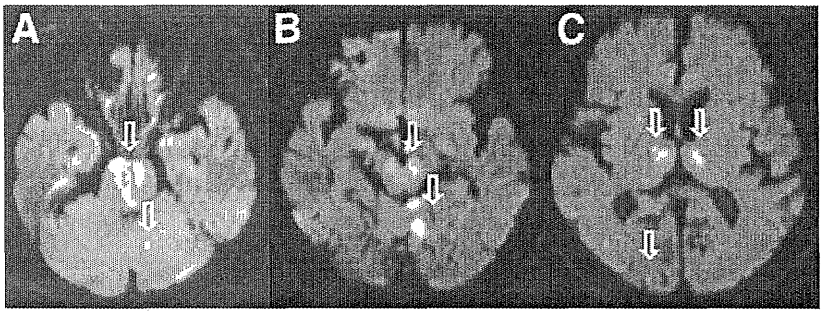

Figure 1. *Example of a patient with basilar artery occlusion with diffusion-weighted imaging revealing early ischemic changes in the pons (arrow; 2 points; A), left cerebellum (arrow; 1 point; A and B), midbrain (arrow; 2 points), right posterior lobe (arrow; 1 point; C), and bilateral thalamus (2 arrows; 1 + 1 = 2 points; C) infarction. The posterior circulation Acute Stroke Prognosis Early Computed Tomography Score on diffusion-weighted imaging was 2.*

Org 10172 in Acute Stroke Treatment (TOAST) classification.[26]

Outcomes included the following: (1) early neurologic improvement (ENI; a reduction of ≥8 points from the baseline NIHSS score or a score of 0)[27,28]; (2) early neurologic deterioration (END; an increase of ≥4 points from the baseline NIHSS score) within the initial 24 hours[29,30]; (3) intracranial hemorrhage (ICH; a computed tomography–proven hematoma); (4) symptomatic ICH (sICH; ICH with an increase of ≥4 points from the baseline NIHSS score) within 36 hours; (5) independence (modified Rankin scale [mRS] score ≤2); and (6) death at 3 months.

One control group consisted of patients in the SAMURAI rt-PA Registry who were diagnosed as having occlusion of the trunk of the middle cerebral artery (MCA) or its branches on the MRA conducted at admission (before rt-PA infusion). Another control group consisted of stroke patients with BAO who were treated with higher-dose IV rt-PA (0.9 mg/kg alteplase) in the Basilar Artery International Cooperation Study (BASICS) and the Helsinki Stroke Thrombolysis Registry (HSTR).[31,32]

Statistical analysis was performed using JMP software (version 9.0; SAS, Inc, Cary, NC). Baseline characteristics, stroke features, and clinical outcomes were compared between patients with BAO and those with MCA occlusion (MCO), between BAO patients with initial pc-ASPECTS being more than the median value and those with pc-ASPECTS being the median value or less, and between BAO patients with and without recanalization of the BA. These comparisons were performed using the Fisher, unpaired *t*, and Wilcoxon tests as appropriate. Outcomes were also compared after multivariate adjustment for sex, age, and the initial NIHSS score (quartile). All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Among the 600 consecutive patients in the SAMURAI rt-PA Registry, 44 (7.3%) had occlusion at the vertebrobasilar or posterior cerebral artery; of these, 25 patients (4.2%; 8 women ranging from 32-92 years of age) had BAO. BAO was identified on MRA in 18 patients, on CTA in 3 patients, and on ultrasonography in 4 patients. A group of 267 patients with MCO was used as controls. Table 1 shows baseline characteristics and stroke features of BAO patients and MCO patients. Baseline NIHSS scores were higher in BAO patients than in MCO patients ($P = .033$). The most common stroke subtype was cardioembolic in both patient groups.

Table 2 shows individual data regarding imaging findings and outcomes in BAO patients. Of 20 patients undergoing pretreatment DWI (patients 1-20), acute ischemic change was present in the pons or medulla in 11 (55%), in the midbrain in 10 (50%), in the cerebellum in 10 (50%), in the thalamus in 8 (40%), and in the posterior lobe in 2 (10%) patients. The median pc-ASPECTS score was 7 (interquartile range [IQR] 5-8). Eighteen of 23 patients who underwent follow-up MRA (22 patients) or DSA (1 patient) during acute hospitalization had partial or complete recanalization. Of these, 9 patients were

Table 1. *Baseline characteristics and stroke features*

	Basilar artery occlusion	Middle cerebral artery occlusion
No. of patients	25	267
Women, n (%)	8 (32)	107 (40)
Age, y, median (IQR)	74 (62.5-81)	74 (67-79)
Risk factors and comorbidities, n (%)		
Hypertension	16 (64)	160 (60)
Diabetes mellitus	5 (20)	38 (14)
Dyslipidemia	5 (20)	52 (19)
Previous ischemic stroke	2 (8)	42 (16)
Baseline NIHSS score, median (IQR)	16 (9-30.5)	14 (9-19)*
Onset to treatment time, min, median (IQR)	150 (133-159)	139 (120-161)
Stroke subtype, n (%)		
Cardioembolic stroke	15 (60)	204 (76)
Large artery atherosclerosis	4 (16)	26 (10)
Small artery occlusion	0	3 (1)
Other	6 (24)	34 (13)

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

*$P < .05$ versus basilar artery occlusion.

Table 2. *Imaging findings and outcomes in patients with basilar artery occlusion*

Case no.	Sex	Age, y	Baseline NIHSS	Early ischemic changes					pc-ASPECTS*	Recanalization of basilar artery†	Outcomes			
				Pons or medulla	Midbrain	Cerebellum	Thalamus	Posterior lobe			ENI	END	ICH	3M-mRS
1	M	64	9						10	+, <36 hrs		+	+	4
2	F	87	39						10	+, <36 hrs				5
3	M	81	9				+		9	+, at day 8				2
4	M	67	15	+					8	+, <36 hrs	+			0
5	F	76	30			+	+		8	+, at day 7	+			1
6	M	63	5	+					8	+, <36 hrs		+	+‡	2
7	F	69	23		+				8	–, <36 hrs	+			3
8	M	78	16		+				8	–, <36 hrs		+		5
9	M	62	20	+		+			7	+, at day 3	+			1
10	M	32	8	+		+			7	+, <36 hrs				2
11	F	92	12	+		+			7	+, <36 hrs	+			4
12	F	81	39		+		++		6	+, at day 12	+			2
13	M	87	19	+	+				6	+, at day 2	+			4
14	F	62	27		+	+	++		5	+, <36 hrs	+			1
15	M	76	27	+	+		+		5	+, at day 6	+			2
16	F	88	35		+	++	+		5	+, at day 13	+			4
17	M	87	31	+	+	++			4	+, at day 6	+		+	4
18	M	69	8	+		+	++	+	4	–, <36 hrs		+	+‡	5
19	M	71	4	+	+	++			4	–, at day 30		+		5
20	M	77	34	+	+	++	++	++	0	+, <36 hrs	+			5
21	M	60	13	*Pons and/or midbrain, bilateral cerebellum*				–		+, <36 hrs				4
22	M	75	9	*Pons and/or midbrain*				–		Untested		+	+	4
23	M	42	14	*Pons, bilateral cerebellum*				–		+, at day 18	+			0
24	M	74	37	*Pons, bilateral cerebellum, bilateral thalamus*				–		Untested				6
25	F	33	15	*Unidentified*				–		–, <36 hrs	+			1

Abbreviations: ++, positive early ischemic changes in bilateral regions; 3M-mRS, modified Rankin Scale score at 3 months; END, early neurologic deterioration; ENI, early neurologic improvement; F, female; ICH, intracranial hemorrhage; M, male; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early Computed Tomography Score.

For 5 patients who did not undergo pretreatment magentic resonance imaging scans (cases 21-25), distribution of outcome infarcts are listed in italics.

*Diffusion-weighted magnetic resonance imaging was used to assess pc-ASPECTS in this study.

†+and – indicate the presence or absence of recanalization at the described timing of angiography.

‡Symptomatic ICH.

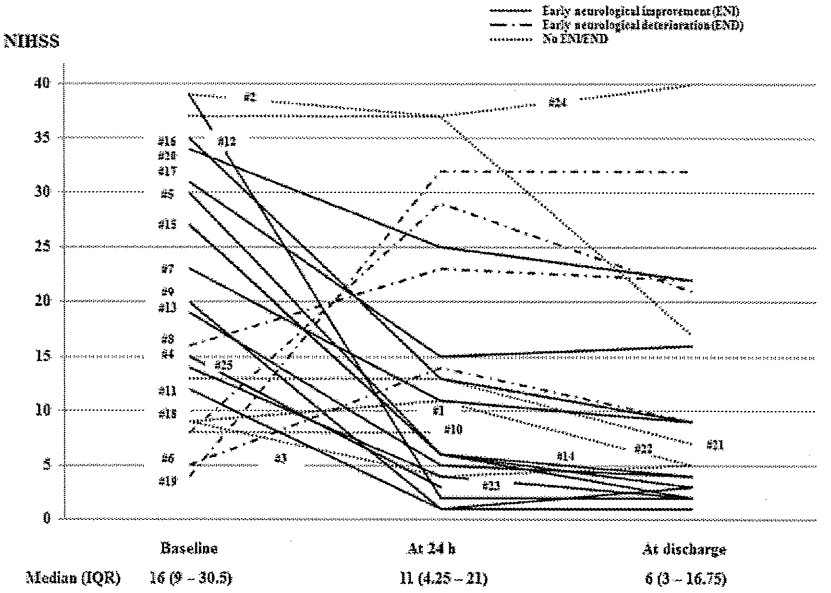

Figure 2. *Changes in the National Institutes of Health Stroke Scale score in patients with basilar artery occlusion.*

diagnosed with recanalization within 36 hours of rt-PA therapy.

The changes in NIHSS scores in 25 BAO patients are shown in Figure 2. Fourteen patients (64%) had ENI and 4 (16%) had END within the initial 24 hours. Outcomes are summarized in Table 3. Within the initial 36 hours, 5 (20%) of 25 BAO patients developed ICH, including 2 (8%) with sICH. At 3 months, 11 (44%) showed independence and 1 (4%) had died. When 2 patients with premorbid mRS scores ≥3 were excluded, independence was achieved in 11 of 23 patients (48%). After multivariate adjustment, ENI was more common (odds ratio [OR] 2.50; 95% confidence interval [CI] 1.06-5.97), and END tended to be more common (OR 3.13; 95% CI 0.81-10.25) in BAO patients than in MCO patients.

Table 4 shows the relationship between imaging findings and outcomes in BAO patients. Low pc-ASPECTS tended to be associated with ENI ($P = .092$). The identification of BAO recanalization was inversely associated with END ($P = .029$).

Finally, outcomes of the present BAO patients were compared with those in the BASICS[31] and HSTR[32] (Fig 3). Baseline characteristics of patients in those studies are listed in Table 5. Independence was relatively more frequent (44%, 34%, and 26%, respectively), mortality was relatively less frequent (4%, 34%, and 41%, respectively), and sICH was similarly frequent (8%, 6%, and 16%, respectively) in the present study when compared with the other 2 studies. Recanalization of the BA was identified in 67% of patients in the BASICS and in 60% of patients in the HSTR at a median of 1 day after thrombolysis when compared with 78% in our study.

Discussion

This study investigated the effect of low-dose alteplase for acute ischemic stroke associated with BAO. We found that 56% of the patients had neurologic improvement, 16% had neurologic deterioration, 8% developed sICH early after the therapy, and 44% achieved independence

Table 3. *Clinical outcomes*

	BAO (n = 25)	MCO (n = 267)	OR (95% CI)	*P* value
Early neurologic improvement, n (%)	14 (56)	78 (31)	2.50 (1.06-5.97)	.036
Early neurologic deterioration, n (%)	4 (16)	18 (7)	3.13 (0.81-10.25)	.093
ICH, n (%)	5 (20)	62 (23)	0.71 (0.23-1.86)	.501
Symptomatic ICH, n (%)	2 (8)	12 (5)	2.27 (0.32-10.01)	.360
Independence at 3 months, n (%)*	11 (48)	130 (52)	0.95 (0.35-2.56)	.913
Death at 3 months, n (%)	1 (4)	15 (6)	0.57 (0.03-3.16)	.571

Abbreviations: BAO, basilar artery occlusion; CI, confidence interval; ICH, intracranial hemorrhage; MCO, middle cerebral artery occlusion; OR, odds ratio.

Multivariate-adjusted by sex, age, and the baseline National Institutes of Health Stroke Scale score (quartile).

*Assessed for 23 BAO patients and 248 MCO patients with premorbid modified Rankin Scale score ≤2.

Table 4. *Relationship between imaging findings and outcomes in patients with basilar artery occlusion*

	pc-ASPECTS (n = 20)		Recanalization (n = 23)	
	>7 (median value)	≤7	Present	Absent
Patient no.	8	12	18	5
Women, n (%)	3 (38)	4 (33)	6 (33)	2 (40)
Age, y, median (range)	72.5 (64.8-80.3)	76.5 (63.8-87)	76 (32-92)	69 (33-78)
Initial NIHSS score, median (range)	15.5 (9-28.3)	23.5 (9-33.3)	19.5 (5-39)	15 (4-23)
ENI, n (%)	3 (38)	9 (75)*	12 (67)	1 (20)
END, n (%)	3 (38)	2 (17)	2 (11)	3 (60)†
ICH, n (%)	2 (25)	2 (17)	3 (17)	1 (20)
Symptomatic ICH, n (%)	1 (13)	1 (8)	1 (6)	1 (20)
Independency at 3 months, n (%)‡	4 (50)	5 (42)	10 (59)	1 (25)
Death at 3 months, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: END, early neurologic deterioration; ENI, early neurologic improvement; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early Computed Tomography Score.

Multivariate analysis cannot be assessed because of the small number of patients.

*$.05 < P < .1$ versus ">7."

†$P < .05$ versus "present."

‡Assessed for 23 basilar artery occlusion patients with a premorbid modified Rankin Scale score ≤2.

at 3 months. Because the present registry did not have untreated controls, results were compared with those from patients with MCO from this registry who underwent thrombolysis and with those from patients with BAO in previous European studies (the BASICS[31] and HSTR[32] studies).

When compared with patients in the BASICS[31] and HSTR[32] studies, patients from the present study had relatively lower initial NIHSS scores, relatively shorter onset to treatment times, and a relatively higher frequency of cardioembolism (Table 5). Such differences in baseline conditions among studies may account for the higher percentages of BA recanalization and 3-month independence in the present study relative to those in the other studies. Studies of endovascular therapy indicate that early initiation of thrombolysis is associated with a higher percentage of BA recanalization.[7,8] Embolic BAO often occurs at the distal segment of the BA, typically at the top of the BA,[33,34] and distal BAO is more easily recanalized than proximal BAO.[5-8,10,11,32] In contrast, residual BA stenoses are often identified after thrombolysis in atherothrombotic patients, which is associated with an increased risk of recurrence of BAO.[35,36] IV rt-PA plus continuous sonothrombolysis with microbubbles is a promising strategy for early recanalization of BAO[37]; because it uses a transforaminal window, this strategy can be implemented in Asian patients who tend to have poor temporal bone windows.

Of note, mortality was much lower in our cohort than in previous cohorts. Low-dose alteplase was associated with a relatively lower incidence of sICH (8%), which may account for the improved mortality. In general, mortality after rt-PA was low, but patients with severe functional damage were relatively frequent in the Japanese population,[13,14,27] presumably because of the philosophy of maintaining intensive therapy even for terminal patients in Japan. Low-dose rt-PA for Japanese patients was associated with similar or somewhat better chronic outcomes when compared with regular-dose rt-PA for Western patients.

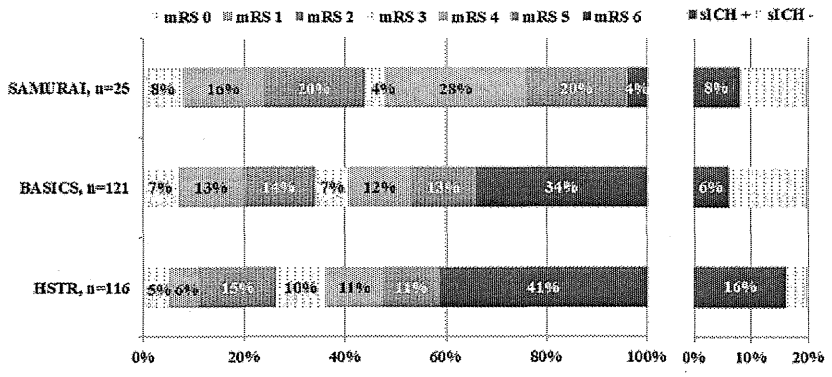

Figure 3. *Distribution of modified Rankin Scale (mRS) score at 3 months (left) and symptomatic intracranial hemorrhage (sICH) at 36 hours after intravenous recombinant tissue plasminogen activator (right). Abbreviations: BASICS, Basilar Artery International Cooperation Study; HSTR, Helsinki Stroke Thrombolysis Registry; SAMURAI, Stroke Acute Management with Urgent Risk factor Assessment and Improvement recombinant tissue plasminogen activator registry.*

Table 5. *Comparison of patient characteristics among 3 studies*

	SAMURAI (N = 25)	BASICS (N = 121)	HSTR (N = 116)
Design	Multicenter	Multicenter	Single-center
Region	Japan	International	Finland
Period	2005-2008	2002-2007	1995-2008
Pretreatment vascular examination	MRA, DSA, and US	MRA, CTA, and DSA	MRA, CTA, and DSA
Definition of symptomatic intracranial hemorrhage	≥4-point increase from the baseline NIHSS score within 36 hours	Each investigators judgment	ECASS II definition
Baseline NIHSS score, median (IQR)	16 (9-30.5)	21 (12-28)	23 (18)
Thrombolysis	IVT 0.6 mg/kg alteplase	IVT (0.9 mg/kg alteplase), including subsequent IAT (n = 41)	IVT (0.9 mg/kg alteplase) 94%, IAT 6%
Onset to treatment	<3 hrs for all	<3 hrs for 55%; >9 hrs for 12%	Median 8.7 hours
Recanalization	78%	67%	65%
Subtype or mechanism	CES 60%, ATBI 16%	Embolic 40%, atherosclerotic 31%	CES 26%, ATBI 33%

Abbreviations: ATBI, atherothrombotic brain infarction; BASICS, Basilar Artery International Cooperation Study; CES, cardioembolic stroke; CTA, computed tomography angiography; DSA, digital subtraction angiography; ECASS-II, European Co-operative Acute Stroke Study-II; HSTR, Helsinki Stroke Thrombolysis Registry; IAT, intra-arterial therapy; IVT, intravenous thrombolysis; SAMURAI, Stroke Acute Management with Urgent Risk factor Assessment and Improvement recombinant tissue plasminogen activator registry; US, carotid duplex ultrasonography.

In a study that compared early outcomes after IV rt-PA in BAO and MCO patients, median NIHSS score at 7 days or at discharge was higher in BAO patients than in MCO patients (14 *v* 6), although the baseline NIHSS score was also higher in BAO patients (23 *v* 17).[38] The present study was the first comparison of long-term outcomes in BAO and MCO patients. In our registry, approximately half of patients achieved independence at 3 months in both the BAO and the MCO groups. In addition, ENI was identified in more than half of BAO patients and was more common than in MCO patients, although END was also marginally more common in BAO patients than in MCO patients. Consciousness and language ability comprise a significant portion of the NIHSS score, and prompt recovery and fluctuation of consciousness after rt-PA result in ENI/END. Alteration of consciousness was actually more common as an initial symptom in BAO patients than in MCO patients (75% *v* 39%; $P < .001$, data not shown). These data indicate that low-dose rt-PA is similarly effective in BAO and MCO patients in a Japanese population.

Practical quantitative scoring of early ischemic change in the posterior circulation is required to determine the association between ischemic changes and clinical outcomes. Originally, pc-ASPECTS for BAO patients was assessed using CT angiography source images (CTA-SI).[24,25] DWI is considered the diagnostic standard in patients with posterior circulation stroke.[39] When compared to CTA-SI, DWI does not need contrast medium and could detect small ischemic lesions, which was proposed to identify patients with BAO who potentially benefit from thrombolysis.[40,41] DWI was therefore used to assess pc-ASPECTS in this study. In contrast to previous studies, this study failed to show a positive relationship between pc-ASPECTS on DWI and outcomes,[24,25] possibly because of the small number of patients and the differences between CTA-SI and DWI. Although CTA-SI demarcates irreversible infarct, DWI was sensitive to susceptibility gradient and could cause susceptibility artifact especially in the base of brain. In addition, because pc-ASPECTS is semiquantitative, a subtle or patchy ischemic change and extended change in the whole region of interest are equally evaluated. Recently, another DWI-based score was proposed for the BAO patients.[42,43]

This study has several limitations. First, this was a multicenter retrospective study including a relatively small patient cohort, which could cause statistical bias. Second, data were not available from BAO patients who did not receive thrombolysis in the present registry. Third, the timing of follow-up angiography to assess for the presence of recanalization was not uniform. Fourth, using the same cutoff score of the difference between NIHSS for ENI and END between BAO patients and MCO patients might not be appropriate, because we previously reported that the NIHSS score appears to have limitations with respect to its use when comparing the neurologic severity of posterior circulation stroke and anterior circulation stroke.[44]

In conclusion, the use of low-dose alteplase therapy resulted in similar outcomes when comparing acute BAO and MCO patients and was associated with relatively better outcomes in BAO patients in the present study when compared with previous studies of BAO patients. Although BAO can be devastating disease, the early

initiation of intravenous rt-PA can improve outcomes in patients with acute BAO.

Acknowledgment: Dr. Koga received research support from the Japan Cardiovascular Research Foundation (Bayer Scholarship for Cardiovascular Research). Dr. Nakagawara received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Dr. Okada received an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. Dr. Minematsu received research support from the Ministry of Health, Labor and Welfare, Japan and received research grants for Cardiovascular Diseases, Grants-in-Aid, the Foundation for Biomedical Research and Innovation, the Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc, and the Hitachi Medical Corporation. Dr. Toyoda received research support from Grants-in-Aid from the Ministry of Health, Labor and Welfare, Japan and from the Mitsubishi-Tanabe Pharma Corporation.

References

1. Mattle HP, Arnold M, Lindsberg PJ, et al. Basilar artery occlusion. Lancet Neurol 2011;10:1002-1014.
2. Hacke W, Zeumer H, Ferbert A, et al. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. Stroke 1988;19: 1216-1222.
3. Brandt T, von Kummer R, Muller-Kuppers M, et al. Thrombolytic therapy of acute basilar artery occlusion: Variables affecting recanalization and outcome. Stroke 1996;27:875-881.
4. Levy EI, Firlik AD, Wisniewski S, et al. Factors affecting survival rates for acute vertebrobasilar artery occlusions treated with intra-arterial thrombolytic therapy: A meta-analytical approach. Neurosurgery 1999;45:539-545.
5. Eckert B, Kucinski T, Pfeiffer G, et al. Endovascular therapy of acute vertebrobasilar occlusion: early treatment onset as the most important factor. Cerebrovasc Dis 2002;14:42-50.
6. Arnold M, Nedeltchev K, Schroth G, et al. Clinical and radiological predictors of recanalization and outcome of 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. J Neurol Neurosurg Psychiatry 2004;75:857-862.
7. Huemer M, Niederwieser V, Ladurner G. Thrombolytic treatment for acute occlusion of the basilar artery. J Neurol Neurosurg Psychiatry 1995;58:227-228.
8. Cross DT 3rd, Moran CJ, Akins PT, et al. Relationship between clot location and outcome after basilar artery thrombolysis. AJNR Am J Neuroradiol 1997;18: 1221-1228.
9. Sliwka U, Mull M, Syelzer A, et al. Long-term follow-up of patients after intra-arterial thrombolytic therapy of acute vertebrobasilar artery occlusion. Cerebrovasc Dis 2001;12:214-219.
10. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: A systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006;37:922-928.
11. Weimar C, Goertler M, Harms L, et al. Distribution and outcome of symptomatic stenosis and occlusions in patients with acute cerebral ischemia. Arch Neurol 2006; 63:1287-1291.
12. Lindsberg PJ, Häppölä O, Kallela M, et al. Door to thrombolysis: ER reorganization and reduced delays to acute stroke treatment. Neurology 2006;67:334-336.
13. Toyoda K, Koga M, Naganuma M, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: General outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591-3595.
14. Nakagawara J, Minematsu K, Okada Y, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: The Japan post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41:1984-1989.
15. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581-1587.
16. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): An observational study. Lancet 2007;369:275-282.
17. Nezu T, Koga M, Kimura K, et al. Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010;75:555-561.
18. Naganuma M, Koga M, Shiokawa Y, et al. Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: SAMURAI rt-PA Registry. Cerebrovasc Dis 2011;31:123-129.
19. Nezu T, Koga M, Nakagawara J, et al. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: Stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. Stroke 2011; 42:2196-2200.
20. Koga M, Shiokawa Y, Nakagawara J, et al. Low-dose intravenous recombinant tissue-type plasminogen activator therapy for patients with stroke outside European indications: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry. Stroke 2012;43:253-255.
21. Guideline Committee for Intravenous rt-PA (alteplase) in Acute Ischemic Stroke. Guidelines for intravenous application of rt-PA (alteplase) [in Japanese]. Jpn J Stroke 2005;26:327-354.
22. Biedert S, Winter R, Staudacher T, et al. Doppler sonography in basilar artery occlusion. Neuroradiology 1985; 27:430-433.
23. Kim ES, Thompson M, Nacion KM, et al. Radiologic importance of a high-resistive vertebral artery Doppler waveform on carotid duplex ultrasonography. J Ultrasound Med 2010;29:1161-1165.
24. Puetz V, Sylaja PN, Coutts SB, et al. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke 2008;39:2485-2490.
25. Puetz V, Sylaja PN, Hill MD, et al. CT angiography source images predict final infarct extent in patients with basilar artery occlusion. Am J Neuroradiol 2009; 30:1877-1883.
26. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24:35-41.
27. Nakashima T, Toyoda K, Koga M, et al. Arterial occlusion sites on magnetic resonance angiography influence

the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. Int J Stroke 2009; 4:425-431.
28. Brown DL, Johnston KC, Wagner DP, et al. Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. Stroke 2004;35:147-150.
29. Grotta JC, Welch KM, Fagan SC, et al. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke 2001;32:661-668.
30. Saqqur M, Molina CA, Salam A, et al. Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: A multicenter transcranial Doppler study. Stroke 2007;38:69-74.
31. Schonewille WJ, Wijman CA, Michel P, et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): A prospective registry study. Lancet Neurol 2009;8:724-730.
32. Sairanen T, Strbian D, Soinne L, et al. Intravenous thrombolysis of basilar artery occlusion: predictors of recanalization and outcome. Stroke 2011;42:2175-2179.
33. Caplan LR. Vertebrobasilar embolism. Clin Exp Neurol 1991;28:1-22.
34. Devuyst G, Bogousslavsky J, Meuli R, et al. Stroke or transient ischemic attacks with basilar artery stenosis or occlusion: Clinical patterns and outcome. Arch Neurol 2002;59:567-573.
35. Smith WS. Intra-arterial thrombolytic therapy for acute basilar occlusion. Stroke 2007;38:701-703.
36. Lin DD, Gailloud P, Beauchamp NJ, et al. Combined stent placement and thrombolysis in acute vertebrobasilar ischemic stroke. J Neuroradiol 2003;24:1827-1833.
37. Pagola J, Ribo M, Alvarez-Sabin J, et al. Timing of recanalization after microbubble-enhanced intravenous thrombolysis in basilar artery occlusion. Stroke 2007; 38:2931-2934.
38. Pagola J, Ribo M, Alvarez-Sabin J, et al. Thrombolysis in anterior versus posterior circulation strokes: Timing of recanalization, ischemic tolerance, and other differences. J Neuroimaging 2011;21:108-112.
39. Muir KW, Buchan A, von Kummer R, et al. Imaging of acute stroke. Lancet Neurol 2006;5:755-768.
40. du Mesnil de Rochemont R, Neumann-Haefelin T, Berkefeld J, et al. Magnetic resonance imaging in basilar artery occlusion. Arch Neurol 2002;59:398-402.
41. Ostrem JL, Saver JL, Alger JR, et al. Acute basilar artery occlusion: Diffusion-perfusion MRI characterization of tissue salvage in patients receiving intra-arterial stroke therapies. Stroke 2004;35:e30-e34.
42. Renard D, Landragin N, Robinson A, et al. MRI-based score for acute basilar artery thrombosis. Cerebrovascular Dis 2008;25:511-516.
43. Nagel S, Nerweh C, Kohrmann M, et al. MRI in patients with acute basilar artery occlusion—DWI lesion scoring is an independent predictor of outcome. Int J Stroke 2012;7:282-288.
44. Sato S, Toyoda K, Uehara T, et al. Baseline NIH Stroke Scale Score predicting outcome in anterior and posterior circulation strokes. Neurology 2008;70:2371-2377.

Intravenous thrombolysis for patients with reverse MRA-DWI mismatch: SAMURAI and NCVC rt-PA registries

Yuki Sakamoto, M.D. Masatoshi Koga, M.D. Kazumi Kimura, M.D. Kazuyuki Nagatsuka, M.D. Satoshi Okuda, M.D. Kazuomi Kario, M.D. Yasuhiro Hasegawa, M.D. Yasushi Okada, M.D. Hiroshi Yamagami, M.D. Eisuke Furui, M.D. Jyoji Nakagawara, M.D. Yoshiaki Shiokawa, M.D. Takuya Okata, M.D. Junpei Kobayashi, M.D. Eijirou Tanaka, M.D. Kazuo Minematsu, M.D. Kazunori Toyoda, M.D.

Abstract

Background and purpose: Characteristics of reverse MRA-DWI mismatch, defined as large DWI lesion despite absence of the major artery occlusion (MAO), remain unknown, especially in patients treated with IV rt-PA. This study aimed to clarify the frequency, associated factors, and outcomes of patients showing reverse MRA-DWI mismatch prior to IV rt-PA therapy.

Methods: From the multicenter (SAMURAI) and additional single-center (NCVC) rt-PA registries, patients with the MCA territorial stroke were included. Early ischemic changes (EIC) were assessed with the Alberta Stroke Program Early CT score (ASPECTS) on pretreatment DWI. MAO was defined as ICA or M1 occlusion on MRA. Patients were divided into 4 groups: the large-EIC match (LM) group (MAO, ASPECTS <7); the reverse mismatch (RMM) group (no MAO, ASPECTS <7); the conventional mismatch (CMM) group (MAO, ASPECTS ≥7); and the small-EIC match (SM) group (no MAO, ASPECTS ≥7). Outcomes included sICH per ECASS II criteria, and mRS 0-2 and death at 90 days. Multivariate backward stepwise logistic regression analysis was performed to identify independent clinical characteristics (demographic factors, risk factors, stroke subtypes by TOAST classification, and blood tests) associated with the reverse MRA-DWI mismatch and to compare the outcomes among the 4 groups.

Results: Of the 486 patients (167 women, median age 74 years) enrolled, reverse MRA-DWI mismatch was observed in 24 (5%, RMM group); 108 belonged to LM, 161 to CMM, and 193 to SM groups. Among clinical characteristics, cardioembolism (RMM 92%, LM 76%, CM 69%, SM 49%) was only independently associated with the RMM group (OR 5.49, 95%CI 1.25-24.1). Median initial NIHSS score was 18 in RMM, 18 in LM, 13 in CMM, and 8 in SM ($p<0.001$). MRS 0-2 (RMM 54%, LM 19%, CMM 46%, SM 69%) was more common in the RMM than the LM group (OR 4.02, 95% CI 1.28-12.7). SICH (RMM 13%, LM 6%, CMM 2%, SM 2%) and death (RMM 8%, LM 12%, CMM 9%, SM 2%) were not different between the RMM and LM groups after multivariate analysis.

Conclusion: Reverse MRA-DWI mismatch was observed in 5% of patients eligible for rt-PA. Cardioembolism was independently associated with reverse mismatch. Patients with reverse mismatch may benefit from thrombolysis, compared to those with extensive EIC with MAO.

SAMURAI rt-PA Registryに見る わが国の脳梗塞静注血栓溶解療法の現状

豊田一則

循環器病研究の進歩(通巻52号)
Vol.XXXIII No.1(2012.11)p.31～38

臨床研究

SAMURAI rt-PA Registryに見るわが国の脳梗塞静注血栓溶解療法の現状

豊田一則

はじめに

循環器疾患のなかでも，脳卒中はとくに東アジア人に多く，わが国においても国民病と言える。また，東アジア諸国のなかでも逸早く高齢化社会に達した日本の脳卒中医療は，一世代程度の遅れで同様の高齢化社会を形成しつつある他の国々にとって，良くも悪くも手本となる。

わが国における急性期虚血性脳血管障害患者への遺伝子組み換え組織型プラスミノゲン・アクティベータ（recombinant tissue-type plasminogen activator：rt-PA）静注療法は，米国に9年遅れて2005年に承認された。この遅れの一因に，東アジア人が欧米人より高率に頭蓋内出血を起こす事実などを考慮して，独自のrt-PA投与量に基づく国内臨床試験（Japan Alteplase Clinical Trial：J-ACT）[1]を実施したことが挙げられる。したがって，国際的な用量であるアルテプラーゼ0.9mg/kgに対して，国内では同薬の0.6mg/kgが承認されている。

Key word
acute stroke
Japanese
recombinant tissue-type plasminogen activator
thrombolysis

SAMURAI rt-PA Registry and current status of intravenous thrombolysis for acute stroke in Japan
Kazunori Toyoda：
Department of Cerebrovascular Medicine,
National Cerebral and Cardiovascular Center
国立循環器病研究センター 脳血管内科

このように独自の治療法を敢行したわが国の事情を踏まえ，市販後の詳細な治療成績の検討が必要と考えられた。承認より2年間にわたって全国的な市販後調査であるJapan post-Marketing Alteplase Registration Study（J-MARS）[2]が行われ，推定使用患者8,313例の9割に当たる7,492例の治療成績が公表された。筆者らはこれと別に，独自の多施設共同登録研究で，治療成績への寄与因子を究明することを目指し，表題に掲げたSAMURAI rt-PA Registryでの一連の研究を発表した。ここでは筆者らの取り組みを中心に概説するとともに，最近の国内治療事情について紹介する。

Ⅰ．SAMURAI rt-PA Registryの全体成績

SAMURAI rt-PA Registryの名はStroke Acute Management with Urgent Risk-factor Assessment and Improvementの略であり，危険因子や各種背景要因を詳しく吟味し，最終的にはこれらの要因に急性期介入を行うことで，脳梗塞急性期治療の向上を目指そうとの思いを込めた。同時に，海外へ向けて積極的に研究成果を発表しようとの気概を，サムライの言葉に託した。

本研究は，厚生労働科学研究としての助成を受けて2008年度から3年間にわたって行った『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』（いわゆるSAMURAI研究）の研究群の一つである。研究参加施設を表1に示す。なお，同

表1．厚生労働科学「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」（SAMURAI研究）の研究者

苅尾　七臣	自治医科大学循環器内科
中川原譲二	中村記念病院脳神経外科
古井　英介	財団法人広南会広南病院脳血管内科
塩川　芳昭	杏林大学脳神経外科
長谷川泰弘	聖マリアンナ医科大学神経内科
奥田　　聡	国立病院機構名古屋医療センター神経内科
山上　　宏	神戸市立医療センター中央市民病院脳卒中センター
木村　和美	川崎医科大学脳卒中医学
岡田　　靖	国立病院機構九州医療センター　脳血管内科
豊田　一則（主任） 古賀　政利，永沼　雅基（事務局）	国立循環器病研究センター　脳血管内科

表2．研究対象600例の脳梗塞性状

主要血管閉塞部位	546例
内頸動脈	91（16.7％）
中大脳動脈水平部	159（29.1％）
中大脳動脈分枝	108（19.8％）
心原性脳塞栓症	380（63.3％）
ASPECTS（CT）	10（8～10）
ASPECTS（MRI）	8（7～10）
発症-治療開始時間（分）	145（121～166）
rt-PA前の降圧薬静注	164（27.6％）
エダラボン併用	502（83.7％）

※例数（％）または中央値（四分位値）
ASPECTS：Alberta Stroke Program Early CT Score
（文献3より改変引用）

研究は，2011年度以降に同じく厚生労働科学研究である『急性期脳卒中への内科複合治療の確立に関する研究』に引き継がれ，同じ研究グループで研究継続中である。

SAMURAI rt-PA Registryは，上記10施設で2005年10月～2008年7月にrt-PA静注療法を受けた症例を対象とした，後ろ向きの登録調査研究である。全体成績は，2009年に雑誌発表された[1]。その概要を記す。登録患者は600例（女性223例，72±12歳，治療前National Institutes of Health stroke scale〔NIHSS〕中央値13，表2）で，同時期に国内で治療を受けたと推定される約13,500例の4.4％に当たる。36時間以内の症候性頭蓋内出血（NIHSS 1以上の増悪）を3.8％（95％信頼区間2.6～5.7％）に，同じくPH Ⅱ型のNIHSS 4以上増悪例を基準とした場合に1.3％（0.7～2.6％）に認めた。また3カ月以内の死亡を7.2％（5.4～9.5％）に，3カ月後の完全自立（modified Rankin scale〔mRS〕0-1）を33.2％（29.5～37.0％）に認め，欧州での適応基準（80歳以下，NIHSS 24以下，脳梗塞既往と糖尿病が併在しないこと）に合わせて患者を限ると40.6％（35.9～45.5％）が完全自立した（図1）。背景要因で補正した後に，年齢がより若いこと，初期軽症，内頸動脈閉塞を伴わないこと，早期虚血所見軽度，治療前に降圧を要しないことの5項目が3カ月後の完全自立に関連し，心不全と入院時血糖高値が死亡に関連した（表3）。

本研究で示された治療成績は，J-MARSでの症候性頭蓋内出血発症率（NIHSS 4以上の増悪）3.5％（95％信頼区間3.1～3.9％）や3

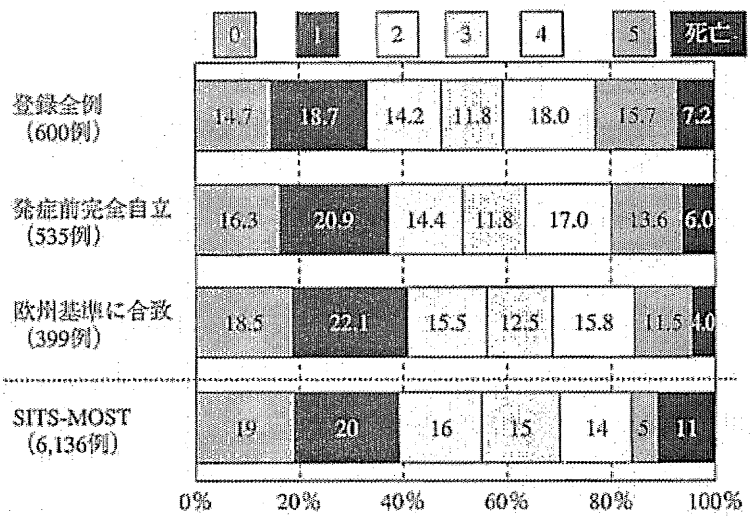

図1．3カ月後のmodified Rankin Scale（文献3より改変引用）

表3．3カ月後完全自立（mRS 0-1）と死亡に関連する要因

		OR	95％CI	P値
完全自立	年齢，毎10歳	0.74	0.59～0.91	0.006
	NIHSS，毎1点	0.92	0.88～0.95	＜0.001
	内頸動脈閉塞	0.27	0.11～0.61	0.003
	ASPECTS（CT），毎1点	1.25	1.06～1.51	0.013
	rt-PA前静注降圧	0.38	0.21～0.67	0.001
死　亡	心不全	5.90	2.74～12.27	＜0.001
	血糖，毎1mmol/L	1.14	1.03～1.26	0.015

（文献3より改変引用）

カ月後完全自立率33.1％（31.8～34.4％）に近く，欧州基準適応例に限った成績では，欧州の大規模市販後調査であるSafe Implementation of Thrombolysis in Stroke-MOnitoring Study（SITS-MOST：6,483例，女性2,581例，中央値68歳，NIHSS中央値12）の3カ月後の完全自立率40.6％（35.9～45.5％）と同等であった[4]。欧州でのアルテプラーゼ0.9mg/kgによる治療と，国内での0.6mg/kgによる治療が，同等の有効性を示していることが判明した。

Ⅱ．サブ解析の成績

SAMURAI rt-PA Registryの主目的は，繰り返すが治療成績への寄与因子の究明であり，分担研究者や研究協力者によって多くの研究が発表された。ここでは，そのうち既に英文誌に掲載または掲載許可された原著9編を，簡単に解説する。

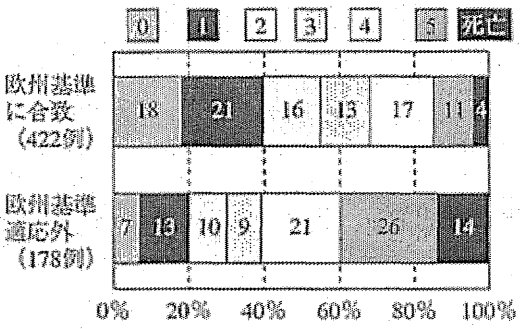

図2．欧州基準適応・適応外と3カ月後のmodified Rankin Scale（文献5より改変引用）

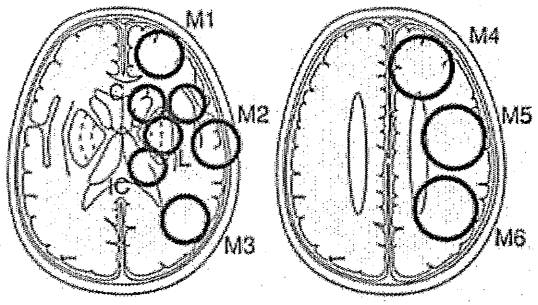

図3．ASPECTS（Alberta Stroke Program Early CT Score）における一側中大脳動脈灌流域内の10カ所の関心領域

各領域の早期虚血所見の有無に基づく10点満点の尺度

C：尾状核，I：島，L：レンズ核，IC：内包（膝・後部のみ），M1～M6：皮質領域

1．適応基準[3]

年齢や初期重症度は治療成績と強く関連し，国内の適正治療指針においても高齢者や初期重症例が慎重投与項目に挙げられる。欧州では81歳以上，NIHSS値25以上，糖尿病と脳梗塞既往の合併を適応外項目としているが，この適応基準には批判的意見も見られる。本研究の600例のうち，上記3つの欧州における適応外項目を有する例が178例（女性93例，82±9歳，29.7％）を占め，このうちNIHSS 25以上は40例，81歳以上は129例，糖尿病を伴う脳卒中既往は25例であった[3]。これらの患者は基準を満たした患者422例（女性130例，68±10歳）に比べて，多変量解析で3カ月後のmRS 5-6（オッズ比2.48，95％信頼区間1.55～3.94，図2）や死亡（2.04，1.02～4.04）が有意に多いが，逆に36時間以内の全ての頭蓋内出血が有意に少なかった（0.50，0.29～0.84）。また糖尿病を伴う脳卒中既往患者の治療成績は，他の適応外項目該当患者に比べて相対的に良かった。

2．早期虚血変化[4,5]

頭部画像での広汎な早期虚血性変化はrt-PA静注療法の適応外項目であるが，その判定はしばしば困難である。近年ではCTでの早期虚血性変化を半定量的に判定するAlberta Stroke Program Early CT Score（ASPECTS）が用いられる機会が増えた。ASPECTSは一側中大脳動脈灌流域を10個の関心領域に分け，各部位で早期虚血性変化を認めれば，10点満点から1点ずつ減点していく[4]（図3）。本研究では，この尺度をMRIの拡散強調画像（diffusion-weighted image：DWI）に応用した。

発症前mRS 0-2で，かつ投与前のMRI拡散強調画像（DWI）所見が解析可能であった477例において，DWI-ASPECTS（10点法）の中央値は8（IQR 7-10）であった[5]。この477例のうち15例（3.1％）に治療後36時間以内の症候性頭蓋内出血（NIHSS 4以上の増悪）を認め，3カ月後に245例（51.4％）がmRS 0-2，29例（6.1％）が死亡した。mRS 0-2の患者はmRS 3-6の患者に比べてASPECTSが高く（中央値9対8，$p<0.001$），ROC分析でmRS 0-2を予測する至適ASPECTSは7以上であった。変数減少法を用いた多変量解析で，ASPECTS≧7はmRS 0-2に有意に関連した（オッズ比1.85，95％信頼区間1.07～3.24）。同様にASPECTS≦4は死亡に（3.61，1.23～

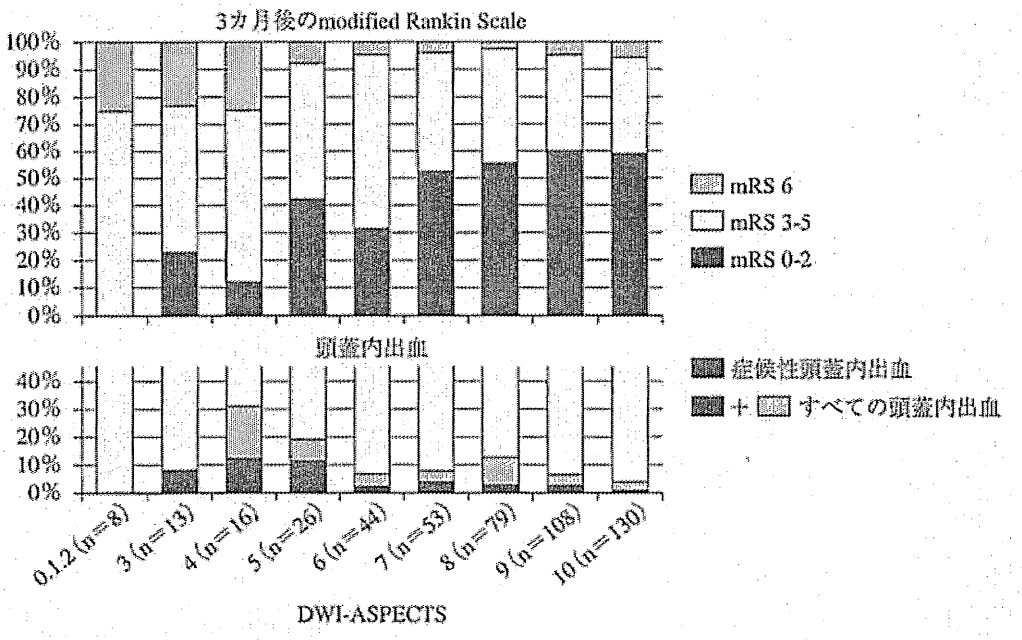

図4．MRI拡散強調画像でのASPECTSと転帰（文献6より改変引用）

9.91），ASPECTS≦5は症候性頭蓋内出血に有意に関連した（4.74，1.54～13.64）。以上のように，対象患者においてDWI-ASPECTSが3カ月後転帰を予測する良い指標となった（図4）。

この477例のうち，中大脳動脈領域の初発脳梗塞患者360例を対象に，CTとDWIの早期虚血変化を比べると，両者の撮像開始時間の差は中央値19分で，ASPECTSはDWIが平均0.92（95％信頼区間0.74～1.10）低かった[7]。ROC分析で3カ月後のmRS 0-2を予測するCT-ASPECTSのAUCは0.621（95％信頼区間0.564～0.674），同じくDWI-ASPECTSのAUCは0.639（0.580～0.694）であった。

3．腎機能障害[9,10]

近年，軽度の腎機能低下，いわゆる慢性腎臓病が脳卒中を含む循環器疾患の独立した危険因子であることが解明され，また腎機能低下と脳卒中の転帰との関連にも関心が高まっている[10]。

緊急入院時の血中クレアチニン値から推算した糸球体濾過率が60mL/min/1.73m²未満の場合を腎機能障害ありと判定すると，発症前mRS 0-3の578例中186例（32.2％）が該当し，多変量解析によって腎機能障害は36時間以内のすべての脳出血（オッズ比1.81，95％信頼区間1.16～2.84，p＝0.009），症候性頭蓋内出血（2.64，1.10～6.56，p＝0.031），3カ月後のmRS 4-6（1.55，1.01～2.38，p＝0.046），3カ月後の死亡（2.94，1.38～6.42，p＝0.006）に独立して有意に関係した[9]。

腎機能障害患者のうち4例は維持血液透析患者であり，1例は透析中，1例は透析終了直後に脳梗塞を発症した[10]。1例がrt-PA投与後に無症候性の異所性頭蓋内出血を発症し，3カ月後のmRSは0が1例，2が2例，4が1例であった。

4．スタチン，脂質値[10]

脂質異常症やスタチンの脳梗塞発症前服用が脳梗塞転帰に及ぼす影響には，一定の見解が得られていない。発症前に自立しており入院時の脂質諸値が明らかな489例のうち，60例が発症前にスタチンを服用していた[10]。血中脂質諸値のうちHDLコレステロールのみが，3カ月後のmRS 0-1に独立して有意に関係した（1mmol/L毎にオッズ比1.95，95％信頼区間1.10～3.47）。この関係は，とくに非心原性脳梗塞患者で強く現れた。スタチン服用歴は，転帰に関連しなかった[10]。

5．心房細動患者におけるCHADS$_2$スコア[11]

CHADS$_2$スコアは，心房細動患者の塞栓症リスクを定量的に判定する尺度であるが，同スコアがrt-PA治療成績の予測尺度となり得るかを調べた。発症前mRS 0-2で，かつ心房細動を有する218例において，脳梗塞発症前のCHADS$_2$スコアは中央値2で，分布は0：35例，1：66例，2：64例，3：29例，4：19例，5：5例，6：0例であった。3カ月後のmRS 0-2の頻度は，CHADS$_2$スコア0：57.1％，1：45.5％，2：31.3％，3-5：28.3％で，同スコアはmRS 0-2に独立して有意な負の関係を示した（オッズ比0.72，95％信頼区間0.55～0.93，p＝0.015）。同じくmRS 5-6に独立して有意な正の関係を示した（1.58，1.21～2.11，p＝0.001）。

6．早期症状進行[12]

24時間以内のNIHSS値4以上の増加を早期症状進行と定義すると，治療24時間後のNIHSS値が明らかな566例中56例（9.9％）に進行を認めた。多変量解析で，高血糖，NIHSS低値，内頸動脈閉塞が，早期症状進行に独立して有意に関連した。また，進行群に有意に症候性頭蓋内出血が多く（オッズ比12.90，95％信頼区間2.76～67.4，p＝0.002），早期症状進行が3カ月後のmRS 3-6（20.44，6.96～76.93，p＜0.001）や死亡（19.43，7.75～51.44，p＜0.001）に，独立して有意に関連した。

7．脳底動脈閉塞[13]

椎骨脳底動脈領域の脳梗塞に対するrt-PA静注療法の効果は，頭動脈系と違った観点で評価すべきかもしれない。600例中25例（女性8例，32～92歳，NIHSS中央値16）に，治療前にMRAなどで脳底動脈閉塞を同定した。このうち15例（60％）が心原性脳塞栓症で，また治療後24時間以内に14例（56％）にNIHSS 8以上の改善を認めた。この脳底動脈閉塞例と中大脳動脈閉塞267例を比べると，36時間以内の頭蓋内出血（8％：5％），3カ月後のmRS 0-2（48％：52％），死亡（4％：6％）はいずれも同程度であった。

この他にも，発症から治療開始までの時間とNIHSS値の積算値（川崎医科大学），投与後24時間の血圧変動（自治医科大学，当センター），発症前の抗血小板薬服用（神戸市立医療センター中央市民病院）と治療成績の関係などを論文化して投稿中であり，他にも多くのサブ解析を発表している。わが国はrt-PA静注療法の承認が遅れたこともあって，これらのサブ解析研究のなかには海外に同様の既報を認めるものもあるが，日本人患者での特徴を明らかにすることは，欧米と民族的に異なり，また独自の用量を用いるわが国での血栓溶解療法の成果を理解する上で，重要と考える。

Ⅲ．最近の国内血栓溶解療法の事情

欧米では，臨床試験European Cooperative Acute Stroke Study（ECASS）Ⅲ[14]の成功を根拠に，2009年以降治療開始可能時間を従来の発症後3時間以内から4.5時間以内に延長

することが承認された。わが国では，2009年に厚生労働省からの意見公募に対して日本脳卒中学会からこの治療開始可能時間の変更意見が提出され，2012年8月に4.5時間以内のアルテプラーゼ投与に対して保険適用が可能となった。他にも国内承認後7年を経て，国内使用経験が蓄積され，国内外で新たなエビデンスが明らかにされ，また新規薬剤，新規治療機器の承認など医療環境も大きく変わった。こうした状況の変化に対応するため，脳卒中学会では『rt-PA（アルテプラーゼ）静注療法適正治療指針』の改訂作業に踏み切り，適応基準などを中心に大幅な見直しを行った。2012年10月に改訂版を公表予定である（2012年9月執筆時）。

2005年以降，rt-PA静注療法が超急性期脳梗塞患者への有効性を強く示したほぼ唯一の治療手段であったが，閉塞した脳動脈内の血栓を直接回収する機械的再開通療法が近年開発され，わが国では2010年にMERCIリトリーバーが，2011年にPenumbraシステムが，いずれも発症後8時間以内の脳梗塞患者で，rt-PA静注療法が適応外，または同治療で血流再開が得られなかった患者に対する再開通治療手段として承認された。新たな治療法とrt-PA静注療法を効率的に組み合わせ，脳梗塞患者の転帰改善効果を飛躍的に高めることで，国民病である脳梗塞を「確実に治せる病気」へ変えていく必要がある。

§ 文 献

1）Yamaguchi T, Mori E, Minematsu K, et al : Alteplase at 0.6mg/kg for acute ischemic stroke within 3 hours of onset : Japan Alteplase Clinical Trial. Stroke 2006;37:1810-5.

2）Nakagawara J, Minematsu K, Okada Y, et al : Thrombolysis With 0.6mg/kg Intravenous Alteplase for Acute Ischemic Stroke in Routine Clinical Practice. The Japan post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41: 1984-9.

3）Toyoda K, Koga M, Naganuma M, et al : Routine use of intravenous low-dose rt-PA in Japanese patients : general outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591-5.

4）Wahlgren N, Ahmed N, Dávalos A, et al : Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) : an observational study. Lancet 2007;369:275-82.

5）Koga M, Shiokawa Y, Nakagawara J, et al : Low-dose intravenous recombinant tissue-type plasminogen activator therapy for patients with stroke outside European indications : Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry. Stroke 2012;43: 253-5.

6）Nezu T, Koga M, Kimura K, et al : Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA : SAMURAI rt-PA Registry. Neurology 2010;75:555-61.

7）Nezu T, Koga M, Nakagawara J, et al : Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy : stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. Stroke 2011;42:2196-200.

8）Barber PA, Demchuk AM, Zhang J, et al : Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355:1670-4.

9）Naganuma M, Koga M, Shiokawa Y, et al : Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA : the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. Cerebrovasc Dis 2011;31:123-9.

10）Naganuma M, Mori M, Nezu T, et al : Intravenous recombinant tissue plasminogen activator therapy for stroke patients receiving maintenance hemodialysis : the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. Eur Neurol 2011;66:37-41.

11）Toyoda K : The cerebro-renal interaction in stroke

neurology. Neurology 2012;78:1898-9.
12) Makihara N, Okada Y, Koga M, et al : The effect of serum lipid levels on stroke outcome after rt-PA therapy : SAMURAI rt-PA Registry. Cerebrovasc Dis 2012;33:272-9.
13) 牧原典子，岡田　靖，古賀政利，他：rt-PA静注療法施行症例におけるスタチンの頭蓋内出血および転帰に及ぼす影響：Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry，臨床神経学 2010;40:225-31.
14) Koga M, Kimura K, Shibazaki K, et al : CHADS2 score is associated with 3-month clinical outcomes after intravenous rt-PA therapy in stroke patients with atrial fibrillation : SAMURAI rt-PA Registry. J Neurol Sci 2011;306:49-53.
15) Mori M, Naganuma M, Okada Y, et al : Early neurological deterioration within 24 hours after intravenous rt-PA therapy for stroke patients : the Stroke Acute Management with Urgent Risk Factor Assessment and Improvement rt-PA Registry. Cerebrovasc Dis 2012;34:140-6.
16) Miyagi T, Koga M, Shiokawa Y, et al : Intravenous alteplase at 0.6mg/kg for acute stroke patients with basilar artery occlusion : the SAMURAI rt-PA Registry. J Stroke Cerebrovasc Dis 2012 ; Epub ahead of print.
17) Hacke W, Kaste M, Bluhmki E, et al : Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.

JOS JOURNAL OF STROKE

Journal of Stroke 2013;15(1):21-26
http://dx.doi.org/10.5853/jos.2013.15.1.21

Review

Epidemiology and Registry Studies of Stroke in Japan

Kazunori Toyoda

Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

Stroke is the most prevalent cardiovascular disease in Japan. This review introduces two epidemiologic studies and four registry studies of stroke in Japan. The Hisayama Study was begun as a population-based prospective cohort study of cerebrovascular and cardiovascular diseases in 1961 in the town of Hisayama. Most of the deceased subjects of the study underwent autopsy examinations from the beginning of the study. Changes in stroke trends in the last 50 years were clarified by comparison of data from different study cohorts registered every 13 to 14 years. The Suita Study was based on a random sampling of Japanese urban residents. Several reports from this study showed the significance of pre-hypertension, as well as hypertension, as a risk factor for stroke by itself and in combination with other underlying characteristics. In addition, the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC), the Japan Standard Stroke Registry Study, the Fukuoka Stroke Registry, and the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry are explained as registry studies involving Japanese stroke patients.

Correspondence: Kazunori Toyoda
Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
Tel: +81-6-6833-5012
Fax: +81-6-6835-5267
E-mail: toyoda@hsp.ncvc.go.jp

Received: November 20, 2012
Revised: December 26, 2012
Accepted: December 27, 2012

The authors have no financial conflicts of interest.

Keywords Acute stroke; Asian; Incidence; Japan; Thrombolysis

Introduction

Stroke is the most prevalent cardiovascular disease and the most prevalent neurological disease in Asia.[1] Many countries in East Asia and Southeast Asia have higher mortality rates from stroke than from ischemic heart disease, the opposite of Western countries.[1] The prevalence of intracerebral hemorrhage (ICH) and intracranial arterial sclerosis is another unique feature of Asian patients.[2,3] Among Asian countries, Japan was the first to become an aging society; the others, in particular Korea, have been rapidly approaching one. Thus, the epidemiologic characteristics of stroke in Japan seem to be good examples for other countries.

In this review, epidemiological studies and patients' registry studies of stroke in Japan are briefly introduced.

The Hisayama Study

The Hisayama Study was begun as a population-based prospective cohort study of cerebrovascular and cardiovascular diseases in 1961 in the town of Hisayama, a suburban community adjacent to the Fukuoka metropolitan area, Kyushu, in western Japan. Four study cohorts were established from Hisayama residents ≥ 40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. One of the strengths of this study is that most of the deceased subjectsof the study underwent autopsy examinations from the beginning of the study (80% between 1962 and 1994),[4] and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort. The study was initiated to respond to the doubts of Western researchers in the pre-

CT era that the very high mortality from ICH in Japan might be due to overdiagnosis of ICH. The autopsy results in the consecutive residents proved that the prevalence of ICH was not so high as was believed by Japanese physicians but also showed that ICH was still more common than ischemic stroke as a cause of death in Japan.[5]

Of the many studies on stroke and other neurological diseases including dementia, those on stroke incidence and mortality are briefly introduced here. After 12-year follow-up for each of the first three study cohorts, the age-adjusted incidences of total stroke were 1,210 per 100,000 person-years for men and 598 for women in the first cohort (1961); they declined steeply in both sexes from the first to the second cohort (1974) and then declined relatively moderately in both sexes from the second to the third cohort (1988, Figure 1).[6] Changes in the incidence among cohorts differed greatly between ischemic stroke and ICH. The incidence of ischemic stroke declined by 37% for men from the first to the second cohort, while the incidence of ICH declined by 61% for men. In contrast, the age-adjusted incidences of coronary heart disease were 340 per 100,000 person-years for men and 113 per 100,000 person-years for women in the first cohort, and they increased for both sexes in the newer cohorts, although they were much smaller than the stroke incidences in all of the cohorts. The different tendencies in the changes in incidence between stroke and coronary heart disease seem to be partly due to changes in prevalence of cardiovascular risk factors among the three cohorts: severe hypertension and current smoking became significantly less frequent, while glucose intolerance, dyslipidemia, and obesity became more frequent. Stroke mortality declined continuously as a result of changes in stroke incidence and significant improvements in acute stroke management; the age-adjusted stroke mortalities among the three cohorts were 634 (the first cohort: 1961), 232 (the second cohort: 1974), and 138 (the third cohort: 1988) per 100,000 person-years, respectively, for men and 286, 162, and 102 per 100,000 person-years, respectively, for women.

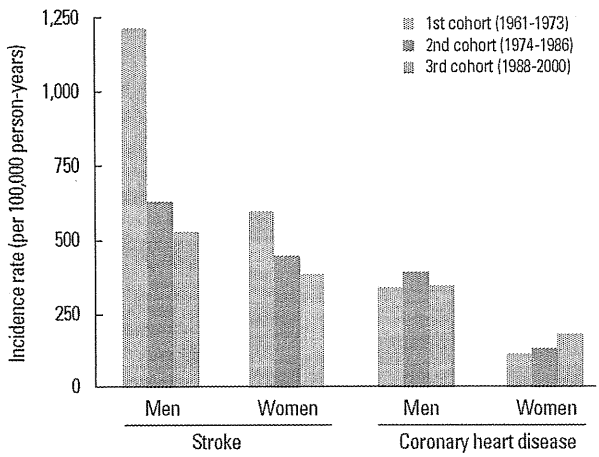

Figure 1. Age-specific incidences of stroke and coronary heart disease among the 3 cohorts of the Hisayama Study, with 12-year follow-up in each cohort.[6]

Among the ischemic stroke subtypes, the age-adjusted incidence of lacunar infarction declined significantly from the first to the third cohort for both sexes (5.68 per 100,000 person-years in the first cohort and 1.59 per 100,000 person-years in the third cohort for men during the 13-year follow-up), whereas the incidences of atherothrombotic and cardioembolic infarctions did not change during this period.[7] As a result, the proportion of ischemic stroke subtypes differed greatly among the 3 cohorts; two-thirds of the male patients had lacunar infarction in the first cohort, compared to two-fifths in the third cohort. The high incidence in the first cohort and recent decline of lacunar infarction were similar to those for ICH, suggesting that intracranial small artery disease has been prevalent in the Japanese population and that the effect of recent developments in preventive therapy, especially antihypertensive therapy, are protective from development of the small artery disease.

Of the 410 patients in the first cohort who developed first ever stroke during 32-year follow-up, 108 (26%) experienced recurrent stroke within 10 years after the index stroke.[8] The cumulative recurrence rates at 1, 5, and 10 years were: 10.0%, 34.1%, and 49.7% after ischemic stroke; 25.6%, 34.9%, and 55.6% after ICH; and 32.5%, 55.0%, and 70.0% after subarachnoid hemorrhage (SAH), respectively.

Of the 333 patients in the first cohort who developed first-ever stroke during 26-year follow-up, 268 (80.5%) died within 10 years after the index stroke, of whom 239 (89.2%) underwent autopsy examinations.[9] The risk of death was greatest in the first year (men 40.3%; women 43.7%). The 30-day case fatality rate was substantially greater in patients with ICH (63.3%) or SAH (58.6%) than in patients with ischemic stroke (9.0%). The risk of dying after the index stroke was twelve times higher during the first year and two times higher during the overall 26-year period as compared to the risk for stroke-free controls. The most common cause of death was the index stroke in the first year, and the impact of recurrent stroke increased gradually thereafter.

The Hisayama Study is one ofthe first sophisticated epidemiological study and one of the most successful epidemiological study of cerebrovascular and cardiovascular diseases in the world. Several unique characteristics of Asian stroke patients were ascertained by this study. The Hisayama Study is still developing by expanding the target diseases into common nonvascular diseases and by adding genomic information for the analysis.

http://dx.doi.org/10.5853/jos.2013.15.1.21

The Suita Study

Following the Hisayama Study, several epidemiological projects on cerebrovascular and cardiovascular diseases were started in Japan. Most of the study cohorts involved rural or suburban residents, since they are likely to continue to live in the area. The Suita Study was unique in that urban residents were registered.

Suita city, which contains the National Cerebral and Cardiovascular Center where the author works, is located adjacent to Osaka city, which is the second largest metropolitan area in Japan. The Suita Study was based on a random sampling of 12,200 Japanese urban residents. At baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality's population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6,485 people underwent regular health checkups between 1989 and 1994. During an average 11.7-year (64,391 person-years) follow-up period, 213 strokes, consisting of 141 ischemic stroke, 32 ICH, 22 SAH, and 18unclassified strokes, and 133 myocardial infarctions were documented.[10,11] Thus, the incidence of stroke did not differ much as compared to that of myocardial infarction in contrast to the high stroke incidence in the Hisayama Study (especially in its first cohort; the age-adjusted incidence of total stroke for menbeing 1,210 per 100,000 person-years and that of coronary heart disease being 340 per 100,000 person-years), although adjustments for age and other conditions are needed for accurate comparison between the studies. These findings suggest that the data from the Suita Study were influenced by the Western lifestyle, particularly diet.

Among the many publications from the Suita Study, those on the association between blood pressure (BP) levels and stroke incidence are briefly introduced here. The association between high-normal BP and cerebrovascular and cardiovascular disease had not been well studied in the Asian population. The percentages of the participants with optimal, normal, and high-normal BP and hypertension Stage 1 and Stage ≥2, according to the ESH-ESC 2007 criteria, were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively.[9] Compared with the optimal BP group, the multivariate hazard ratios (HRs) (95% confidence intervals [CIs]) of stroke for normal and high-normal BP and hypertension Stage 1 and Stage ≥2 were 2.12 (1.04 to 4.30), 2.43 (1.21 to 4.86), 2.62 (1.35 to 5.09), and 4.38 (2.24 to 8.56) in men and 1.05 (0.49 to 2.24), 1.29 (0.63 to 2.67), 1.21 (0.61 to 2.45), and 2.20 (1.07 to 4.50) in women, respectively; the risk of myocardial infarction for each BP category was similar to that of stroke. Population-attributable fractions of high-normal BP and hypertension for combined stroke and myocardial infarction were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively (Figure 2). These findings indicate the significance of pre-hypertension as a vascular risk factor and the necessity for pre-hypertensive patients to attempt to control BP through lifestyle modifications.

The combined impacts of BP categories and other risk factors were also thoroughly investigated in the Suita Study. A study on glucose abnormalities and that on chronic kidney disease (CKD) are summarized.[11,12] The percentages of subjects with normoglycemia, impaired fasting glucose, and diabetes mellitus, defined according to the 2003 American Diabetes Association recommendations, were 59%, 35%, and 6% for men and 75%, 21%, and 4% for women, respectively.[12] Compared with normoglycemic subjects, the multivariate HRs (95% CIs) for stroke were 1.11 (0.81-1.52) in individuals with impaired fasting glucose and 2.08 (1.29-3.35) in individuals with diabetes mellitus. Compared with normoglycemic and optimal BP subjects, increased risks of combined stroke and coronary heart disease were observed in the normoglycemic subjects with high-normal BP or hypertension, in impaired fasting glucose subjects with normal or higher BP, and in diabetic subjects regardless of BP category (*P*-value for interaction = 0.046). The percentages of CKD subjects, defined as an estimated glomerular filtration rate

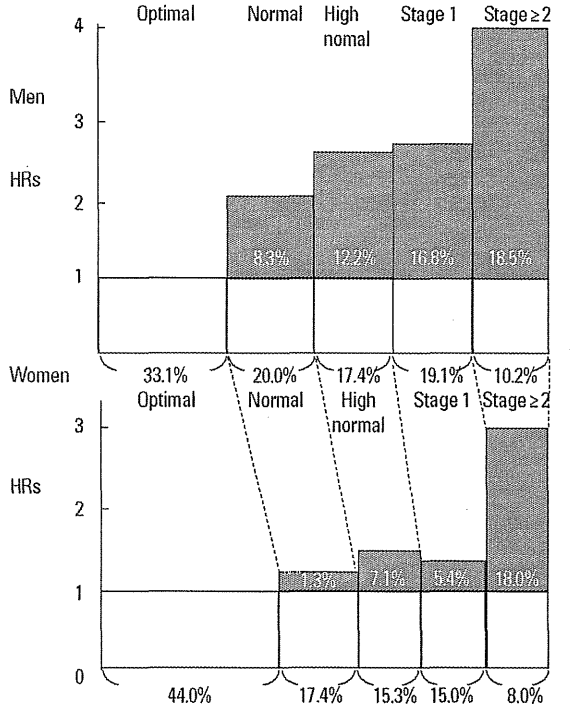

Figure 2. The HRs and positive fractions attributable to exposure to each blood pressure category at baseline for cardiovascular disease (including stroke): the Suita Study. The gray area displays the excessive incidence of CVD due to normal and high-normal blood pressures and hypertension stages 1 and ≥2 (From reference 10 with permission).