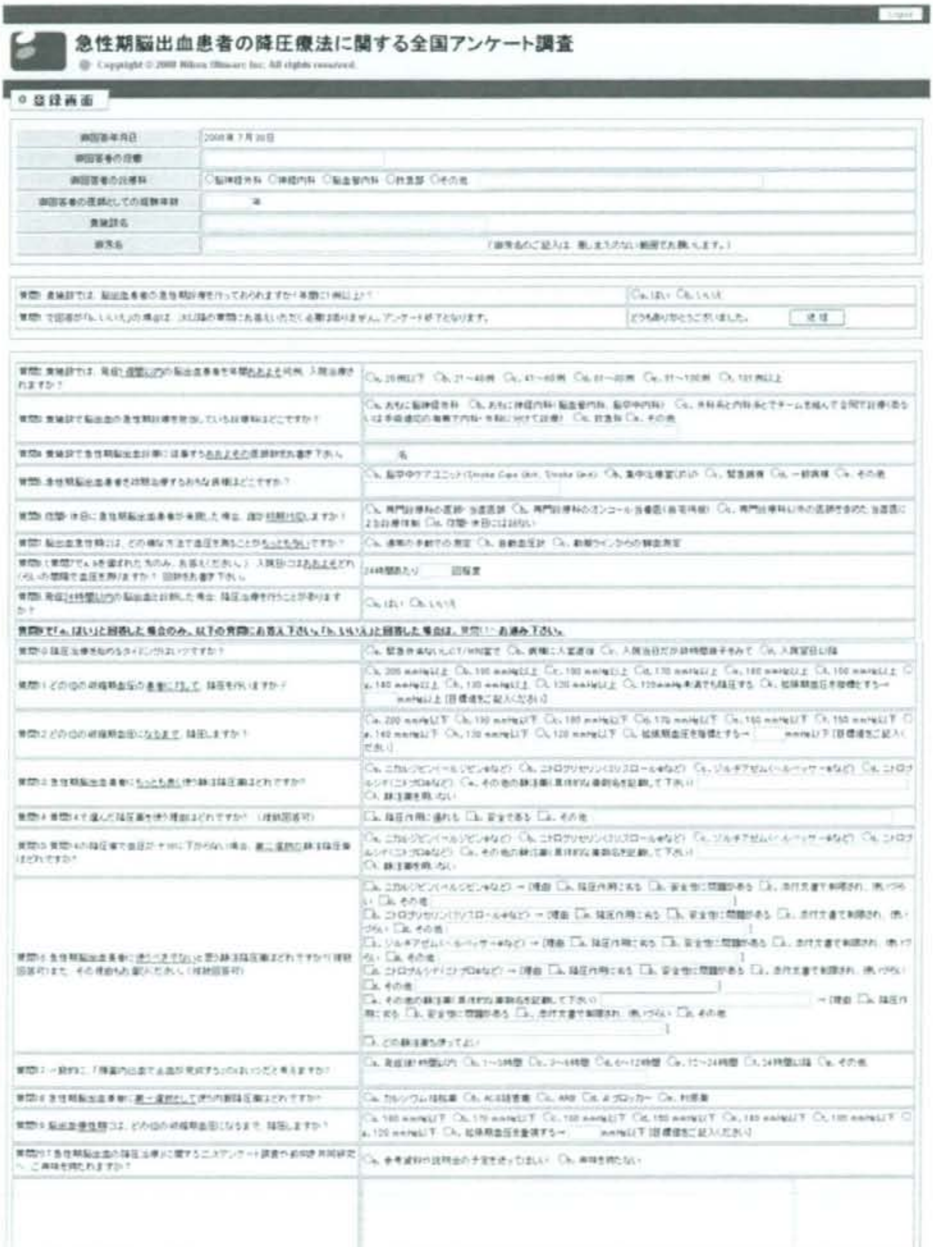
わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究 2：超急性期脳出血への降圧療法に関する研究」：
Web アンケート調査票



Hyperacute blood pressure lowering in intracerebral hemorrhage and early clinical outcome

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総括研究報告：資料 2-c

Sources of Fundings

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Conflicts of Interest

✓ None.

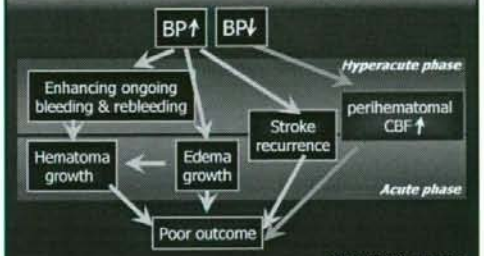
総括研究報告：資料 2-c

Background

- ✓ A high BP is associated with a poor outcome, partly due to hematoma expansion.
  - ✓ *Qureshi AI: N Engl J Med. 2001; Willmot M: Hypertension 2004*
- ✓ There is a consensus that an extremely high BP in acute ICH should be controlled.
- ✓ AHA/ASA guidelines advocates treating patients having SBP >=180 mmHg or DBP >=105 mmHg so as to maintain a modest BP reduction.
  - ✓ *Broderick JP: Stroke 2007*
- ✓ A run-in phase of INTERACT proved that intensive BP lowering to target SBP of 140 mmHg is well tolerated and seems to reduce hematoma growth. ATACH is also ongoing.
  - ✓ *Anderson CS: Lancet Neurol 2008; Qureshi AI: Neurocrit Care 2007*

総括研究報告：資料 2-c

High BP in Acute ICH



総括研究報告：資料 2-c

Objectives

✓ To determine which level of BP lowering within the initial 24 h of hospitalization contributed to a favorable early clinical outcome in hyperacute ICH patients

総括研究報告：資料 2-c

Patients

688 Japanese pts w/nontraumatic ICH
- ✓ Admitted within 24 h, Jan '99 – Oct '03

Inclusion:
- ✓ Initial SBP/DBP ≥180/105 mmHg
- ✓ IV antihypertensive therapy

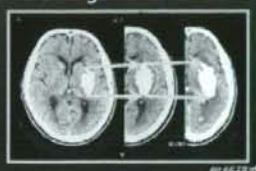
Exclusion:
- ✓ Fatal within 24 h
- ✓ Surgical hematoma evacuation
- ✓ Premorbid mRS ≥2
- ✓ Trauma, tumor, aneurysm, dural AVF, AVM

244 pts (140 men, 65±12 y)

総括研究報告：資料 2-c

Brain CT

- ✓On admission & 24-h F/U
- ✓Hematoma volume: ABC/2 method
- ✓Hematoma enlargement: Δvolume >40%



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Patient features

- ✓ Background characteristics
  - ✓age, sex, hypertension, diabetes, hyper- & hypocholesterolemia, smoking, alcohol, Prior stroke, heart disease, liver disease, prior antithrombotic therapy
- ✓ Admission blood glucose, APTT
- ✓ Onset-to-arrival time
- ✓ Admission NIHSS

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Blood Pressure

- ✓BP within 24 h (BP_{24h}) :
  mean of 3 BP values at 6, 12, & 24 h
- ✓ $\Delta BP = 100 - BP_{24h} \times 100/BP_{initial}$ (%)
- ✓IV antihypertensive agents
  - ✓Nicardipine, nitroglycerine, diltiazem

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Outcomes

- ✓Primary outcome:
  - ✓mRS 0-1 at 3 weeks
- ✓Secondary outcomes:
  - ✓Hematoma enlargement within 24 h
  - ✓Mortality at 3 weeks

総括研究報告：資料 2-c

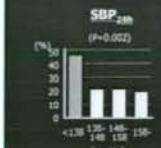
Results Patient characteristics

	mRS 0-1 (n=66)	mRS 2-6 (n=178)	*p* Value
Age, y	60.8+-10.6	66.0 +- 12.6	0.003
Alcohol, >2 drinks/d	16 (24%)	23 (13%)	0.032
Systolic BP, mmHg	194.0 +- 19.0	204.1 +- 23.2	0.002
Blood glucose, mg/dl	128.3 +- 49.6	154.6 +- 65.7	0.003
APTT, sec	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, median (range)	4 (0-17)	14 (1-36)	<0.001
Hematoma volume, ml	6.0 +- 6.3	19.9 +- 24.4	<0.001

総括研究報告：資料 2-c

BP lowering & primary outcome

mRS 0-1 at 3 weeks



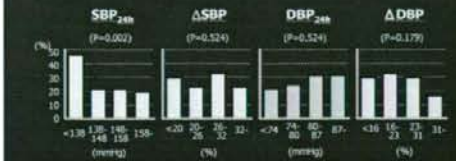
SBP_{24h}, mmHg	OR	95%CI	*P*
158 -	1.00	(reference)	
148 - 158	1.72	0.45-6.62	0.433
138 - 148	1.34	0.33-5.48	0.680
<138	**4.36**	**1.10-17.22**	**0.036**

adjusted for age, sex, glucose,O-to-A time, NIHSS score, hematoma volume

総括研究報告：資料 2-c

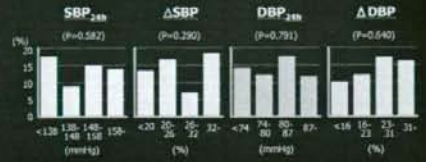
BP lowering & primary outcome

mRS 0-1 at 3 weeks



総括研究報告：資料 2-c

Nonsignificant association of BP lowering with Hematoma enlargement



総括研究報告：資料 2-c

Nonsignificant association of BP lowering with mortality at 3 weeks

総括研究報告：資料 2-c

Conclusion

- ✓ Lowering SBP to <138 mmHg during the initial 24 h appears to be predictive of favorable early functional outcome in ICH patients.
  - ✓ *Similar goal (140 mmHg) in INTERACT, ATACH*
  - ✓ *Cause or result?*
  - ✓ *Needs for a randomized prospective study*

総括研究報告：資料 2-c

The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage

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Objective Blood pressure lowering in acute intracerebral hemorrhage patients may prevent hematoma growth and neurological deterioration. The optimal goal of hyperacute antihypertensive therapy for intracerebral hemorrhage patients to obtain a favorable early clinical outcome was investigated.

Methods Of 688 consecutive patients who were admitted to our stroke care units within 24 h after intracerebral hemorrhage onset, 244 patients who emergently received intravenous antihypertensive therapy due to admission blood pressure at least 180/105 mmHg were assessed. The average systolic and diastolic blood pressure values 6, 12, and 24 h after admission and the percentage reduction of the blood pressure value with respect to the admission blood pressure value were used for analysis.

Results At 3 weeks, 66 patients (27%) had a completely independent activity level corresponding to a modified Rankin Scale score of 1 or less. After adjustment for baseline characteristics, a favorable functional outcome was more common in patients with the lowest quartile of average systolic blood pressure in the initial 24 h (<138 mmHg, odds ratio 4.36, 95% confidence interval 1.10–17.22), and was similarly common in those with the middle two quartiles (138–148 mmHg, 148–158 mmHg) than in those with the highest quartile of systolic blood pressure (≥158 mmHg). Analyses using patient quartiles on the basis of the average diastolic blood pressure or the reduction of systolic or diastolic blood pressure did not show an association with early outcome.

Conclusion Lowering the systolic blood pressure to less than 138 mmHg during the initial 24 h appears to be predictive of favorable early outcome in intracerebral hemorrhage patients. Randomized controlled trials to answer this question are needed. *J Hypertens* 26:2016–2021 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: antihypertensive therapy, blood pressure, hypertension, intracerebral hemorrhage, mortality, stroke outcome

Abbreviations: ADL, activity of daily living; APTT, activated partial thromboplastin time; ATACH, Antihypertensive Treatment in Acute Cerebral Hemorrhage; CBF, cerebral blood flow; ICH, intracerebral hemorrhage; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial; MBP, mean blood pressure; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale

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Introduction

An elevated blood pressure (BP) is common after intracerebral hemorrhage (ICH) [1–3]. Several studies have reported that a high BP is associated with a poor outcome, which is partly because of hematoma expansion [1–7]. Thus, there is a consensus that an extremely high BP in acute ICH should be controlled. Current guidelines recommend intravenous (i.v.) antihypertensive therapy for acute ICH patients who have elevated BP levels. The American Heart Association (AHA) [8,9] advocates treating patients having systolic blood pressure (SBP) at least180 mmHg, diastolic blood pressure (DBP) at least 105 mmHg, or mean blood pressure (MBP) at least 130 mmHg so as to maintain a target BP less than 180/105 mmHg. The International Society of Hypertension (ISH) [2] introduced the notion that BP more than 220/120 mmHg should be reduced by less than 20%. However, some studies involving a small number of patients recommended a lower target BP to prevent hematoma growth or neurological deterioration [10,11]. Recently, a run-in phase of Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) [12], involving 404 patients with hyperacute ICH, proved that intensive BP lowering to target SBP of 140 mmHg is well tolerated and seems to reduce hematoma growth. As other trials on acute BP management for ICH patients, Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) [13], Efficacy of Nitric Oxide in Stroke (ENOS) trial (ISRCTN99414122), and Scandinavian Candesartan Acute Stroke Trial (SCAST, ClinicalTrials.gov Identifier: NCT00120003) are ongoing.

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We previously reported that a very high BP affected ICH patients' outcomes [14]. Thus, we usually give antihypertensive therapy to patients with acute hypertension according to the above AHA criteria (≥180/105 mmHg) [8,9]. A recent prospective study [15] showed that i.v. nicardipine when given to ICH patients with acute hypertension had a high rate of tolerability. However, several issues remain to be elucidated, including: to which level the acute BP should be reduced, whether SBP or DBP is the optimal indicator for acute antihypertensive therapy, and whether the absolute BP value or the percentage reduction of the BP should be used as the indicator of good control. To resolve these issues, an observational study was done using the prospective databases of two stroke centers. The purpose of this study was to determine which level of BP lowering within the initial 24 h of hospitalization contributed to a positive early clinical outcome in hyperacute ICH patients.

Methods

A total of 688 consecutive Japanese patients with nontraumatic ICH who were admitted to stroke care units in the National Cardiovascular Center, Osaka, and the National Hospital Organization Kyushu Medical Center, Fukuoka, within 24 h after stroke onset were registered in our database from January 1999 through October 2003. Of these patients, consecutive patients who were given i.v. antihypertensive therapy for initial SBP (SBP_i) at least 180 mmHg, initial DBP (DBP_i) at least 105 mmHg, or initial MBP ($MBP_i = DBP_i$ + pulse pressure/3) at least 130 mmHg were enrolled in the study. In principle, all the ICH patients in our institutes who met the above criteria for initial BP were given antihypertensive therapy. Patients who died within the initial 24 h, those who underwent surgical hematoma evacuation, those who had a disability prior to ICH onset corresponding to a modified Rankin scale (mRS) score of at least 2, and those with secondary hemorrhages due to trauma, tumor, aneurysm, dural arteriovenous fistula, or arteriovenous malformation were excluded. The regional ethics and hospital management committees approved the study (#15–22, 30 September 2003). Written informed consent to participate in the study was obtained from the patient, or from a relative if patients could not give consent themselves.

In all patients, the ICH was verified on computed tomography (CT) immediately following admission and then again approximately 24 h later. The hematoma volume was measured using the ABC/2 method by neurologists blinded to the patient's clinical history [16]. Early hematoma enlargement was defined as an increase in hematoma volume by more than 40% from the admission CT to the 24-h CT [14,17,18].

Using the prospective database, the following background characteristics were investigated: age, gender, hypertension (BP ≥140/90 mmHg before stroke onset or taking regular antihypertensive drugs), diabetes mellitus (fasting blood glucose ≥126 mg/dl, random blood glucose ≥200 mg/dl, hemoglobin A1c ≥6.5%, or taking antidiabetic medication), hypercholesterolemia (serum total cholesterol ≥220 mg/dl or taking antihyperlipidemic drugs), hypocholesterolemia (serum total cholesterol <130 mg/dl on admission without taking antihyperlipidemic drugs), current or previous smoking habit, alcohol consumption at least two drinks per day, history of symptomatic stroke (ischemic or hemorrhagic), heart disease (including atrial fibrillation, valvular disease, cardiomyopathy, and ischemic heart disease), liver disease (liver cirrhosis or active hepatitis), and taking antithrombotic therapy (antiplatelets or anticoagulants) before stroke onset. On admission, the blood glucose level, the activated partial thromboplastin time (APTT), time interval between symptom onset and hospital arrival (onset-to-arrival time), and the severity of neurological deficits according to the National Institutes of Health Stroke Scale (NIHSS) were also recorded.

The BP within the initial 24 h (BP_{24h}) was defined as the mean of the three BP values obtained at 6, 12, and 24 h after admission. The reduction in BP_{24h} compared with BP_i (ΔBP) was calculated using the formula: $\Delta BP = 100 - BP_{24h} \times 100/BP_i$ (%). Each time, the BP was measured by a trained nurse using a mercury sphygmomanometer with the patient supine; the average of two consecutive measurements within an interval of 1–2 min, as well as additional measurements if the first two were quite different, was used for analyses [19]. In all patients, antihypertensive agents were given i.v. immediately after CT detection of the hematoma; nicardipine or nitroglycerine was primarily used, and diltiazem was added if needed. In general, the i.v. antihypertensive therapy was continued during the initial several days, and oral antihypertensive medication was given subsequently if needed.

The primary outcome was completely independent activity of daily living (ADL) at 3 weeks post-ICH, corresponding to an mRS score of 1 or less. The score was assessed by vascular neurologists in charge at the clinic or hospital with full physical examination. Secondary outcomes included hematoma enlargement within the first 24 h and mortality at 3 weeks post-ICH.

Statistical analysis was performed using the SPSS 11.0J statistical software package (SPSS Inc., Chicago, Illinois, USA). The clinical characteristics of the patients with and without having the above three outcomes were compared using Student's *t*-test, the chi-squared test, and Mann–Whitney's *U* test, as appropriate. To identify the relationship between BP_{24h} and the early outcomes, patients were divided into four groups according to the SBP_{24h}, ΔSBP, DBP_{24h}, and ΔDBP. Using the Cox proportional

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, (mmHg)	194.0 ± 19.0	204.1 ± 23.2	0.002
DBP, (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, (mmHg)	225.3 ± 29.3	200.1 ± 21.5	<0.001
DBP, (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, (mmHg)	203.8 ± 22.7	199.7 ± 21.3	0.318
DBP, (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

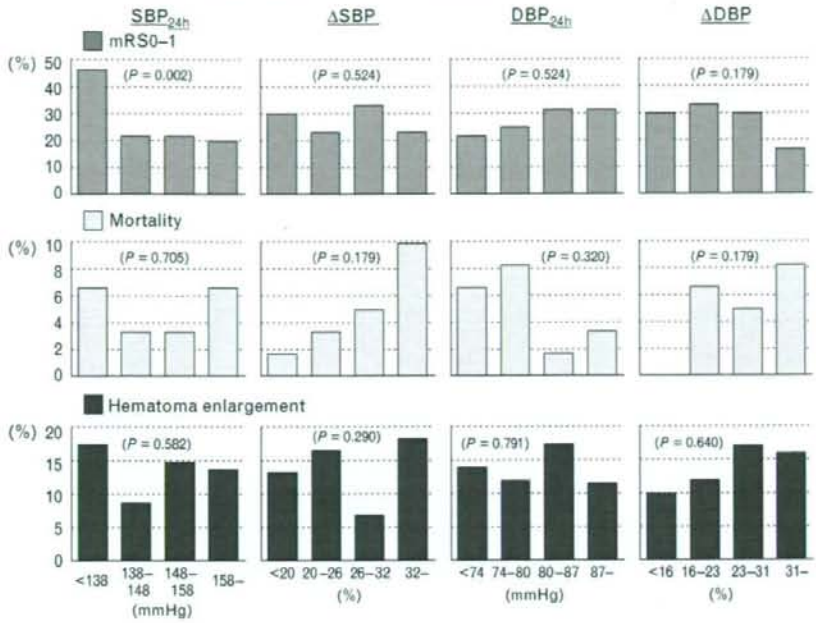
Overall, 244 patients (140 men, 65 ± 12 years old) were assessed; 229 (94%) had SBP_i at least 180 mmHg, 123 (50%) had DBP_i at least 105 mmHg, and 168 (69%) had MBP_i at least 130 mmHg. The median SBP_{24h} was 148 mmHg (interquartile range 138–158 mmHg), median ΔSBP was 26%, (20–32%), median DBP_{24h} 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} × 100/SBP_r; DBP_{24h}: the mean of the three DBP values at 6, 12, and 24 h; ΔDBP: 100 − DBP_{24h} × 100/DBP_r. 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} × 100/SBP_r; DBP_{24h}: the mean of the three DBP values at 6, 12, and 24 h; ΔDBP: 100 − DBP_{24h} × 100/DBP_r. 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 ≤ 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.

Acknowledgements

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There are no conflicts of interest.

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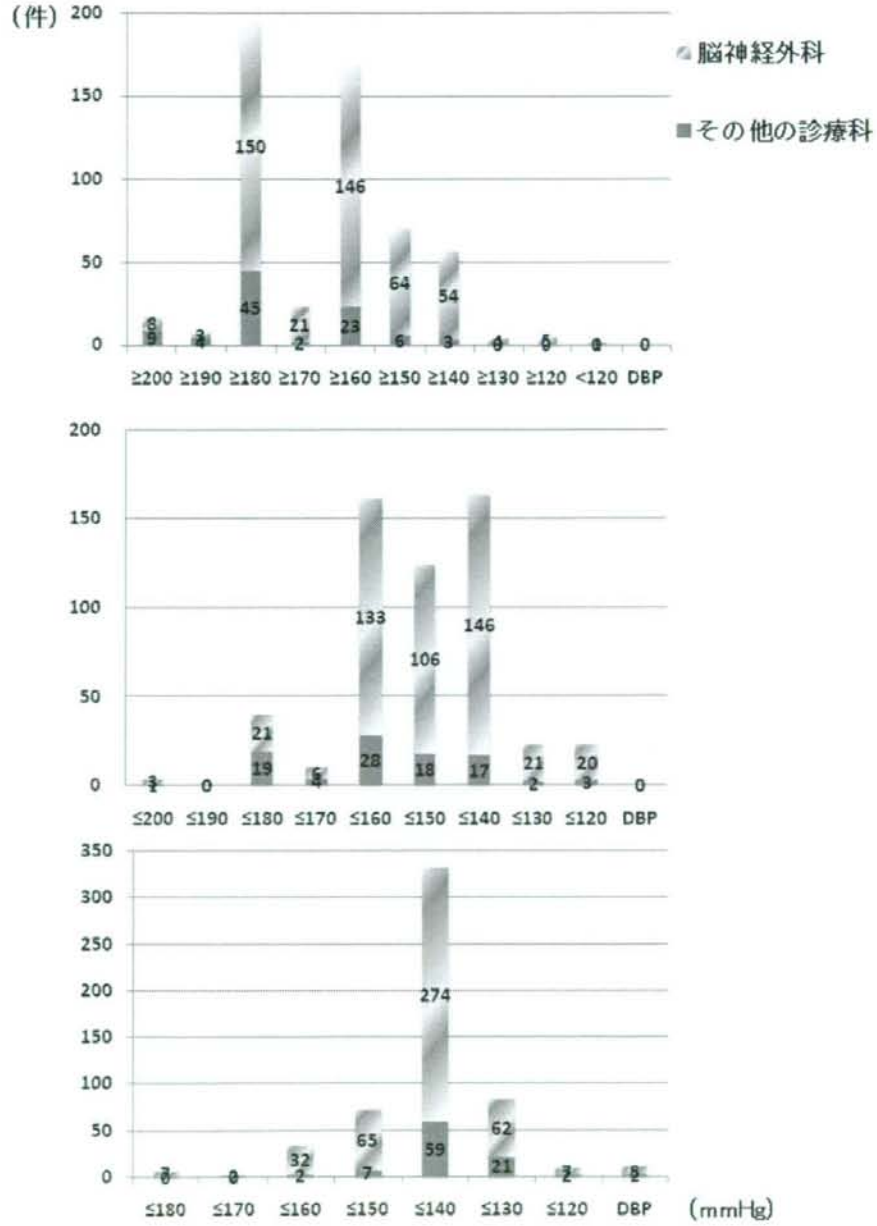
わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究2：超急性期脳出血への降圧療法に関する研究」：
Webアンケート調査成績

			回答数	%
診療科		脳神経外科	472	78.7
		神経内科	77	12.8
		脳血管内科	12	2.0
		救急部	3	0.5
		その他	36	6.0
経験年数	中央値（4分位値）		23(18-28)年	
質問1.	脳出血診療の有無	はい	550	91.7
		いいえ	50	8.3
質問2.	一年間の脳出血患者診療数	20例以下	88	16.0
		21-40例	118	21.5
		41-60例	113	20.5
		61-80例	85	15.5
		81-100例	63	11.5
		101例以上	83	15.1
質問3.	急性期脳出血の診療担当診療科	脳神経外科	437	79.5
		神経内科	44	8.0
		脳神経外科・神経内科ﾁｰﾑ	58	10.5
		救急科	2	0.4
		その他	9	1.6
質問4.	医師数、中央値（4分位値）		3(2-5)人	
質問5.	初期治療を行う病棟	Stroke (Care) Unit	70	12.7
		Intensive Care Unit	190	34.5
		緊急病棟	110	20.0
		一般病棟	153	27.8
		その他	27	4.9
質問6.	初期対応する医師	専門医師24/7	182	33.1
		専門医師オンコール	157	28.5
		他科を含む当直	206	37.5
		夜間・休日は診ない	5	0.9
質問7.	もっとも多い血圧測定方法	通常の手動での測定	71	12.9
		自動血圧計	447	81.3
		動脈ラインからの観血測定	32	5.8
質問8.	入院日24時間あたりの血圧測定回数、中央値（4分位値）		24(14-48)回	
質問9.	24時間以内の降圧を行うことがあるか	はい	548	99.6
		いいえ	2	0.4
質問10.	降圧治療を始めるタイミング	緊急外来ないしCT/MRI室	466	85.0
		病棟に入室直後	60	10.9
		入院当日だが様子みて	22	4.0
		入院翌日以降	0	0.0

			回答数	%
質問 11.	降圧を開始する収縮期血圧 (SBP)	200mmHg 以上	17	3.1
		190mmHg 以上	7	1.3
		180mmHg 以上	195	35.6
		170mmHg 以上	23	4.2
		160mmHg 以上	169	30.8
		150mmHg 以上	70	12.8
		140mmHg 以上	57	10.4
		130mmHg 以上	4	0.7
		120mmHg 以上	5	0.9
		120mmHg 未満でも降圧	1	0.2
		DBP を目標	0	0.0
質問 12.	降圧の目標とする SBP	200mmHg 以下	4	0.7
		190mmHg 以下	0	0.0
		180mmHg 以下	40	7.3
		170mmHg 以下	10	1.8
		160mmHg 以下	161	29.4
		150mmHg 以下	124	22.6
		140mmHg 以下	163	29.7
		130mmHg 以下	23	4.2
		120mmHg 以下	23	4.2
		DBP を目標	0	0.0
質問 13.	もっとも良く使う静注降圧薬	ニカルジピン	313	57.1
		ニトログリセリン	38	6.9
		ジルチアゼム	191	34.9
		ニトロプルシド	0	0.0
		その他	1	0.2
		静注薬なし	5	0.9
質問 14.	質問１３でニカルジピンを選んだ理由 （複数回答可）	降圧作用	301	96.2
		安全	85	27.2
		その他	20	6.4
	質問１３でニトログリセリンを選んだ理由 （複数回答可）	降圧作用	19	50.0
		安全	28	73.7
		その他	4	10.5
	質問１３でジルチアゼムを選んだ理由 （複数回答可）	降圧作用	72	37.7
		安全	95	49.7
		その他	70	36.6
	質問１３でニトロプルシドを選んだ理由 （複数回答可）	降圧作用	0	0
		安全	0	0
		その他	0	0
	質問 13 でその他を選んだ理由 (複数回答可)	降圧作用	1	100.0
		安全	0	0
		その他	0	0
	質問 13 で静注薬以外を選んだ理由	降圧作用	1	20.0
		安全	2	40.0
		その他	2	40.0
質問 15.	質問 13 の降圧薬で血圧が十分に下がらない場合の第二選択静注降圧薬	ニカルジピン	146	26.5
		ニトログリセリン	132	24.0
		ジルチアゼム	159	28.9
		ニトロプルシド	5	0.9
		その他	13	2.4
		静注薬なし	93	16.9

			回答数	%
質問 16.	使うべきでないと思う静注降圧薬 （複数回答可）	ニカルジピン	141	25.6
		ニトログリセリン	123	22.4
		ジルチアゼム	55	10.0
		ニトロプルシド	83	15.1
		その他	7	1.3
		どの静注薬もよい	266	48.4
	ニカルジピンを使うべきでない理由	降圧作用に劣る	0	0.0
		安全性に問題	14	9.9
		添付文書で制限	127	90.1
		その他	10	7.1
	ニトログリセリンを使うべきでない理由	降圧作用に劣る	30	24.4
		安全性に問題	23	18.7
		添付文書で制限	65	52.8
		その他	22	17.9
	ジルチアゼムを使うべきでない理由	降圧作用に劣る	16	29.1
		安全性に問題	19	34.5
		添付文書で制限	8	14.5
		その他	19	34.5
	ニトロプルシドを使うべきでない理由	降圧作用に劣る	10	12.0
		安全性に問題	18	21.7
		添付文書で制限	44	53.0
		その他	16	19.3
	その他を使うべきでない理由	降圧作用に劣る	0	0.0
		安全性に問題	3	42.9
		添付文書で制限	1	14.3
		その他	4	57.1
質問 17.	頭蓋内出血で止血が完成する時期	発症後 1 時間以内	48	8.7
		1-3 時間	74	13.5
		3-6 時間	156	28.4
		6-12 時間	121	22.0
		12-24 時間	90	16.4
		24 時間以降	47	8.5
		その他	14	2.5
質問 18.	内服降圧薬の第 1 選択	カルシウムブロッカー	360	65.5
		ACE 阻害薬	25	4.5
		ARB	165	30.0
		βブロッカー	0	0.0
		利尿薬	0	0.0
質問 19.	慢性期に目標とする SBP	180mmHg 以下	7	1.3
		170mmHg 以下	2	0.4
		160mmHg 以下	34	6.2
		150mmHg 以下	72	13.1
		140mmHg 以下	333	60.5
		130mmHg 以下	83	15.1
		120mmHg 以下	9	1.6
		DBP を目標	10	1.8
質問 20.	「急性期脳出血の降圧」に関する二次アンケート調査や前向き研究への興味	あり	414	75.3
		なし	123	22.4

上図：急性期脳出血症例の降圧開始の目安とする収縮期血圧　（設問11への回答）
中図：急性期脳出血症例の降圧目標とする収縮期血圧　（設問12への回答）
下図：慢性期脳出血症例の降圧目標とする収縮期血圧　（設問19への回答）



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」：
INTERACT および ATACH のパイロット試験成績の要旨

□Intensive blood pressure reduction in acute cerebral haemorrhage trial: INTERACT□

BACKGROUND: There is much uncertainty about the effects of early lowering of elevated blood pressure (BP) after acute intracerebral haemorrhage (ICH). Our aim was to assess the safety and efficiency of this treatment, as a run-in phase to a larger trial.

METHODS: Patients who had acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated systolic BP (150-220 mm Hg), and no definite indication or contraindication to treatment were randomly assigned to early intensive lowering of BP (target systolic BP 140 mm Hg; n=203) or standard guideline-based management of BP (target systolic BP 180 mm Hg; n=201). The primary efficacy endpoint was proportional change in haematoma volume at 24 h; secondary efficacy outcomes included other measurements of haematoma volume. Safety and clinical outcomes were assessed for up to 90 days. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00226096.

FINDINGS: Baseline characteristics of patients were similar between groups, but mean haematoma volumes were smaller in the guideline group (12.7 mL, SD 11.6) than in the intensive group (14.2 mL, SD 14.5). From randomisation to 1 h, mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg, 95% CI 8.9-17.6 mm Hg; p<0.0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg, 95% CI 7.7-13.9 mm Hg; p<0.0001). Mean proportional haematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%, 95% CI 0.6-44.5%; p=0.04) at 24 h. After adjustment for initial haematoma volume and time from onset to CT, median haematoma growth differed between the groups with p=0.06; the absolute difference in volume between groups was 1.7 mL (95% CI -0.5 to 3.9, p=0.13). Relative risk of haematoma growth >or=33% or >or=12.5 mL was 36% lower (95% CI 0-59%, p=0.05) in the intensive group than in the guideline group. The absolute risk reduction was 8% (95% CI -1.0 to 17%, p=0.05). Intensive BP-lowering treatment did not alter the risks of adverse events or secondary clinical outcomes at 90 days.

INTERPRETATION: Early intensive BP-lowering treatment is clinically feasible, well tolerated, and seems to reduce haematoma growth in ICH. A large randomised trial is needed to define the effects on clinical outcomes across a broad range of patients with ICH.

FUNDING: National Health and Medical Research Council of Australia.

出典：
Anderson CS, et al: Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008 May;7(5):391-9.

□Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Trial:□

Introduction: This study evolved from numerous case series evaluating the treatment of acute hypertension in patients with intracerebral hemorrhage (ICH). We report the results of a three-year multicenter open-labeled pilot trial funded by the National Institutes of Neurological Diseases and Stroke.

Objective: To determine the tolerability and safety of three escalating levels of antihypertensive treatment goals for acute hypertension in subjects with supratentorial ICH within 6 hours after symptom onset.

Methods: The trial was designed as a traditional dose escalation trial recruiting 18–22 patients with ICH for each of the pre-specified three treatment targets. Nicardipine was infused to maintain systolic blood pressure (SBP) in one of three tiers (170–200 mm Hg, 140–170 mm Hg, or 110–140 mm Hg) for 24 hours after onset of symptoms. Treatment success was measured by achieving and maintaining the SBP within goals. Safety outcomes were the rate of neurological deterioration during treatment, and the rate of serious adverse events related to nicardipine. Safety stopping rules were pre-specified and were overseen by an external Data Safety and Monitoring Board.

Results: A total of 60 patients were recruited (aged 62±15.1 years; 56.7% were men) with 18, 20, and 22 patients recruited in each of the tiers of blood pressure reduction of increasing intensity. The mean time interval between symptom onset and presentation to the hospital was 1.8±1.4 hours and mean time to initiation of study treatment was 4.2±1.7 hours. Primary treatment failure was observed in 6 of 60 patients, all in the last tier. A total of 3 secondary treatment failures were observed, all in the third tier. Overall, a total of 9 of 60 patients had primary or secondary treatment failures. The safety stopping rule was not activated in any of the tiers. Seven neurological deteriorations were observed: 1, 2, and 4 in the first, second, and third tier, respectively. These were related to hematoma expansion (n=6) and hydrocephalus (n=1). The three month mortality ranged from 10% to 22% between the tiers. The age, initial GCS score, hematoma volume and intraventricular extension adjusted mortality did not differ between the three tiers. The age, initial GCS score, hematoma volume and intraventricular extension adjusted three month favorable outcome did not differ between the three tiers.

Conclusions: Aggressive SBP reduction to 110–140 mm Hg in the first 24 hours using intravenous nicardipine was well tolerated with a low risk of hematoma expansion, neurological deterioration and in-hospital mortality. The results favor pharmacological reduction of SBP in patients with acute ICH.

出典：

Qureshi AI, et al: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Trial: Final Results. Stroke 2009, on web, abstract of International Stroke Conference 2009

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」：
ATACH2 試験計画の要旨

研究デザイン：
第三相多施設共同非盲検無作為化並行二群間比較試験

作業仮説：
発症 3 時間以内の脳出血患者にニカルジピン静注で収縮期血圧（SBP）≤140 mmHg に積極的に降圧すると、SBP ≤180 mmHg の標準的降圧に比べて 3 か月後の死亡または機能障害が 10%以上減る。

主要評価項目：
3 か月後の modified Rankin Scale 4-6

副次評価項目：
1. EuroQol での 3M 後の生活の質の比較
2. 血腫拡大　(>33%)
3. 72h 以内の SAE

予定症例数：
1280 例

参加予定施設：
約 80

研究期間：
5 年間　（登録：4 年間）

患者登録基準：
1. 18y 以上
2. 発症後 2.5 時間以内で割りつけ、3 時間以内で治療開始
3. 脳卒中に該当する症状、かつ CT での血腫同定
4. GCS ≥5
5. 血腫量 <60 cc
6. 天幕上の脳出血
7. 入院時 SBP >180 mmHg

おもな除外基準：
1. 腫瘍・AVM・瘤の既往
2. 外傷性出血
3. 広範な脳室内出血
4. 30 日以内の妊娠・授乳・分娩
5. 出血素因・coagulopathy
6. INR≥1.7
7. 血小板数 <50,000/mm3

患者割り付け：
標準降圧群：積極降圧群 = 1：1

降圧方法：
1. 標準降圧群：　SBP 140-180 mmHg
2. 積極降圧群：　SBP 110-140 mmHg
3. 第一選択薬：　ニカルジピン静注
4. 第二選択薬：　ラベタロール静注

フォローアップ：
1か月後に電話インタビュー
3か月後に診察

統計解析：
generalized linear model w/ log link function, 登録時の重症度(GCS of 5-8, 9-12, or 13-15; 血腫量≤30 ml or >30 ml; IVHの有無)で補正

研究費：
NIHに申請中

標準降圧群の降圧方法：

- ✓ ニカルジピン静注5 mg/hで開始
- ✓ 15分後にSBP≥180 mmHgならば 2.5 mg/hずつ増量
- ✓ 15分毎の増量を、最大15 mg/hまで続ける
- ✓ <180 mmHgに達したら以後1～2.5 mg/hずつ微調整
- ✓ ニカルジピン静注 15 mg/hで≥180 mmHgが30分続けば、ラベタロール静注5-20 mg bolus 毎15分を続ける。
- ✓ <140 mmHg: ニカルジピン静注を15分毎に2.5 mg/hずつ減らす。

積極降圧群の降圧方法：

- ✓ ニカルジピン静注5 mg/hで開始
- ✓ 15分後にSBP≥140 mmHgならば 2.5 mg/hずつ増量
- ✓ 15分毎の増量を、最大15 mg/hまで続ける
- ✓ <140 mmHgに達したら以後1～2.5 mg/hずつ微調整
- ✓ ニカルジピン静注 15 mg/hで≥140 mmHgが30分続けば、ラベタロール静注5-20 mg bolus 毎15分を続ける。
- ✓ <110 mmHg: ニカルジピン静注を中止する。

その他の資料

3. 第1回班会議　(2008年5月15日、横浜)　プログラム　議事録
4. 第2回班会議　(2008年8月8日、豊中)　プログラム　議事録
5. 第3回班会議　(2008年11月5日、東京)　プログラム　議事録
6. 第4回班会議　(2009年2月27日、豊中)　プログラム　議事録
7. 第1回国際超音波線溶療法カンファレンス参加報告書
8. 第10回血栓溶解と急性期脳卒中治療に関する国際シンポジウム参加報告書

平成20年度厚生労働科学研究(循環器疾患等生活習慣病対策総合研究事業)

「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」

[H20 - 循環器等(生習) - 一般 - 019、主任研究者 豊田 一則]

平成 20 年度 第 1 回班会議(キックオフミーティング)

日時 2008/5/15(木曜)、5/16(金曜) 12:00～

(11:30 より昼食を準備しています)

場所 パシフィコ横浜会議センター 2 階 211 会議室

議事次第

1. 挨拶および研究班の概要について

   主任研究者　国立循環器病センター内科脳血管部門 医長　豊田 一則

   厚生労働省健康局 生活習慣病対策室 室長補佐　渡 路子

   研究者紹介

2. 後ろ向き共同研究の内容

   『rt-PA 静注療法施行患者への急性期危険因子管理・後続抗血栓療法の実態と治療成績との関連』

3. 前向き共同研究に関する意見交換

4. 事務連絡

   - 平成 20 年度の予定
     - ✓ 5 月　キックオフミーティング(第 1 回班会議)
     - ✓ 5 月頃　補助金の受領
     - ✓ 6 月　後ろ向き共同研究計画書・申請書の作成、倫理委員会等申請手続きの開始
     - ✓ 8～9 月　第 2 回班会議:後ろ向き共同研究の進行状況確認、前向き共同研究の内容に関する検討
     - ✓ 10 月　前向き共同研究計画書・申請書の作成、倫理委員会等申請手続きの開始
     - ✓ 1 月　後ろ向き共同研究のデータ提出
     - ✓ 1 月　継続申請に係る研究計画書の作成・提出
     - ✓ 1～2 月　第 3 回班会議:後ろ向き共同研究集計結果の報告、前向き共同研究の進行状況確認
     - ✓ 2 月　中間評価委員会
     - ✓ 4 月　事業実績報告書および研究報告書の作成・提出
   - 厚生労働科学研究費事務処理について