded. Of them, 18 had patients who experienced bradycardia or atrioventricular block and one had a patient who developed arrhythmia during diltiazem administration. Nicardipine caused phlebitis (n=6), tachycardia (n=3) and liver dysfunction (n=2). One respondent described a decrease of oxygen partial pressure in arterial blood in a patient receiving nitroglycerin. A total of 10 respondents replied that i.v. drug administration did not cause side effects.

DISCUSSION

This study shows the current strategies regarding AHT for acute ICH patients in Japan. The first major finding was that 60% of the respondents start AHT on the basis of a threshold SBP level that is lower than that recommended by guidelines (180 mm Hg). The second major finding was that 80% of the respondents lowered SBP to a maximum of 140, 150 or 160 mm Hg, and 40% intensively lowered SBP to ⩽140 mm Hg. These two findings mainly reflect the opinions of neurosurgeons, as they accounted for 80% of the respondents. Both the threshold SBP level required to initiate AHT and the target SBP level were higher according to responses from other physicians (mainly neurologists and vascular neurologists) compared with those from neurosurgeons. The third major finding was that nicardipine is the most effective i.v. drug to reduce BP of patients with acute ICH, although such usage conflicts with the official Japanese label.

The threshold SBP level required to initiate AHT and the target SBP level recommended in the guidelines are not identical and are not based on sophisticated trials; over half of the respondents set lower values for these two parameters than those recommended by the AHA/ASA guidelines. The present findings indicate that most Japanese neurosurgeons prefer stricter AHT for ICH patients than that

recommended by the current guidelines. This tendency might be because a stricter AHT than the usual one is recommended when surgical therapy is scheduled for ICH in Japanese guidelines, although the evidence level is not high.[20] A lower target SBP than the guidelines recommend has been reported recently. Ohwaki *et al.*[20] assessed 76 patients with ICH and found that an SBP target of $\leqslant$150 mm Hg was less significantly associated with hematoma growth than that of $\geqslant$160 mm Hg. Our observational study of 244 patients with ICH showed that lowering SBP to $<$138 mm Hg during the initial 24 h after admission seems to predict a favorable early outcome.[21] Two major clinical trials are ongoing to determine the safety and efficacy of intensively lowering BP for acute ICH: the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)[22] and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH).[23] The vanguard phase of INTERACT showed that early intensive lowering of BP with a targeted SBP of 140 mm Hg and careful monitoring was feasible, safe and might have modestly attenuated hematoma growth in 346 randomized patients in the standard best practice stroke unit care.[22] Phase I of ATACH investigated the potential consequences of controlling BP with i.v. nicardipine at the sequential levels of 170–200, 140–170 and 110–140 mm Hg in 60 patients.[23] The result was announced in a recent conference.[22]

This survey clarified a contradiction regarding the prevalence of nicardipine administration to Japanese patients with ICH regardless of the following contraindications described on the official label; 'nicardipine is contraindicated for (I) ICH patients with a suspicion of ongoing intracranial bleeding not to enhance bleeding and for (II) acute stroke patients with elevated intracranial pressure not to accelerate intracranial pressure elevation.' When nicardipine was originally approved for commercial use as an ameliorant of cerebral circulation, not as an antihypertensive agent, in Japan in 1981, a description of the above contraindications was listed on the label following that of another ameliorant of cerebral circulation. As far as we can determine, the limited administration of nicardipine for patients with ongoing intracranial bleeding or high intracranial pressure is not supported by any scientific evidence. The description on the label has another problem in that the time when active intracranial bleeding ceases is not as clear as stated in the answer to Q19. On the basis of the results of this survey, a formal request for reassessment of the official label of nicardipine was submitted to the Ministry of Health, Labour and Welfare of Japan by the Japan Stroke Society, Japan Neurosurgical Society and the Japanese Society of Hypertension in October 2008. Diltiazem was the second most frequently administered drug, which seems to be associated with an influence on cardiac rhythms. On the basis of Japanese official labels, nitroglycerin is not administered to lower BP except for patients with acute heart failure, unstable angina or perioperative conditions, and nitroprusside is limited to patients with severely damaged cerebral circulation. A limitation of this study was that we did not ask in the web questionnaires whether respondents know the contraindication of nicardipine listed on the official label. It is important to know how many doctors use nicardipine with or without knowing this contraindication.

Calcium channel blockers and angiotensin II receptor blockers were the choices of oral antihypertensive drugs after i.v. administration in 65.5 and 30.0% of respondents, respectively. The most frequent target SBP according to our respondents (140 mm Hg) was identical to the level recommended by the guidelines of the Japanese Society of Hypertension[23] and higher than that in the guidelines from the European Society of Hypertension and European Society of Cardiology (130 mm Hg).[24]

In conclusion, current Japanese strategies based on this survey regarding acute BP lowering for ICH patients, especially by neurosurgeons, differ considerably from strategies recommended in various guidelines. We are planning to conduct a multicenter, randomized clinical trial of Japanese patients with ICH to determine the optimal BP target of AHT based on the results of this survey.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med* 1992; **326**: 733–736.
2 Furlan AJ, Whisnant JP, Elveback LR. The decreasing incidence of primary intracerebral hemorrhage: a population study. *Ann Neurol* 1979; **5**: 367–373.
3 Drury I, Whisnant JP, Garraway WM. Primary intracerebral hemorrhage: impact of CT on incidence. *Neurology* 1984; **34**: 653–657.
4 Brott T, Thalinger K, Hertzberg V. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. *Stroke* 1986; **17**: 1078–1083.
5 Schutz H, Bodeker RH, Damian M, Krack P, Dorndorf W. Age-related spontaneous intracerebral hematoma in a German community. *Stroke* 1990; **21**: 1412–1418.
6 Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, Pessin MS, Bleich HL. The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology* 1978; **28**: 754–762.
7 Qureshi AI, Suri MA, Safdar K, Ottenlips JR, Janssen RS, Frankel MR. Intracerebral hemorrhage in blacks. Risk factors, subtypes, and outcome. *Stroke* 1997; **28**: 961–964.
8 Carlberg B, Asplund K, Hagg E. The prognostic value of admission blood pressure in patients with acute stroke. *Stroke* 1993; **24**: 1372–1375.
9 Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. *Stroke* 1986; **17**: 861–864.
10 Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. *Stroke* 1997; **28**: 1396–1400.
11 Terayama Y, Tanahashi N, Fukuuchi Y, Gotoh F. Prognostic value of admission blood pressure in patients with intracerebral hemorrhage. Keio Cooperative Stroke Study. *Stroke* 1997; **28**: 1185–1188.
12 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke* 1997; **28**: 2370–2375.
13 Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A. Dysautoregulation in patients with hypertensive intracerebral hemorrhage. A SPECT study. *Neurosurg Rev* 1995; **18**: 237–245.
14 Qureshi AI, Bliwise DL, Bliwise NG, Akbar MS, Uzen G, Frankel MR. Rate of 24-h blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. *Crit Care Med* 1999; **27**: 480–485.
15 Qureshi AI, Wilson DA, Hanley DF, Traystman RJ. Pharmacologic reduction of mean arterial pressure does not adversely affect regional cerebral blood flow and intracranial pressure in experimental intracerebral hemorrhage. *Crit Care Med* 1999; **27**: 965–971.
16 Powers WJ, Zazulia AR, Videen TO, Adams RE, Yundt KD, Aiyagari V, Grubb Jr RL, Diringer MN. Autoregulation of cerebral blood flow surrounding acute (6–22 h) intracerebral hemorrhage. *Neurology* 2001; **57**: 18–24.
17 Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstern L, Ogilvy CS, Vespa P, Zuccarello M. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007; **38**: 2001–2023.
18 Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the Management of Stroke 2004 and subsequent revision. *Int J Stroke* 2008; **3**: 55–62.
19 Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, Juvela S, Marchel A, Chapot R, Cognard C, Unterberg A, Hacke W. Recommendations for the management of intracranial haemorrhage—part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. *Cerebrovasc Dis* 2006; **22**: 294–316.
20 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004; **35**: 1364–1367.

21 Itabashi R, Toyoda K, Yasaka M, Kuwashiro T, Nakagaki H, Miyashita F, Okada Y, Naritomi H, Minematsu K. The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage. *J Hypertens* 2008; **26**: 2016–2021.
22 Qureshi AI, Qureshi Z, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial: final results. *Stroke* 2009; **40**: e111 (abstract).
23 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H, on behalf of The Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
24 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.

わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究 2：超急性期脳出血への降圧療法に関する研究」
脳卒中急性期および慢性期再発予防としての降圧療法の現状

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緒　言

高血圧は脳卒中の最大の危険因子であり、かつ脳卒中は日本人にとって最多の高血圧性臓器障害である。しかしながら、脳卒中患者への血圧管理法は、十分に確立しているとは言い難い。血圧高値が頭頸部の動脈硬化を助長して脳卒中発症を惹起する反面で、血圧低値が脳卒中患者（とくに急性期患者）の脳への潅流を損ねかねないという逆説的な現象などが、脳卒中患者への適切な降圧指針を決め難くしている。しかしながら、近年の多くの疫学研究や介入試験で、一次予防については原則として血圧をより下げるほど脳卒中を起こし難くなること（the lower, the better）が明らかにされている。では、脳卒中をひとたび起こした患者への血圧管理は、どのように考えられているであろうか。

わが国の脳卒中合同ガイドライン委員会による「脳卒中治療ガイドライン」が 2009 年秋に 5 年ぶりに改訂され、この数年間に国内外で発表された多くの新知見を反映して、血圧管理に関する情報が前回版よりも大幅に更新された。このガイドラインを基に、同世代の脳卒中医家で協力してより実際的な解説を加えた総説群が、「血圧」誌 2009 年 11 月号（特集：脳卒中治療ガイドライン 2009 と血圧管理、先端医学社）に掲載された。ここでは、脳卒中急性期、慢性期の血圧管理の最新の知見を、この総説群の記載内容を踏まえて紹介する。

脳梗塞急性期の血圧管理

脳梗塞の急性期に血圧は上昇し、急性期の血圧がより高い例は概して急性期死亡や予後不良の転帰をとり易い。自験例でも、入院後 12～36 時間の収縮期血圧高値が、入院時と比べて 3 週間後の神経症候増悪に独立して寄与した[1]。しかしながら急性期の降圧治療は、長年にわたって原則として禁忌とみなされてきた。その主な根拠として、この時期には全身血圧の変動にかかわらず脳血流量を一定に保つ「脳血流自動調節能」が損なわれ、軽度の血圧低下でも脳血流量を低下させ虚血を増悪させ得ることが挙げられる。これに対して、比較的少数例での 11 試験の成績をまとめると、急性期の降圧に伴い脳血流量や脳血流速度は変わらなかった [2]。また急性期の血栓溶解療法や各種抗血栓療法の普及に伴い、出血性合併症を防ぐためにあまりに高い血圧を容認しづらくなってきた。

国内外の最新の治療指針では、220/120 mmHg を超える血圧に対して前値の 85%程度までの降圧を推奨している。ただし、大動脈解離や急性心筋梗塞、心不全など血圧高値を保持することが病態に悪影響を及ぼす疾患を合併する場合には、より厳しい降圧レベルを設ける。組織プラズミノゲン・アクティベータ（tPA）静注療法の治療中や治療後 24 時間には 180/105 mmHg 未満への降圧が求められる。

近年では、より積極的な降圧を目指した研究が報告されている。Acute Candesartan Cilexetil Evaluation in Stroke Survivors（ACCESS）試験[3]では、発症後 6～24 時間に 200/110 mmHg 以上、あるいは 24～36 時間に 180/105 mmHg 以上の高血圧を呈する脳梗塞患者 342 例に対して、アンジオテンシン受容体拮抗薬（ARB）のカンデサルタンないし偽薬を 7 日間投与し、8 日目以降の 1 年間はほぼ全例がカンデサルタンを服用した。この結果、1 年を過ぎた時点での脳血管障害を含む血管病発症ないし死亡の割合が実薬群で有意に低かった（図 1 左）。両群間に急性期の 7 日間を含めて有意な血圧差が生じなかったため、降圧の直接の効果を反映した成績ではないが、急性期の経口降圧

薬が患者転帰を改善させる可能性を示した。また Controlling hypertension and hypotension immediately post-stroke (CHHIPS) [4]のパイロット試験では、収縮期血圧が 160 mmHg を超える発症 36 時間以内の脳卒中患者（一部脳出血を含む）179 例にβブロッカーのラベタロールまたはアンジオテンシン変換酵素（ACE）阻害薬のリシノプリルないし偽薬を静注または経口、経鼻で 14 日間投与した。この結果、実薬群が偽薬群に比べて収縮期血圧が 8～10 mmHg 程度低く、3 か月後の死亡率が実薬群で半減した（図 1 右）。現在、他にも幾つかの介入試験が進行中である。

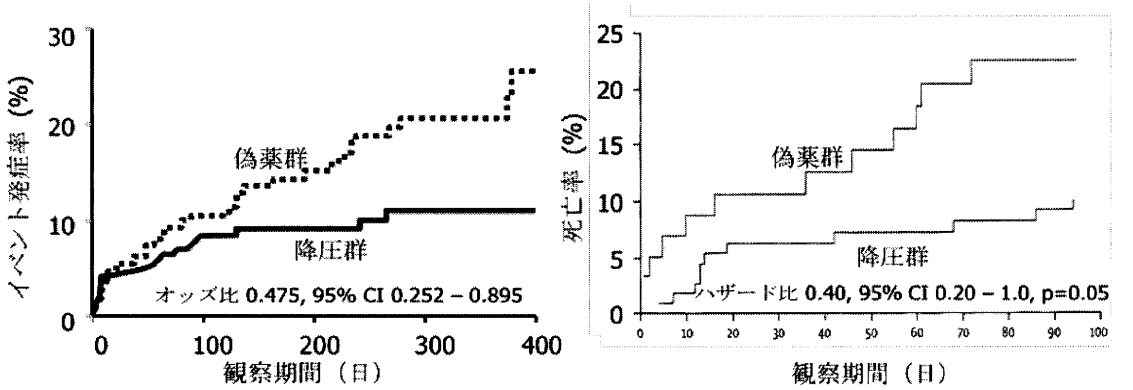

図 1： ACCESS・CHIPPS 試験における急性期降圧治療と転帰
左： ACCESS 試験における死亡ないし脳卒中、心血管病発症の発症率
右： CHIPPS 試験における死亡率
（文献 3, 4 より改変引用）

急性期降圧を考える上での大きな問題は、頭頸部動脈の高度狭窄・閉塞例など、急性期に高度の脳循環代謝不全を呈して降圧が有害な患者も確実に存在することであるが、近年の画像診断の発達によりこのような患者群を比較的迅速に同定できるようになった。患者特性に応じて血圧管理法を分けて考えることも重要であろう。

脳出血急性期の血圧管理

脳出血の急性期にも概して血圧が上昇する。急性期の血腫や浮腫の増大が予後増悪因子として知られるが、これらは血圧の高い患者に起こり易いとの報告が多い。一方、急性期降圧によって血腫周囲に低潅流、虚血を招くことが懸念されるが、総じて、急性期血圧高値は予後不良と考えられる。

急性期降圧の意義が、多くの施設から比較的少数例の研究として報告されている。**筆者らは急性期に静注降圧治療を行った入院時血圧高値の脳出血患者 244 例を、最初の 24 時間以内の収縮期血圧平均値を用いて四等分して 3 週間後の予後を比べた**[5]。**多要因で補正した後も、収縮期血圧平均値がもっとも低かった群（138 mmHg 未満）はもっとも高かった群（158 mmHg 以上）に比べて 3 週間後に完全自立に復する割合が有意に高かった（オッズ比 4.36、95% CI 1.10 – 17.22）。また**現在 Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) [6]や Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) [7]などの大規模介入試験が組まれ、ともにパイロット試験を終えて、本試験が開始、または企画されている。このうち INTERACT では、登録時の収縮期血圧値が 150～220 mmHg を示す発症 6 時間以内の脳出血患者 404 例を、異なる降圧目標値（収縮期血圧 180 mmHg 程度、および 140 mmHg 程度）の二群に分けて比べた結果、24 時間後の血腫拡大率はより厳しい降圧の患者群で有意に低かったが、慢性期予後に有意な差を認めなかった[6]。とくに登録時収縮期血圧と血腫拡大との間には有意な関係を認めなかった一方で、**最初の 24 時間以内の収縮期血圧平均値は血腫の相対的・**

絶対的拡大率にともに有意な関係を示した(図 2)[8]。

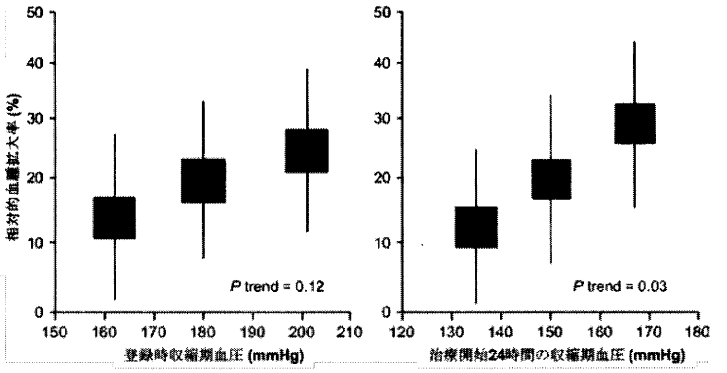

図 2: INTERACT 試験における収縮期血圧(3 分位)と 24 時間後の相対的血腫拡大率
(文献 8 より改変引用)

国内外の指針は収縮期血圧 180 mmHg 以上または平均血圧 130 mmHg 以上を降圧開始の目安としている。また国際高血圧学会は、220/120 mmHg を超える患者に、血圧値で 20%程度までの降圧を推奨している。降圧目標値として、米国の指針は平均血圧 110 mmHg または血圧 160/90 mmHg を例示している。前述した INTERACT の結果に基づき、米国の指針では収縮期血圧 150～220 mmHg の患者に対する 140 mmHg までの急性期降圧が安全であることが、新たに推奨された。

急性期に用いる静注用降圧薬として、米国の指針ではラベタロール（国内では静注薬未販売）やニカルジピンが推奨されるが、国内でのニカルジピンの添付文書には、頭蓋内出血で止血が完成していない患者や脳卒中急性期で頭蓋内圧亢進の患者には使用禁忌とされることが書かれている。しかしながら渉猟し得る範囲で、ニカルジピンが血腫増大や予後増悪に関連したことを示す基礎的・臨床的研究は無い。筆者が主宰する厚生労働科学研究班（Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] study）が 2008 年に行った国内アンケート調査では、降圧開始の目安とする収縮期血圧は 180 mmHg 以下、160 mmHg 以下との回答が多く、到達目標値は 140 mmHg 以下、150 mmHg 以下、160 mmHg 以下との回答が 84%を占めた[9]。静注降圧薬として、過半数の施設が急性期脳出血患者の静注降圧治療における第一選択薬にニカルジピンを挙げ、ほとんどの回答者が選択理由として優れた降圧効果を挙げた反面、添付文書による使用制限を問題点として指摘している。脳出血治療の国際的標準化を図る上でも、日米の指針において同一薬の評価が全く異なる矛盾を、早急に解決する必要がある。

慢性期の血圧管理

日本を含む 10 か国で実施された多施設前向き共同の Perindopril Protection Against Recurrent Stroke Study（PROGRESS）試験[10]が、脳卒中再発予防としての降圧療法の妥当性を示す、大きな科学的根拠となった。この研究では、脳卒中・一過性脳虚血発作既往患者（うち 11%が脳出血）を対象に、既に服用中の降圧薬に上乗せして ACE 阻害薬のペリンドプリルないし偽薬を投与し、ペリンドプリルで降圧が不十分な過半数の例には利尿薬インダパミドの追加投与も認めた。4 年間の追跡期間中に、実薬投与により血圧は 147/86 mmHg から 9.0/4.0 mmHg 低下した。主要評価項目である脳卒中再発について、実薬群で偽薬群に比べて、28%の有意な相対リスクの軽減効果が示され、心血管イベントや認知機能障害、要介護などの副次評価項目の相対リスクも、実薬群で有意に低かった。同研究の層別解析では、脳梗塞の臨床カテゴリー、性・年齢・人種や心

血管病危険因子の有無、あるいは治療開始時の収縮期血圧レベルの相違にかかわらず（正常血圧者においても）、実薬群での脳卒中再発抑制効果を認めた。その一方で、近年発表された Prevention Regimen for Effectively Avoiding Second Strokes（PRoFESS）試験[11]は、発症 90 日以内の脳梗塞患者 20332 例を対象に ARB テルミサルタンと偽薬との脳卒中再発抑制効果を比べたが、テルミサルタンによる抑制効果は有意でなかった（ハザード比 0.94, 95% CI 0.87 - 1.01）。この結果に対して、対象者の 37%が既に ACE 阻害薬を服用していた点や観察期間が比較的短かった点などが、問題点として指摘されている。PROGRESS や PRoFESS を含めた 13 試験のメタ解析では、積極的降圧によって脳卒中再発が有意に抑制された（統合相対危険 0.82, 95% CI 0.73 - 0.92、図 3）[12]。

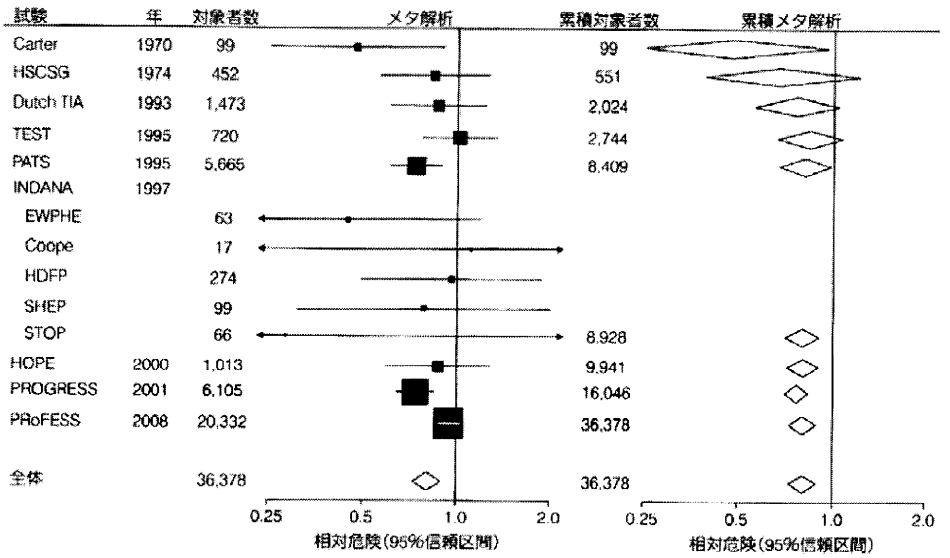

図 3 降圧療法の脳卒中再発予防効果を検討した無作為化比較試験のメタ解析および累積メタ解析
■：各試験の相対危険（面積は各研究の重みに比例）、—：各試験の相対危険の 95%信頼区間、
◇：統合相対危険および 95%信頼区間

PROGRESS 等の成績を踏まえて、国内外の治療指針はいずれも脳卒中再発予防としての降圧療法を強く推奨している。高血圧治療ガイドライン 2009 や脳卒中治療ガイドライン 2009 では、慢性期患者の降圧目標を 140/90 mmHg 未満に設定している。一方、欧州のガイドライン 2007 は、130/80mmHg 未満へのより厳しい降圧目標を推奨している。科学的根拠に基づいた降圧目標を示すため、Secondary Prevention of Small Subcortical Strokes （SPS3）などの介入試験が進行中である。PROGRESS では、治療中の収縮期血圧レベルが低い群ほど脳卒中再発率が低く、115/75 mmHg 程度の高度降圧が、より緩徐な降圧よりも再発抑制効果が高かった[13]。

では、一部脳梗塞患者への過度降圧による脳梗塞再発、すなわち J カーブ現象は、存在しないのだろうか。このような危険を持つ患者は、従来懸念されていたほど多くないと、推察できる。しかしながら、頭頸部動脈の狭窄性病変を有する患者の中には、降圧に非常に慎重にならざるを得ない、または降圧すべきでない患者が、少数ながら存在する。脳卒中専門医がこのような患者を確実に抽出し、彼らへの長期的な血圧管理方針をたてて、その情報を漏らさずかかりつけ医に伝えることが重要である。そうすることで、その他の圧倒的多数の脳卒中患者が、適切な降圧治療を確実に受けることが出来るであろう。

降圧薬として、脳卒中治療ガイドライン 2009 は特定のクラスの降圧薬の優位を示す根拠は十分ではないと言及し、欧州の指針は「降圧で得られる利得のほとんどは、降圧自体に依存する」のですべての降圧薬が奨められると記している。米国合同委員会

の 7 次報告は PROGRESS 試験の成績を尊重し、ACE 阻害薬と利尿薬を第一選択薬としている。とくに利尿薬について、わが国では脱水による脳循環への悪影響を懸念されて脳梗塞患者への使用が敬遠されがちであったが、PROGRESS 以降は次第に使用頻度が増えている。

抗血栓薬服用患者の血圧管理

脳梗塞患者の多くは、再発予防に抗血栓薬を欠かせない。抗血栓薬の必然的な副作用に出血合併症が挙げられ、出血を避けるために適切な血圧管理が必要であろう。脳卒中治療ガイドライン 2009 にも、「ラクナ梗塞の再発予防に抗血小板薬の使用が奨められるが、十分な血圧のコントロールを行う必要がある」と記載されている。しかしながら、抗血栓薬服用者における適切な血圧管理指針は、国内外のいずれのガイドラインにも明記されていない。本稿の最後に、筆者らが多施設共同研究 Bleeding with Antithrombotic Therapy Study (BAT 研究)の付随研究として行った、観察対象者の外来血圧値の推移と出血合併症を調べた研究成績を、簡単に紹介する[14]。

脳血管障害や心臓血管病に対して抗血小板薬かワルファリンを服用開始または服用中の患者 4009 例（男性 2728 例、69±10 歳）を、2003 年から 2006 年にかけて登録し、中央値で 19 か月間の観察を行った。観察期間中に頭蓋内出血を起こした 31 例（頭蓋内出血群）、頭蓋内出血以外の重篤または重症出血を起こした 77 例（頭蓋外出血群）、重篤・重症出血を起こさなかった 3901 例（出血なし群）の外来血圧の推移を、調べた。3 群の血圧の推移を、登録時→観察期間中（平均値）→観察終了時（あるいは出血発症直前回の外来時）の 3 点の流れで見ると、登録時には 3 群間の血圧レベルに差がなく、頭蓋内出血群でのみ収縮期・拡張期とも血圧が漸増しており、血圧上昇と頭蓋内出血発症の因果関係が示唆された（図 4）。観察終了時の収縮期・拡張期血圧を各々6 段階に分けると、血圧上昇に応じて頭蓋内出血発症率が直線的に高まっていた。さらに ROC 解析で頭蓋内出血発症の至適カットオフ値を求めると、130/81 mmHg 以上が発症の良い指標となった。抗血栓薬服用患者の脳梗塞再発予防には、国内ガイドラインの推奨レベルよりも低い目標を設定した方が、良いかも知れない。

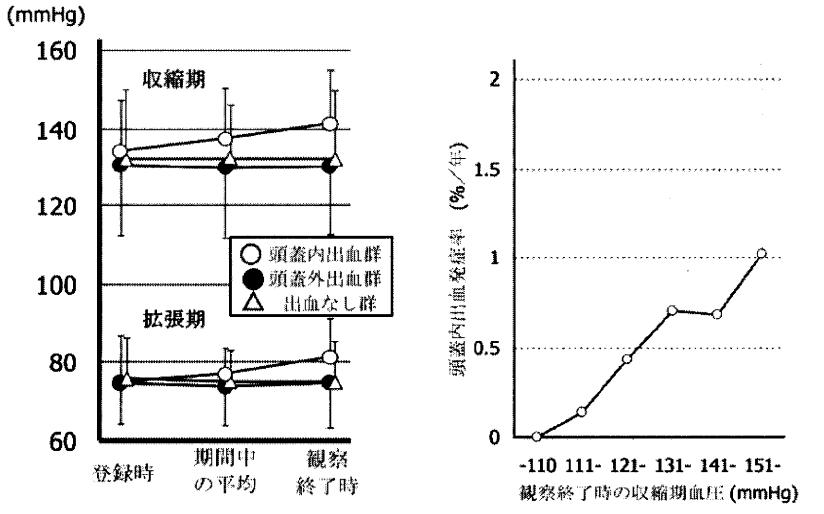

図 4： BAT 研究における出血イベントと外来血圧の推移

左： 出血群における「観察終了時血圧」は出血イベント発症の直前回の外来血圧値（平均±SD）を指す。

右： 観察終了時収縮期血圧と頭蓋内出血年間発症率。縦線は 95% CI を示す。

（文献 14 より改変引用、とくに左図は原文の図をより分かり易くするため大幅に改変）

文 献

1. Toyoda K, Fujimoto S, Kamouchi M, et al. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. Stroke 40: 2585-2588, 2009
2. Sare GM, Gray LJ, Bath PM. Effect of antihypertensive agents on cerebral blood flow and flow velocity in acute ischaemic stroke: systematic review of controlled studies. J Hypertens. 26: 1058-1064, 2008
3. Schrader J, Lüders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke 34: 1699-1703, 2003
4. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol. 8: 48-56, 2009
5. Itabashi R, Toyoda K, Yasaka M, et al. The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage. *J Hypertens*, 26: 2016-2021, 2008
6. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol.* 7:391-399, 2008
7. Qureshi AI, Palesch YY, Martin R, et al. Arch Neurol. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. 67: 570-576, 2010
8. Arima H, Anderson CS, Wang JG, et al. Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. Hypertension. 56: 852-858, 2010
9. Koga M, Toyoda K, Naganuma M, et al. Nationwide survey of antihypertensive treatment for acute intracerebral hemorrhage in Japan. Hypertens Res 32:759-764, 2009
10. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358: 1033-1041, 2001
11. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events. N Engl J Med 359: 1225-1237, 2008
12. 有馬久富： 脳卒中再発予防のための降圧療法：どこまで下げるか？ 血圧 17: 941-944, 2010
13. Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens. 24: 1201-1208, 2006
14. Toyoda K, Yasaka M, Uchiyama S, et al. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. Stroke 41; 1440-1444, 2010

多施設共同研究3：
急性脳主幹動脈閉塞症の実態に関する
後ろ向き多施設共同研究
関連資料

3- a. 研究計画書

3-b. 研究の調査票

3-c. 研究の主要所見

STROKE ACUTE MANAGEMENT WITH URGENT RISK-FACTOR ASSESSMENT AND IMPROVEMENT

SAMURAI

わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究 3：急性脳主幹動脈閉塞症の実態に関する後ろ向き多施設共同研究」
多施設共同前向き観察研究の研究計画書（平成 21 年 9 月作成）

課題名　「急性脳主幹動脈閉塞症の実態に関する後ろ向き多施設共同研究」

1）研究協力の任意性及び撤回の自由

この研究への参加は自由意思で決められる。本研究への参加を強制するものではなく、不利益になることはない。また一旦参加した場合でも、不利益を受けることなく、いつでも参加を撤回することができ、登録データなどの情報は廃棄され、それ以後は研究目的に用いられることはない。ただし、参加を取り消したときすでに研究結果が論文などで公表されていた場合などのように、登録データなどを廃棄することが出来ない場合がある。

2）研究の目的

急性脳血管閉塞に対して一定の条件下でrt-PA静注療法が行われているが、その適応は虚血性脳卒中の3-5%と少ない。とくに内頸動脈閉塞を伴う場合は良好な治療結果を得にくいと言われている[Adams HP, et al: Stroke 2003;34:1056-1083]。局所線溶療法ではPROACT IIおよびMELTで示された条件（Urokinase使用、6時間以内、CTによる患者選択など）では有効と考えられるがやはり限定的な医療である[Furlan A, et al: JAMA. 1999;282: 2003-2011; Ogawa A, et al: Stroke 2007;38:2633-2639]。その他、血管形成術やステント留置術も試みられてきたが、有効性と安全性を確認するには至っていない[Nakano S, et al: Stroke. 2002;33:2872-2876; Levy EI, et al: Neurosurgery. 2006;58:458-463]。現在、諸外国で使用が開始されている再開通治療用医療機器のうち、Merci/ConcentricとPenumbra/Penumbraが医療ニーズの高い医療機器に選定され薬事承認を申請中であるが、本邦への導入にあたっては急性脳主幹動脈閉塞症の治療実態を基に検討すべきという意見もある。そこでrt-PA静注療法が本邦で承認され開始された2005年10月以降の、脳主幹動脈急性閉塞症の実態を後ろ向き調査により明らかにし、今後の治療法の開発や治療の検証に活用する資料とするため本調査を実施する。

3）研究責任者及び研究組織

研究責任者	内科脳血管部門	医長（当時）	豊田一則
研究者	内科脳血管部門	医師（当時）	古賀政利
	内科脳血管部門	レジデント	遠藤　薫　（以下　略）

4）研究の対象及び方法

厚生労働科学研究費補助金による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」班（H20 -循環器等（生習）-一般-019、主任研究者：豊田一則）の班員が所属する別紙1の10施設で、2005年10月から2009年6月に入院した、発症24時間以内の主幹脳動脈（頸動脈、前大脳動脈、中大脳動脈、椎骨動脈、脳底動脈、後大脳動脈）閉塞病変を伴う急性脳梗塞患者を対象とする。方法は、本研究班の中央事務局（国立循環器病センター　内科脳血管部門）が各研究班員の意見を集約して作成したデータベースのワークシートを電子媒体で各班員に配布する。各研究班員は、所属施設の対象症例のデータを登録後に中央事務局に返却する。登録するデータは、個人情報を特定できないものとする。調査項目の詳細を、別紙2に示す。このデータベースをもとに、閉塞血管部位ごとの脳梗塞重症度や転帰を検討する。主な評価項目を、以下に記す。

1. 入院90日後の日常生活自立度（modified Rankin Scale）
2. 調査期間中の全脳卒中入院における脳主幹動脈閉塞症の割合

3. 調査期間中の虚血性脳卒中入院における脳主幹動脈閉塞症の割合
4. 閉塞血管と転帰の関係
5. 治療前NIHSSと転帰の関係

なお、同じ調査が循環器病研究委託費20公-2「カテーテルインターベンションの教育訓練システムの構築と有効性に関する研究」（主任研究者：坂井信幸　神戸市立医療センター中央市民病院脳神経外科部長）でも企画されており、両研究班のデータを合わせた検討も行う。

5）問題発生時の対応

問題発生時は必ず本研究班の中央事務局（国立循環器病センター内科脳血管部門　古賀政利）に連絡し、適切な対応を検討する。また、必要に応じて各班員と班員が所属する施設の倫理委員会に報告する。

6）研究期間

実施場所は、国立循環器病センター内科脳血管部門とする。実施期間は、倫理委員会による承認を受けた日から2010年3月までとする。

7）研究計画等の開示

研究対象者の希望に応じて、本書面のコピーを開示する。

8）予測される危険性

方法に記した登録データが流出する危険があるが、厳重に管理され持ち出しはできず、また解析は無名化して行うため、ほとんどおこりえない。9）被験者の利益及び不利益

後ろ向き研究であり、研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る利益、不利益はない。

10）費用負担に関する事項

本研究に関する経費は、厚生労働科学研究費補助金による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」班（研究課題番号H20 -循環器等（生習）--一般-019、主任研究者：豊田一則）の研究費より支出する。研究対象者に対する謝金、交通費等の支払いは行われない。

11）知的所有権に関する事項

知的所有権が発生した場合、その権利は国・研究機関・研究遂行者などに属し、研究対象者に帰属することはない。

12）倫理的配慮

12-1）医学研究及び医療行為の対象となる個人の人権の擁護

研究対象者の人権の擁護のために、データを登録する前に研究の内容、目的および方法を含めて各施設の掲示板などに掲示する。また、得られたいかなる個人情報について秘密が厳守されることを保証する。

12-2）医学研究及び医療行為の対象となる個人への利益と不利益

利益：後ろ向き研究であり、診療記録等の既存資料のみを用いる観察研究である研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る利益はない。

不利益：後ろ向き研究であり、研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る不利益はない。ただし、個人情報の流出は不利益となるため、以下の方針で臨む。すなわち、本研究は後ろ向きに多施設の研究対象者データをまとめて解析するものであり、各対象者個人を特定できるような検討は行わない。各施設のデータを収集する時点で、研究用の登録番号による管理とし、

各施設のデータとの照合が出来ないように管理する。しかしながら、問題発生時には適切な対応を行う。登録データの研究目的使用に当たっては研究責任者によりデータ管理を徹底し、学会・論文などの研究成果発表以外の部外へ個人プライバシーに関わるデータが流出しないよう注意する。また個人情報の流出により個人のプライバシーを侵害した可能性が生じた場合はすぐに倫理委員会に報告する。

12-3) 医学的貢献度

わが国における急性脳主幹動脈閉塞症の実態については、正確なデータが得られていない。本研究の結果から、虚血性脳卒中における急性脳主幹動脈閉塞症の頻度や、内科治療・血管内治療・外科治療を行った場合の転帰などが明らかとなり、今後の治療法比較試験の基礎資料となると考えられる。

12-4) 医学研究及び医療行為の対象となる個人に理解を求め同意を得る方法

データを登録する前に、研究の内容、目的および方法を含めて班員の所属する施設の掲示板などに掲示する。研究対象者またはその家族等から研究への不参加の申し出があれば、そのデータは破棄し、それ以外の研究対象者のデータを用いて研究を行う。ただし、申し出があったときすでに研究結果が論文などで公表されていた場合などのように、調査結果などを廃棄することが出来ない場合がある。登録データは研究者により厳重に保護されること、臨床成績を医学雑誌などに発表する際には最大限にプライバシー保護に努め、研究対象者の名前や身元などを明らかにするようなことはない。なお、この研究は一般保険診療の枠外で行われるため、患者から診療録閲覧の請求を受けた場合はその対象とならない。

本研究は診療記録等の既存資料のみを用いる観察研究であり、以下の 4 点を満たすため、2007 年 8 月 16 日に改正された文部科学省・厚生労働省の疫学研究倫理指針に従い、研究対象者からの同意書取得を行わずインフォームド・コンセントを掲示板掲示の方式に簡略化して良いと判断する。すなわち、(1)研究対象者に対して最小限の危険を超える危険を含まず、(2)研究内容を掲示板に掲示して広報することが研究対象者の不利益とならず、(3)各対象者から同意書を取得する方法では重症例・死亡例の登録に概して同意を得がたく、研究結果に大きな歪みを来たす危険が高く、(4)本研究の社会的な重要性が高い。

13) 行政機関個人情報保護法に基づく追記事項

13-1) 各班員の所属する施設で方法に記す研究対象者のデータを CD-R や USB メモリに登録する。

13-2) データの管理は解析用 PC1 台で行い、件数は最大 3000 例とする。

13-3) データの保存媒体の安全管理方法： アクセス制御と使用者認証によりシステムは管理し、専用のＰＣ端末の部屋には施錠による盗難防止

同じ調査を行っている循環器病研究委託費 20 公-2「カテーテルインターベンションの教育訓練システムの構築と有効性に関する研究」（主任研究者：坂井信幸 神戸市立医療センター中央市民病院脳神経外科部長）と登録データを共有し、神戸市立医療センター中央市民病院でも同様の安全管理を行う

13-4) 匿名化の方法およびそのタイミング： 匿名化は各班員の所属する施設からデータを登録する時点で行う。解析ソフトは患者名等個人情報を取得しない

13-5) 臨床情報も同じく匿名化し、国立循環器病センターでは豊田一則ないし古賀政利が、神戸市立医療センター中央病院では山上宏が管理する。

13-6) 利用目的を変更された場合は、再び掲示板などに公示する。