Table 2. *Comparison of the prevalence of hypertension, AF, and WMH according to the distribution of MBs*

Variable	MBs-negative (n = 68; 55%)	MBs-positive			*P* value
		Lobar (n = 6; 5%)	Deep (n = 31; 25%)	Diffuse (n = 19; 15%)	
Hypertension, n (%)	55 (81)	6 (100)	30 (97)	18 (95)	.069
AF, n (%)	20 (29)	1 (17)	6 (19)	1 (5)	.146
WMH, n (%)					
Punctate	34 (50)	5 (83)	19 (61)	4 (21)	<.0001
Early confluent	7 (10)	1 (17)	1 (3)	9 (47)	
Confluent	1 (2)	0 (0)	5 (16)	4 (21)	

Pearson's χ^2 test was used for comparisons.

in the diffuse group, including the high prevalence of severe WMH and elevated BP, lend support to this hypothesis.

The possibility that all diffuse MBs are simply the result of hypertensive microangiopathies must be considered. Indeed, chronic hypertension can influence the development of hypertensive microangiopathies anywhere in the brain,[1,29] but CAA is typically found in cortical or leptomeningeal regions and is not necessarily related to hypertension.[30] Histopathologic analysis of MBs found on GE-MRI in pICH have shown that the MBs reflect widespread involvement of the arterioles caused by hypertension, amyloid deposition, or both pathogenetic mechanisms; in fact, some overlap in their distribution has been reported.[1] Thus, both pathogeneses might be mixed in diffuse MBs.

Our finding of no significant differences in BP levels between the MBs-negative and lobar groups was consistent with the Rotterdam scan study,[14] which also demonstrated that *APOE* ϵ4 carriers more often had strictly lobar MBs compared with noncarriers. These results might reflect the pathogenesis of strictly lobar MBs, which is more closely related to CAA and less closely related to hypertension. However, it is important to note that all patients in our lobar group (n = 6) had a history of hypertension. Interestingly, both of our patients with symptomatic single lobar hemorrhage, who were in the lobar group and met the Boston criteria for possible CAA,[31] had a history of hypertension. Thus, even in patients with MBs in the lobar area, strict BP control cannot be disregarded to prevent future CAA-related hemorrhages.

All ABPs except night SBP in ischemic stroke patients, as well as all CBPs on admission in all patients, were significantly higher in both the deep or infratentorial group and the diffuse group compared with the MBs-negative group. The presence of MBs in the deep or infratentorial

Table 3. *Comparison of BP components by topographical distribution of MBs*

Variable	MBs-negative (reference)	MBs-positive		
		Lobar	Deep	Diffuse
CBP				
n	68	6	30	16
SBP, mm Hg	160.6 (24.6)	161 (34.5)	179.1 (30.4)*	185.8 (30.3)*
DBP, mm Hg	84.2 (13.9)	91.8 (20.2)	95.7 (16.5)*	101.9 (11.9)†
ABP‡				
n	58	4	16	7
24-hour SBP, mm Hg	133.2 (20.0)	136.0 (21.2)	149.1 (14.8)*	153.7 (12.1)*
Day SBP, mm Hg	134.5 (20.2)	139.2 (22.3)	150.6 (14.6)*	156.9 (13.5)*
Night SBP, mm Hg	128.1 (21.7)	122.3 (18.2)	141.9 (16.9)	144.4 (13.7)
24-hour DBP, mm Hg	75.6 (9.0)	77.5 (17.6)	85.3 (11.5)*	88.3 (9.6)*
Day DBP, mm Hg	76.7 (9.2)	78.8 (17.6)	86.3 (11.7)*	89.4 (8.5)*
Night DBP, mm Hg	71.4 (9.4)	71.8 (17.5)	81.3 (10.9)*	83.7 (14.7)*
Nondipper, n (%)§	32 (55)	0 (0)	8 (50)	2 (29)

BP values are mean (SD) and compared by analysis of variance using Dunnett's *q* test.
*$P < .05$ versus the MBs-negative group.
†$P < .0001$ versus the MBs-negative group.
‡Evaluated in 85 patients with ischemic stroke (including TIA).
§$P = .117$ compared with Pearson's χ^2 test.

group and the diffuse group could reflect hypertensive organ damage in these ischemic stroke patients, because ABP has been reported to be well correlated with target organ damage and cardiovascular morbidity and mortality.[32,33] ABPM also can provide information about circadian BP patterns (dipper or nondipper types).[34] Nondipper status has been reported to be correlated with more advanced target organ damage and with a poorer cardiovascular disease prognosis compared with dipper status;[35] however, no correlations were found between circadian BP patterns and the presence or their topographical distribution of MBs, due to either monitoring in the acute phase after the stroke onset or decreased patient activity during the hospital stay, resulting in low reproducibility of the day-night differences in ABPM.[36]

In conclusion, we found significant differences between the topographical distribution of MBs and BP levels, stroke subtypes, and severity of WMH in our cohort of stroke survivors. These results suggest that our classification of the topographical distribution of MBs may reflect different pathogenetic processes for microangiopathy in the brain. In particular, the underlying pathogenesis of "diffuse MBs" may be the more severe microangiopathy involved in hypertensive arteriopathy and CAA.

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EXPERT REVIEWS

Candesartan cilexetil in the management of blood pressure for acute and recurrent stroke in Japan: the Challenge-Stroke study

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The Challenge-Stroke study was conducted in Japanese patients initiated on candesartan cilexetil therapy within 3 months of suffering a stroke to investigate the clinical use of candesartan and its efficacy/safety in this therapeutic setting. A total of 869 patients formed the safety analysis set. In total, 79.6% of patients with brain hemorrhage (BH) and 60.2% with brain infarction (BI) began candesartan before post-stroke day 3 and 7, respectively. Baseline average blood pressure (BP) was 152.0/83.2 mmHg in the BH group and 165.2/89.8 mmHg in the BI group; this was reduced to 125.8/75.4 mmHg and 136.3/78.1 mmHg, respectively, at 1 year. The incidence of adverse drug reactions was 6.7 and 8.0%, respectively. There were 12 recurrent strokes in the BH group and 11 in the BI group after 1 year. The risk of recurrent stroke was significantly higher for BH patients with a final systolic BP ≥150 mmHg than for those with a final systolic BP <130 mmHg (hazard ratio: 6.807; p = 0.004). Aggressive antihypertensive therapy is currently employed in Japanese patients with acute stroke. Candesartan was safe and effective for BP control in acute stroke patients. Strict BP management may be useful for secondary prevention of stroke after BH

KEYWORDS: acute stroke • antihypertensive therapy • blood pressure • candesartan cilexetil

Globally, cerebrovascular disease is the second most common cause of death [1]. In 2005, the number of stroke-related deaths was estimated to be 5.7 million worldwide [2]. Approximately 120,000 individuals died from cerebrovascular disease in Japan in 2009, although the numbers appear to have decreased in recent years [101].

Hypertension is the most prevalent modifiable risk factor for stroke and a large-scale meta-analysis has confirmed an association between elevated blood pressure (BP) and increased risk of stroke mortality [3]. Although numerous studies have demonstrated the efficacy of long-term antihypertensive therapy for both the primary and secondary prevention of stroke [4–6], optimal management of BP in patients with acute stroke remains unclear. Studies conducted to date, including several recently published randomized controlled trials (RCTs), have failed to shed sufficient light on this important clinical dilemma because of inadequate power to draw definitive conclusions and/or conflicting results [7–13].

An acute increase in BP is observed in many patients immediately after the occurrence of stroke [14]. It has been reported that approximately 75% of patients with brain infarction (BI) and approximately 80% of patients with brain hemorrhage (BH) show an increase in systolic BP (SBP) to 140 mmHg or more and in diastolic BP (DBP) to 90 mmHg or more during the initial 24–48 h post-stroke period [15]. Although BP usually then declines spontaneously to the pre-stroke level, observational studies have suggested that acute elevation of BP after a stroke has an adverse effect on outcome [16,17].

At the time the present study was initiated, there were no firm recommendations regarding BP management for patients with acute stroke. The Japanese Society of Hypertension (JSH)

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Guidelines for the Management of Hypertension 2004 stated that "aggressive intervention with antihypertensive drugs should not be performed in acute stroke, in principle" [18]. However, these guidelines also recommended that "intervention with antihypertensive drugs be performed in patients with BI if the BP exceeds 220/120 mmHg or if the mean BP exceeds 130 mmHg," although it was noted that sufficient clinical evidence had not been accumulated to support such recommendations. The Japanese Guidelines for the Management of Stroke 2004 recommended that antihypertensive treatment be started in patients with acute BH if a BP higher than 180/105 mmHg or a mean BP (MBP) higher than 130 mmHg persisted for 20 min or longer [19]. However, this recommendation was also not supported by sufficient clinical evidence.

Candesartan cilexetil is an ARB that is approved in Japan for the treatment of hypertension and chronic heart failure. In a randomized placebo-controlled investigation of patients with acute BI and increased BP (the Acute Candesartan Cilexetil Therapy in Stroke Survivors Study [ACCESS] study), a significant reduction in death and cardiovascular events was achieved by modest BP reduction with candesartan in the early treatment of stroke [20], suggesting a potential benefit for ARB therapy in this clinical situation.

Based on the results of the ACCESS study, the current observational study was conducted in Japanese patients who commenced candesartan therapy within 3 months of an acute stroke in order to collect information about the clinical use of this drug, including its safety and efficacy profile in this therapeutic setting.

Methods

Study design

This was a multicenter observational study designed to collect information from everyday clinical practice about the treatment of patients with acute stroke and, specifically, to determine whether candesartan therapy during the acute phase of stroke is useful for managing BP and decreasing stroke recurrence during long-term follow-up.

A total of 84 institutions across Japan participated in the study, which was conducted in accordance with Good Post-Marketing Study Practice (GPSP), a ministerial ordinance concerning standards for the implementation of postmarketing surveys in Japan.

Patients

Participating investigators treated patients with acute stroke according to usual clinical practice based on the patients' individual requirements and their own clinical experience. Patients eligible for inclusion in the study were those initiated on candesartan cilexetil as an initial oral antihypertensive agent within 3 months after experiencing a BH or BI.

The following patients were excluded:

- Those who were given any other oral antihypertensive drug (intravenous antihypertensive agents were allowed) before starting candesartan treatment after the stroke;
- Those with any contraindications to the administration of candesartan;
- Those with asymptomatic BI;
- Those with subarachnoid hemorrhage;
- Those with transient ischemic attacks.

Study procedures

After an investigator confirmed patient eligibility, he/she posted the patient enrollment card to the Central Enrollment Center. The follow-up period was set at 1 year, and follow-up was continued even after candesartan was discontinued. If follow-up was terminated before the scheduled 1-year period had been completed, the reason for early termination was documented in the case report form.

The variables investigated were as follows: baseline characteristics of the subjects (gender, birth date, type of stroke, date of stroke, smoking habits, severity and site of stroke, date of admission to hospital, concurrent diseases, and so on); information about treatment (time of commencing candesartan, concomitant drugs); BP throughout the study duration; and adverse events (recurrent stroke [BH, BI or subarachnoid hemorrhage], cardiovascular events [sudden death, myocardial infarction] and other adverse events).

The patient enrollment phase was from November 2006 to March 2008 and the study period was from November 2006 to September 2009.

Evaluation criteria

The study used the following evaluation criteria:

- Use of candesartan (timing of initiation: median times for initiating candesartan treatment for patients with BH and BI were 2 days and 6 days, respectively. For the purposes of statistical comparison and evaluation, these median values were used as cut-off values);
- Changes in BP, including the rate of reaching target BP (<140/90 mmHg);
- Incidence of recurrent stroke and cardiovascular events, and incidence stratified by the timing of candesartan therapy as described in point 1;
- Incidence of adverse drug reactions (including abnormal changes in laboratory values) and incidence stratified by the timing of candesartan treatment as described in point 1.

Statistical analysis

All patients for whom case report forms were available were included in the safety analysis set (SAS). Patients from the SAS who were subsequently confirmed to be eligible for the study were included in the efficacy analysis set (EAS).

Using data from the SAS, summary statistics stratified by the type of stroke (BH/BI/miscellaneous) and by the timing of candesartan therapy were calculated for the following variables: baseline patient characteristics, duration of candesartan treatment, reason for early termination of follow-up, use of candesartan, and use of other antihypertensive drugs. For numerical variables (e.g., age,

BMI and duration of treatment), mean ± SD was calculated. For categorical variables (e.g., gender, type of stroke and reason for early termination), frequencies and percentages were calculated.

To assess the changes in BP over time, summary statistics were calculated for the BH and BI groups using data from the EAS. In addition to acute BP (mean ± SD) at each assessment time, the rate of achieving the target BP (<140/90 mmHg) during the chronic stage of stroke as recommended by the JSH Guidelines for the Management of Hypertension 2004 [14] was calculated. BP data obtained after discontinuation of candesartan therapy were also included in the analysis.

The number and incidence of patients experiencing recurrent stroke, cardiovascular events or adverse drug reactions (SAS) were calculated after stratification by stroke types (BH/BI/miscellaneous) and by the timing of candesartan therapy. Using Fisher's exact test, the incidence of these events was compared between subgroups stratified by the timing of candesartan therapy.

Kaplan–Meier curves for recurrent stroke were drawn for patient cohorts stratified by stroke type (BH/BI/miscellaneous) and compared by the log-rank test. The same analyses were performed for subsets stratified by timing of candesartan therapy in the BH and BI groups.

For patients without recurrent stroke, irrespective of whether or not they had completed scheduled treatment, data collection was completed at the day of the final study visit.

In addition to analysis of the specified evaluation criteria, the following analyses were performed. In SAS patients with SBP/DBP data from the final study visit, summary statistics regarding final BP were calculated for the subsets with and without recurrent stroke in the BH and BI groups and the results were compared using the t-test. In addition, the relative risk of recurrent stroke was estimated in comparison with that for patients whose SBP was <130 mmHg, using the log-rank test and Cox regression analysis. In patients with recurrent stroke, BP data obtained at the final visit during the 3 months before recurrence were used for this analysis.

Results

Patient disposition

Between November 2006 and March 2008, a total of 878 stroke patients treated with candesartan were enrolled in the study. Case report forms were obtained for 869 patients and this comprised the SAS (445 patients with BH, 415 patients with BI and nine patients with other cerebrovascular diseases). However, 49 patients from the SAS were subsequently found to be ineligible due to initial oral antihypertensive therapy other than candesartan (n = 39), a diagnosis of cerebrovascular disease other than BH or BI (n = 9), and violation of the specified time window for subject enrollment (n = 1). After excluding these patients, the remaining 820 patients comprised the EAS (420 patients with BH and 400 with BI).

Baseline characteristics

The baseline characteristics of the patients in the SAS are summarized in Table 1 stratified by type of stroke and timing of candesartan therapy.

Patient age (mean ± SD: 66.5 ± 11.8 years in the BH group vs 68.6 ± 10.8 years in the BI group), gender distribution (men: 60.9 vs 64.6%), and BMI (22.82 ± 3.48 vs 23.64 ± 3.56) were comparable between the BH and BI groups, as well as between subsets based on the timing of candesartan treatment with a few exceptions. The time from onset of stroke to hospital admission was less than 3 h in 52.8% of patients with BH versus 24.6% of patients with BI. In the BH group, a significant difference in age was noted between the subsets stratified by the timing of candesartan therapy (65.7 ± 11.6 years for patients starting candesartan on days 0–2 vs 68.5 ± 11.9 years for patients starting candesartan on day 3+), but this difference was not considered to be clinically relevant.

Regarding the type of BI, lacunar infarction was the most common (51.8%), followed by atherothrombotic BI (33.3%), cardiogenic brain embolism (10.8%) and miscellaneous (4.3%). Among the concurrent diseases, dyslipidemia (21.6% of the BH group vs 37.8% of the BI group), diabetes (15.7 vs 29.6%) and arrhythmias (2.7 vs 9.6%) were more prevalent in the BI group than the BH group, while hepatic dysfunction was more prevalent in the BH group (10.1 vs 7.7%).

The average BP (SBP/DBP) at the introduction of candesartan therapy was 152.0/83.2 mmHg in the BH group and 165.2/89.8 mmHg in the BI group. There was a significant difference in BP between subsets of the BI group stratified by the timing of candesartan therapy (average SBP/DBP: 168.4/91.9 mmHg for patients starting candesartan on days 0–6 vs 161.3/87.2 mmHg for patients starting candesartan on day 7+; $p < 0.001$ for both SBP and DBP).

Treatment

The time from stroke onset to the start of candesartan treatment (mean ± SD) was 3.1 ± 6.0 days in the BH group and 10.8 ± 14.6 days in the BI group. Approximately 80% of BH patients began candesartan before day 3 after the stroke, while approximately 60% of BI patients did so before day 7. On the other hand, 2.7% of BH patients and 20.2% of BI patients began candesartan therapy after day 15.

The follow-up period after starting candesartan treatment (mean ± SD) was 207.2 ± 190.2 days in the BH group and 268.5 ± 188.2 days in the BI group. In 278 patients (62.5%) from the BH group and 179 patients (43.1%) from the BI group, follow-up ceased before the scheduled 1-year period. The most common reason for early termination of follow-up was "loss to follow-up", primarily change of hospital (253 patients in the BH group and 164 patients in the BI group).

The daily dosage of candesartan (mean ± SD) tended to be higher in the BH group at both the start of treatment (7.6 ± 2.0 mg in the BH group and 6.5 ± 2.3 mg in the BI group) and at the completion of treatment (8.0 ± 2.3 mg vs 7.2 ± 2.5 mg). Table 2 summarizes the use of antihypertensive drugs other than candesartan.

Before the occurrence of stroke, 25.2% of the BH patients and 31.6% of the BI patients were receiving antihypertensive therapy, which was usually a calcium-channel blocker (15.1% of BH patients vs 21.9% of BI patients) or an ARB (6.1 vs 10.8%).

Table 1. Patient baseline characteristics (safety analysis set).

Demographic variables	Sample population	Patients with BH		Patients with BI	
		Treatment started ≤post-stroke day 2	*Treatment started ≥post-stroke day 3*	*Treatment started ≤post-stroke day 6*	*Treatment started ≥post-stroke day 7*
	Variable	n = 311	n = 134	n = 229	n = 186
Age	Mean ± SD	65.7 ± 11.6	68.5 ± 11.9*	68.7 ± 10.8	68.5 ± 10.8
Sex	Men	198 (63.7%)	73 (54.5%)	149 (65.1%)	119 (64.0%)
BMI	Mean ± SD	22.98 ± 3.40	22.41 ± 3.63	23.50 ± 3.59	23.82 ± 3.51
Time from stroke onset to hospital admission	<3 h	175 (56.3%)	60 (44.8%)	59 (25.8%)	43 (23.1%)
	≥3 h	97 (31.2%)	47 (35.1%)	125 (54.6%)	95 (51.1%)
	Unspecified	39 (12.5%)	27 (20.1%)	45 (19.7%)	48 (25.8%)
Brain infarction	Lacunar infarction			127 (55.5%)	88 (47.3%)
	Atherothrombotic brain infarction			70 (30.6%)	68 (36.6%)
	Cardiogenic brain embolism			26 (11.4%)	19 (10.2%)
	Miscellaneous			6 (2.6%)	12 (6.5%)
Concurrent diseases	Dyslipidemia	70 (22.5%)	26 (19.4%)	79 (34.5%)	78 (41.9%)
	Diabetes	51 (16.4%)	19 (14.2%)	71 (31.0%)	52 (28.0%)
	Hepatic function impairment	31 (10.0%)	14 (10.4%)	17 (7.4%)	15 (8.1%)
	Arrhythmias	7 (2.3%)	5 (3.7%)	22 (9.6%)	18 (9.7%)
	Hyperuricemia	14 (4.5%)	8 (6.0%)	16 (7.0%)	7 (3.8%)
	Renal function impairment	9 (2.9%)	6 (4.5%)	17 (7.4%)	7 (3.8%)
Baseline blood pressure					
SBP	Mean ± SD	151.5 ± 23.3	153.1 ± 19.0	168.4 ± 23.4	161.3 ± 19.3**
DBP	Mean ± SD	83.2 ± 16.2	83.1 ± 16.3	91.9 ± 14.7	87.2 ± 13.6**
BP at completion of follow-up					
SBP	Mean ± SD	126.8 ± 18.2	124.9 ± 18.8	135.4 ± 20.2	138.1 ± 19.0
DBP	Mean ± SD	75.8 ± 12.9	73.6 ± 13.0	77.7 ± 15.0	78.3 ± 12.5
Size of hematoma	Mean ± SD	3.00 ± 1.54	3.83 ± 5.56		
	<3 cm	140 (45.0%)	54 (40.3%)		
	≥3 cm	165 (53.1%)	78 (58.2%)		
	Unspecified	6 (1.9%)	2 (1.5%)		
Severity of BI	Small infarction†			142 (62.0%)	103 (55.4%)
	Medium infarction‡			56 (24.5%)	45 (24.2%)
	Multiple small to medium infarction§			19 (8.3%)	31 (16.7%)
	Large infarction#			12 (5.2%)	7 (3.8%)

*p < 0.05.
**p < 0.001.
†Infarct with the greatest dimension of less than 1.5 cm.
‡Infarct intermediate between small and large infarctions.
§Two or more infarcts were observed.
#Infarction extending almost across the whole territory of the anterior, middle or posterior cerebral artery.
For difference between subsets according to timing treatment started (t-test was used for comparison of age, BMI and BP, and Fisher's exact test was used for comparison of other variables.
BH: Brain hemorrhage; BI: Brain infarction; BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

After the stroke, 51.2% of BH patients and 3.1% of BI patients received intravenous antihypertensive therapy prior to the introduction of candesartan, which was most commonly a calcium-channel blocker (47.6% of BH patients and 2.7% of BI patients). Candesartan was used in combination with intravenous antihypertensive therapy for 41.3% of BH patients and 1.9% of BI patients, while other oral antihypertensive drugs were combined with candesartan therapy in 61.8% of BH patients and 35.4% of BI patients. With regard to combination therapy, calcium-channel blockers were most frequently coadministered with candesartan (both intravenously and orally).

Blood pressure

Figure 1 displays the changes of BP in the EAS during the follow-up period. The average BP (SBP/DBP) at the introduction of candesartan therapy was 152.2/83.2 mmHg in the BH group and 165.2/89.9 mmHg in the BI group. BP decreased after 3 months of candesartan treatment, but did not change significantly thereafter. The SBP was slightly higher in the BI group during the course of the study, and the target BP (<140/90 mmHg) was reached in 72.0% of the BH group versus 57.6% of the BI group at the final follow-up visit. The average BP (125.8/75.4 mmHg in the BH group and 136.3/78.1 mmHg in the BI group) was within the target range in both groups.

Events

Table 3 summarizes the incidence of recurrent stroke, cardiovascular events and adverse drug reactions in the SAS. The incidence of recurrent stroke was 2.7% (12 out of 445 patients) in the BH group and 2.7% (11 out of 415 patients) in the BI group. Recurrent stroke was due to BH in seven patients and due to BI in five patients from the BH group, while it was due to BH in one patient and due to BI in ten patients from the BI group. Subarachnoid hemorrhage did not occur in either group.

The incidence of cardiovascular events was 0.2% (n = 1) in the BH group and 0.5% (n = 2) in the BI group.

The incidence of adverse drug reactions was 6.5% (n = 29) in the BH group and 7.0% (n = 29) in the BI group. The most common adverse drug reactions were abnormal changes in laboratory values (3.8% in the BH group and 3.1% in the BI group).

None of the events showed a significant difference in incidence in relation to the timing of candesartan therapy.

Recurrent stroke & timing of candesartan therapy

Figure 2 shows the Kaplan–Meier curves for recurrent stroke in the SAS.

The estimated incidence of recurrent stroke after 1 year of candesartan treatment was 5.1% in the BH group and 3.0% in the BI group. The BI versus BH hazard ratio (HR) for recurrent

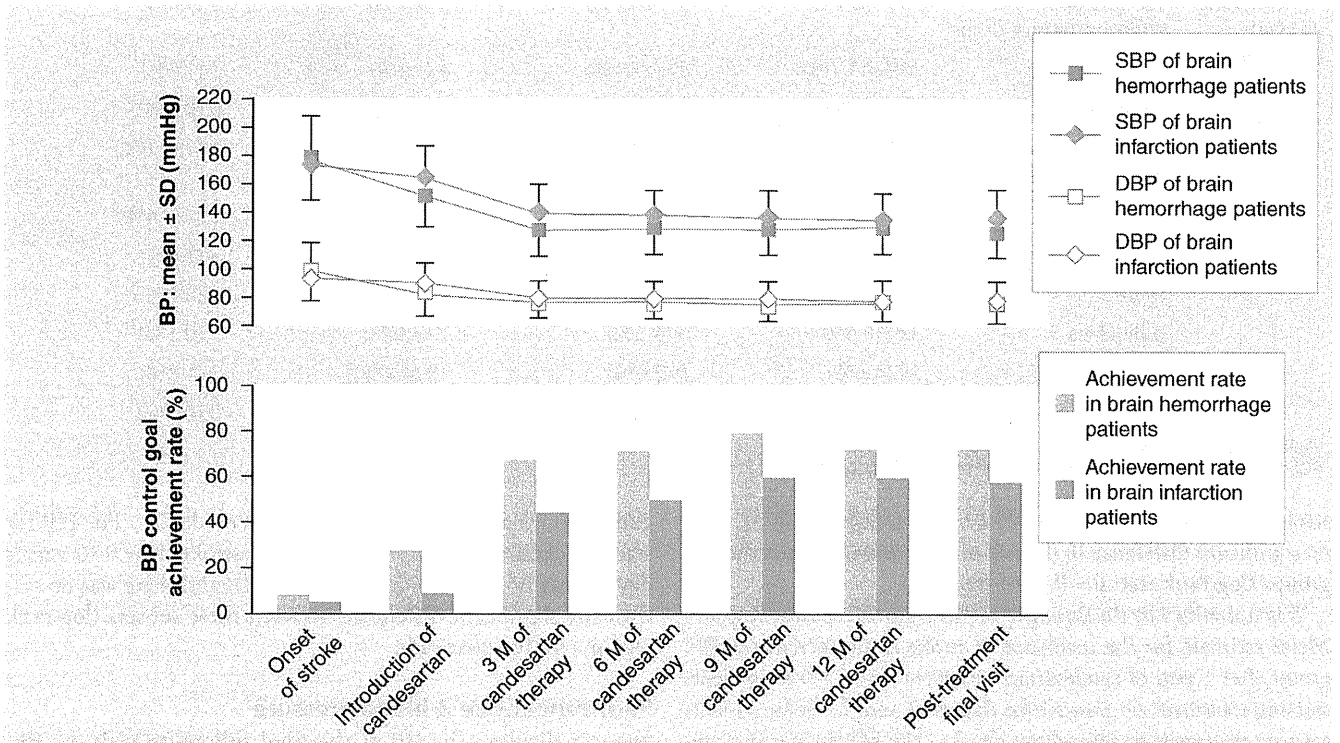


Figure 1. Time course of blood pressure (efficacy analysis set) including patients followed after discontinuation of candesartan.

BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; SD: Standard deviation.

Table 2. Use of antihypertensive drugs other than candesartan (safety analysis set).

Timing	Antihypertensive drugs	Patients with brain hemorrhage		Patients with brain infarction	
		Treatment started ≤post-stroke day 2	*Treatment started ≥post-stroke day 3*	*Treatment started ≤post-stroke day 6*	*Treatment started post-stroke day 7*
		n = 311	n = 134	n = 229	n = 186
Before stroke	Patients on oral antihypertensive drugs†	80 (25.7%)	32 (23.9%)	69 (30.1%)	62 (33.3%)
	ARB	20 (6.4%)	7 (5.2%)	22 (9.6%)	23 (12.4%)
	CCB	47 (15.1%)	20 (14.9%)	46 (20.1%)	45 (24.2%)
	ACE-I	11 (3.5%)	8 (6.0%)	14 (6.1%)	5 (2.7%)
	β-blockers	5 (1.6%)	2 (1.5%)	4 (1.7%)	5 (2.7%)
	Other classes	6 (1.9%)	3 (2.2%)	12 (5.2%)	5 (2.7%)
Between stoke onset and candesartan introduction	Patients on iv. antihypertensive drugs†	158 (50.8%)	70 (52.2%)	8 (3.5%)	5 (2.7%)
	CCB	146 (46.9%)	66 (49.3%)	6 (2.6%)	5 (2.7%)
	Other classes	16 (5.1%)	10 (7.5%)	2 (0.9%)	0 (0.0%)
	Patients on oral antihypertensive drugs†	18 (5.8%)	6 (4.5%)	6 (2.6%)	9 (4.8%)
	CCB	11 (3.5%)	6 (4.5%)	4 (1.7%)	6 (3.2%)
	Other classes	8 (2.6%)	0 (0.0%)	2(0.9%)	4 (2.2%)
Concomitant use with candesartan	Patients on iv. antihypertensive drugs†	153 (49.2%)	31 (23.1%)	5 (2.2%)	3 (1.6%)
	CCB	139 (44.7%)	31 (23.1%)	4 (1.7%)	3 (1.6%)
	Other classes	20 (6.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
	Patients on oral antihypertensive drugs†	213 (68.5%)	62 (46.3%)	90 (39.3%)	57 (30.6%)
	CCB	197 (63.3%)	57 (42.5%)	79 (34.5%)	51 (27.4%)
	ACE-I	22 (7.1%)	2 (1.5%)	6 (2.6%)	3 (1.6%)
	Diuretic	35 (11.3%)	7 (5.2%)	13 (5.7%)	6 (3.2%)
	α blockers	32 (10.3%)	6 (4.5%)	7 (3.1%)	1 (0.5%)
	β blockers	14 (4.5%)	4 (3.0%)	10 (4.4%)	3 (1.6%)
	Other classes	7 (2.3%)	1 (0.7%)	1 (0.4%)	0 (0.0%)

†Patients may have received more than one antihypertensive drug.
ACE-I: ACE inhibitor; CCB: Calcium-channel blocker; iv.: Intravenous.

stroke was estimated to be 0.825 (95% CI: 0.363–1.876), with no significant difference in the risk of recurrence between the two groups (log-rank test: p = 0.646) (Figure 2A).

When stratified by the timing of candesartan therapy, the Kaplan–Meier estimate for the incidence of stroke recurrence in the BH group after 1 year of candesartan treatment was 5.7% for patients starting treatment on post-stroke days 0–2 and 3.2% for patients starting treatment on post-stroke day 3+. The HR for starting candesartan treatment on days 0–2 versus starting treatment on day 3+ was 1.816 (95% CI: 0.397–8.301), with no statistically significant difference between these subsets (log-rank test: p = 0.435) (Figure 2B).

In the BI group, the Kaplan–Meier estimate for the incidence of recurrent stroke after 1 year of candesartan treatment was 4.0% for patients starting treatment on post-stroke days 0–6 and 1.8% for patients starting treatment on day 7+. The HR for starting candesartan treatment on post-stroke days 0–6 versus day 7+ was 1.503 (95% CI: 0.436–5.174), and there was no statistically significant difference between these subsets (log-rank test: p = 0.516) (Figure 2C).

Recurrent stroke & blood pressure

Figure 3A displays the BP at the final follow-up visit for BH patients with and without recurrent stroke (patients from the SAS with final BP data). For patients with recurrent stroke, the BP that was measured within the 3-month period prior to recurrence was used for the analysis. The average final BP (SBP/DBP: mean ± SD) for BH patients with recurrent stroke (n = 10) was 135.9 ± 19.0/75.5 ± 13.1 mmHg, which was

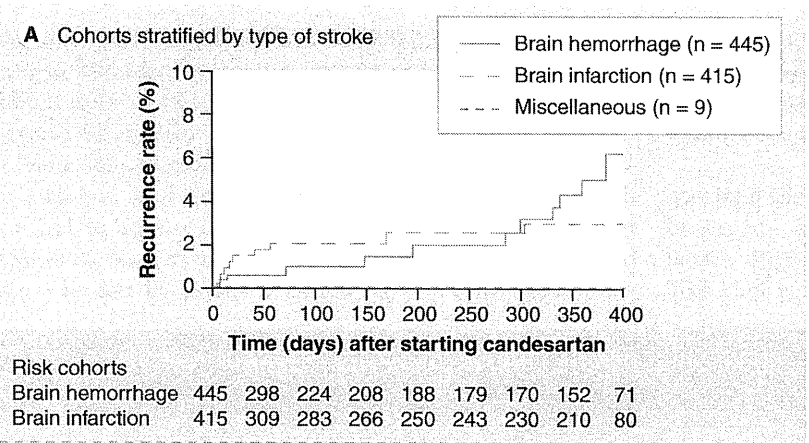
higher than the final BP of 125.7 ± 17.8/75.1 ± 12.9 mmHg for patients without recurrence (SBP: n = 373; DBP: n = 369), at least for SBP (t-test; p = 0.074). This difference was not observed when comparing BPs in BI patients with and without recurrent stroke.

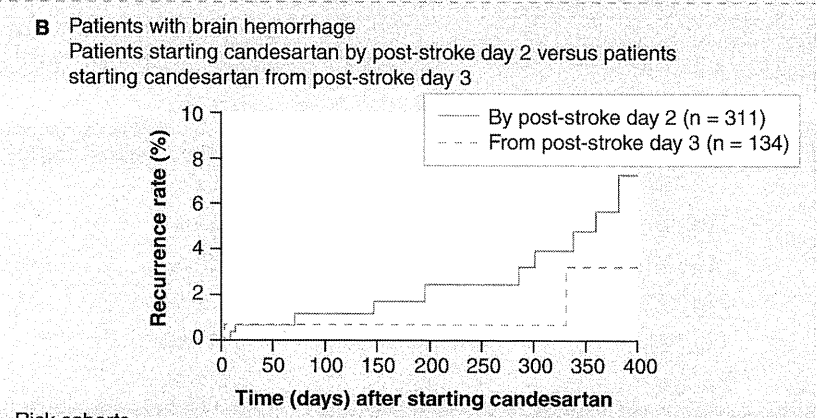
Figure 3B shows the relationship between SBP at the final visit and the risk of recurrent stroke in the BH group. The risk of recurrence was significantly higher for patients with a final SBP ≥150 mmHg compared with patients with a final SBP <130 mmHg (HR: 6.807; 95% CI: 1.52–30.49; p = 0.004). Analysis was also performed on patients with an SBP of ≥130 to <140 mmHg (three recurrences) or ≥140 to <150 mmHg (zero recurrences) and those with an SBP <130 mmHg. However, the actual number of recurrences was too small to demonstrate statistical significance at this level and data for risk of stroke recurrence in patients with an SBP of 130–150 mmHg were therefore combined as shown in Figure 3B. Figure 3C shows that there was no apparent increased risk of stroke

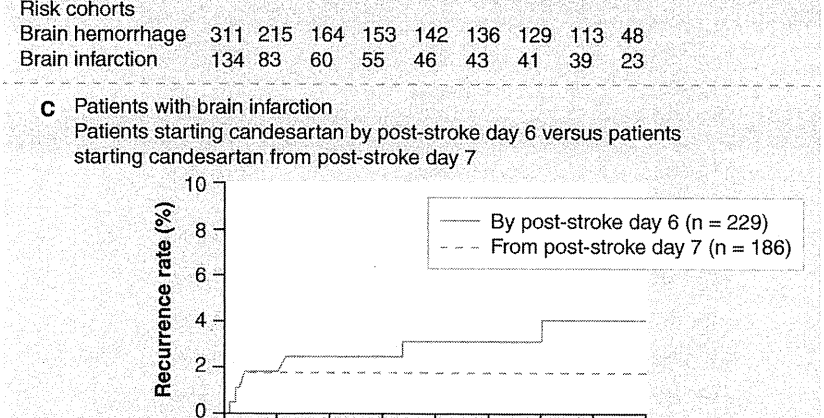
Table 3. Incidence of stroke recurrence, cardiovascular events and adverse drug reactions (safety analysis set).

Event classification	Patients with brain hemorrhage[†]		Patients with brain infarction[†]	
	Treatment started ≤post-stroke day 2	*Treatment started ≥post-stroke day 3*	*Treatment started ≤post-stroke day 6*	*Treatment started ≥post-stroke day 7+*
	n = 311	n = 134	n = 229	n = 186
Recurrence of stroke	*10 (3.2%)*	*2 (1.5%)*	*7 (3.1%)*	*4 (2.2%)*
Brain hemorrhage	6 (1.9%)	1 (0.7%)	1 (0.4%)	0 (0.0%)
Brain infarction	4 (1.3%)	1 (0.7%)	6 (2.6%)	4 (2.2%)
Lacunar infarction	2 (0.6%)	0 (0.0%)	4 (1.7%)	1 (0.5%)
Atherothrombotic brain infarction	1 (0.3%)	0 (0.0%)	0 (0.0%)	3 (1.6%)
Cardiogenic brain embolism	1 (0.3%)	1 (0.7%)	2 (0.9%)	0 (0.0%)
Subarachnoid hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiovascular events	*0 (0.0%)*	*1 (0.7%)*	*1 (0.4%)*	*1 (0.5%)*
Sudden death	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.5%)
Adverse drug reactions	*19 (6.1%)*	*11 (8.2%)*	*18 (7.9%)*	*15 (8.1%)*
Blood and lymphatic system disorders	2 (0.6%)	1 (0.7%)	0 (0.0%)	2 (1.1%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	2 (0.6%)	1 (0.7%)	1 (0.4%)	1 (0.5%)
Hepatobiliary disorders	2 (0.6%)	1 (0.7%)	3 (1.3%)	1 (0.5%)
Infections and infestations	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Investigations	11 (3.5%)	6 (4.5%)	10 (4.4%)	3 (1.6%)
Metabolism and nutrition disorders	2 (0.6%)	0 (0.0%)	4 (1.7%)	1 (0.5%)
Neoplasms (benign, malignant and unspecified)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Nervous system disorders	1 (0.3%)	0 (0.0%)	1 (0.4%)	4 (2.2%)
Psychiatric disorders	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)
Renal and urinary disorders	1 (0.3%)	0 (0.0%)	4 (1.7%)	0 (0.0%)
Reproductive system and breast disorders	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	3 (1.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Vascular disorders	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.5%)

[†]There were no statistically significant differences (p > 0.1) between subsets according to timing treatment started. Fisher's exact test was used for comparison of other variables.







Type of stroke	Timing of intervention with candesartan	Sample size	Patients with recurrence, n (%)		
			Brain hemorrhage	*Brain infarction*	*Total*
Brain hemorrhage	By post-stroke day 2	311	6 (1.9%)	4 (1.3%)	10 (3.2%)
	From post-stroke day 3	134	1 (0.7%)	1 (0.7%)	2 (1.5%)
	Total	445	7 (1.6%)	5 (1.1%)	12 (2.7%)
Brain infarction	By post-stroke day 6	229	1 (0.4%)	6 (2.6%)	7 (3.1%)
	From post-stroke day 7	186	0 (0.0%)	4 (2.2%)	4 (2.2%)
	Total	415	1 (0.2%)	10 (2.4%)	11 (2.7%)
Miscellaneous		9	0 (0.0%)	0 (0.0%)	0 (0.0%)

Figure 2. Kaplan–Meier curves for recurrence of stroke in the safety analysis set.

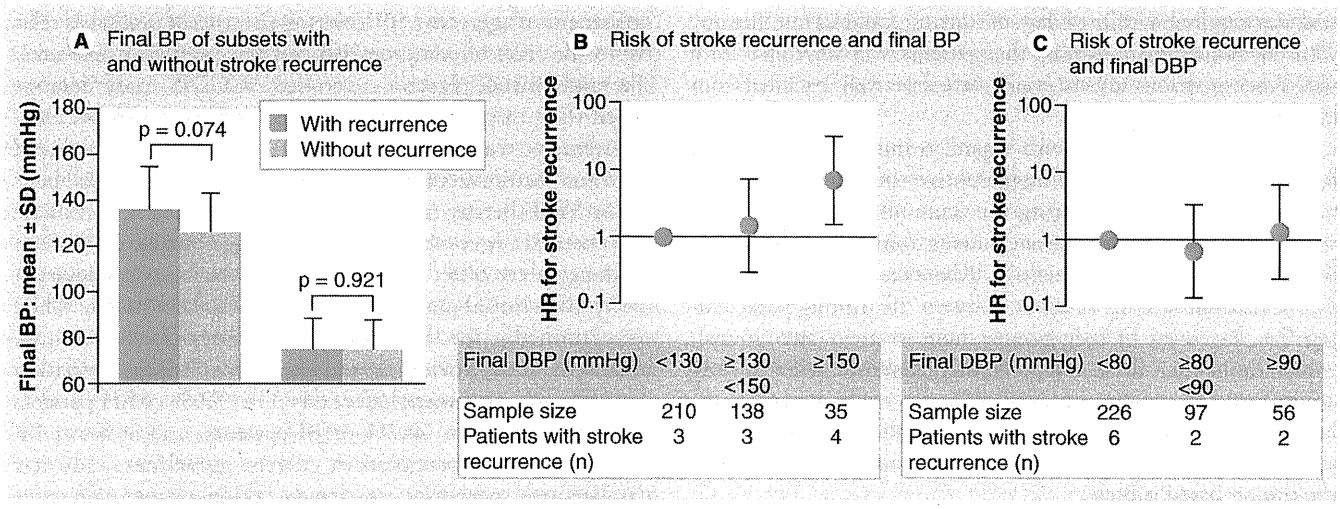
recurrence based upon final DBP (<80, ≥80 to <90, ≥90 mmHg). Furthermore, there were no significant differences between the corresponding BI subgroups.

Discussion

The question of if or when to initiate antihypertensive therapy in patients with acute stroke remains an important clinical dilemma as studies conducted to date have not provided sufficient evidence to reach a consensus on this issue. On the plus side, the ACCESS study demonstrated a significant reduction in mortality and vascular events with modest BP reduction by candesartan in the early treatment of stroke [20]. More recently, CHHIPS reported a halving of 3-month mortality rates (9.7 vs 20.3%; p = 0.05) in patients with hemorrhagic or ischemic stroke and SBP >160 mmHg who were treated within 36 h of symptom onset with labetolol or lisinopril versus placebo [10]. The INTERACT study indicated that early intensive BP lowering (target BP: 140 mmHg) administered within 6 h of hemorrhagic stroke attenuated hematoma growth over the ensuing 72 h [11]. On the other side of the equation, no differences were found between patients who either continued or discontinued pre-existing antihypertensive treatment for 2 weeks within 48 h of suffering a stroke in the COSSACS study [12], and SCAST reported no benefits with the use of candesartan for 7 days to lower BP in patients with acute stroke and SBP >140 mmHg [13].

The Challenge-Stroke study is the first multicenter prospective observational study conducted in Japanese patients to investigate the relationship between antihypertensive therapy for acute stroke and its impact on stroke recurrence. A total of 869 patients were included in the SAS (445 patients with BH, 415 patients with BI and nine patients with other cerebrovascular diseases), and the study provided useful, albeit preliminary, information about current antihypertensive treatment for acute stroke patients in Japan and the rate of recurrent stroke.

Treatment with candesartan was initiated before day 3 after the initial stroke in 79.6% of BH patients and before day 7 in 60.2% of BI patients. The average BP at the time of starting candesartan treatment was 152.0/83.2 mmHg in the BH group and 165.2/89.8 mmHg in the BI group, being lower than the criteria for providing antihypertensive therapy to



Final DBP (mmHg)	<130	≥130 <150	≥150
Sample size	210	138	35
Patients with stroke recurrence (n)	3	3	4

Final DBP (mmHg)	<80	≥80 <90	≥90
Sample size	226	97	56
Patients with stroke recurrence (n)	6	2	2

Figure 3. Relationship between stroke recurrence and blood pressure at the final assessment in patients with brain hemorrhage.
BP: Blood pressure; DBP: Diastolic blood pressure; HR: Hazard ratio; SD: Standard deviation.

acute stroke patients as stated in the 2009 JSH Guidelines for the Management of Hypertension (SBP >180 mmHg/MBP >130 mmHg for BH; and SBP >220 mmHg/DBP >120 mmHg for BI) [21]. The 2009 Japanese Guidelines for the Management of Stroke also propose similar criteria for commencement of antihypertensive therapy, and recommend its careful introduction in patients with acute BI [22]. Nevertheless, this study showed that aggressive antihypertensive therapy is being employed from an early stage after stroke in the clinical setting with a large proportion of patients receiving intravenous or oral antihypertensive agents either before the introduction of candesartan or concomitant with the use of candestartan and prior to post-stroke day 3 in patients with BH and prior to post-stroke day 7 in patients with BI. Furthermore, a recent survey of Japanese stroke centers revealed that 99.6% of physicians specializing in the management of stroke have a positive attitude towards antihypertensive therapy for acute BH patients [23]. This finding, taken together with the results of the present study, suggests that physicians generally favor the use of antihypertensive therapy for Japanese patients with acute stroke.

The BP profile revealed stable control of BP from 3 months to 1 year of candesartan treatment in both the BH and BI groups. The average BP at the final assessment (EAS) was 125.8/75.4 mmHg in the BH group and 136.3/78.1 mmHg in the BI group, being lower than the target for the chronic stage of stroke specified in the JSH Guidelines for the Management of Hypertension (<140/90 mmHg) [21]. These results support the efficacy of candesartan therapy for acute stroke patients.

The incidence of recurrent stroke, cardiovascular events and adverse drug reactions was 2.7, 0.2 and 6.5%, respectively, in the BH group versus 2.7, 0.5 and 7.0%, respectively, in the BI group. The incidence of these events was similarly low across subsets based on the timing of candesartan treatment. These findings support the safety of candesartan for controlling BP in patients with acute stroke.

Kaplan–Meier estimates for the incidence of recurrent stroke after 1 year of candesartan treatment were comparably low in the BH and BI groups, being 5.1 and 3.0%, respectively, and were similar across subsets based on the timing of candesartan therapy in both the BH and BI groups. However, as only a small number of patients (12 in the BH group and 11 in the BI group) experienced recurrent stroke during our investigation, the study had insufficient power to detect differences in the timing of antihypertensive therapy on the risk of recurrence. Moreover, the high number of patients 'lost to follow-up' as discussed in more detail later, may have introduced type 2 errors in the Kaplan–Meier analyses for risk of recurrence. Although not statistically significant, HRs for starting candesartan treatment were higher with early versus later treatment in both the BH and BI groups, possibly reflecting the greater degree of clinical instability in the immediate post-stroke period.

The relationship between BP and acute stroke outcome is known to be U-shaped, with the best outcome reported to be at SBP levels ranging from approximately 140 to 180 mmHg [8]. In the current study, a significant correlation between final SBP and risk of recurrent stroke was found in the BH group (<130 vs ≥150 mmHg; HR: 6.807; p = 0.004). This suggests that stricter management of SBP may be useful for the secondary prevention of stroke after BH, although this requires confirmation in well-controlled studies.

As this was an observational study it was not intended to validate the efficacy or safety of candesartan therapy. Furthermore, the cohort only included patients with acute stroke who received candesartan as initial antihypertensive therapy and so the results need to be viewed carefully for patients receiving other antihypertensive drugs. Since study participants were limited to those patients with acute stroke who received candesartan as initial oral antihypertensive therapy, the results of this study need to be carefully interpreted in relation to patients receiving other antihypertensive drugs. In this study, eligible patients were not enrolled serially and enrollment was done at the investigator's discretion,

and was required within 14 days of starting candesartan therapy. This introduces the possibility that patients who developed early recurrence or serious adverse events were selectively excluded from the study.

Caution is also advised with regard to interpreting the findings based on timing of antihypertensive therapy because consciousness disturbances during the acute phase of stroke (e.g., 1–2 days after onset) may prevent patients from taking medication by the oral route. Consequently, differences may have existed in the baseline severity of stroke between the timing-based subsets (i.e., less severe in early groups; more severe in later groups), which limits their direct comparability. Moreover, whereas early administration groups consisted of acute stroke patients only, late administration groups consisted of both acute and chronic stroke patients, which further limits direct comparisons between the timing-based subsets.

Patient follow-up was terminated earlier than 1 year in a high proportion of patients, mainly due to 'change of hospital' (encompassing 91% of all patients lost to follow-up in both the BH and BI groups). No explanation can be provided for the high rate of early termination; however, its impact on the study results was assessed by comparing baseline characteristics between patients who ceased follow-up early because of loss to follow-up (253 patients in the BH group and 164 patients in the BI group) and patients who completed the scheduled follow-up period (167 and 236 patients, respectively). There was a significant difference between patients lost to follow-up and those completing follow-up with respect to age (68.0 ± 12.2 years for the 'early termination' subset vs 63.6 ± 10.5 years for the 'complete' subset) and DBP at the start of candesartan treatment (81.4 ± 17.4 vs 86.4 ± 14.0 mmHg) in the BH group, as well as with respect to age (70.5 ± 11.0 vs 66.8 ± 10.3 years) and the prevalence of concomitant arrhythmia (14.6 vs 5.9%) in the BI group. Therefore, the incidence of recurrent stroke may have been underestimated in this study since patients with a higher risk of recurrence dropped out early. However, as baseline BP was high in the BH patients who completed follow-up on schedule, it is difficult to assess the influence of these dropouts.

Despite its limitations, the present study revealed that aggressive antihypertensive therapy is currently being used in acute stroke patients in Japan, and the results also confirm the efficacy and safety of candesartan for maintaining BP control in the acute stroke setting. However, we also acknowledge that the results of this study alone are not sufficient to establish criteria/guidelines for antihypertensive therapy in patients with acute stroke, and that further investigations involving more patients followed for longer periods of time are clearly needed.

Expert commentary

Approximately three-quarters of patients with acute stroke show an increase in BP above 140/90 mmHg during the initial 24–48 h post-stroke period, and this acute elevation in BP is known to adversely affect patient outcomes. However, no clear recommendations exist regarding the optimal management of BP in this clinical situation because the jury is still out regarding the benefits of aggressive BP lowering in terms of prognosis relative to the risks of compromised cerebral perfusion pressures. The randomized, placebo-controlled ACCESS study demonstrated that, in patients with acute BI and increased BP, antihypertensive treatment with candesartan significantly reduced death and cardiovascular events [20], suggesting a potential benefit for ARB therapy in patients with acute stroke. To evaluate this potential, we conducted the Challenge-Stroke study, which was designed to collect information about the use of candesartan in everyday clinical practice in patients with acute stroke. While we acknowledge the limitations of an observational study, we believe the study provides several important findings. Initiation of candesartan treatment before day 3 in 79.6% of BH patients and before day 7 in 60.2% of BI patients, and at lower BP values than those proposed in current guidelines, indicates that Japanese specialists are already taking a more aggressive approach to BP management in the initial post-stroke period even in the absence of specific recommendations. The ability of candesartan to lower BP and subsequently maintain it below the target level (140/90 mmHg) throughout the course of the 1-year study, in combination with the low incidence of recurrent stroke, cardiovascular events and adverse drug reactions reported during the study, support its efficacy and safety in this therapeutic setting. Insight gained from the Challenge-Stroke study will assist in the design and conduct of RCTs intended to confirm whether a positive relationship exists between the aggressive management of BP in patients with acute stroke and the likelihood of recurrent stroke.

Five-year view

The benefits of long-term antihypertensive therapy for the primary and secondary prevention of stroke are well established, but a knowledge gap exists with regard to the optimal management of BP in patients with acute stroke. The findings of the Challenge-Stroke study suggest that antihypertensive treatment within 2 days of BH and 6 days of BI is not only feasible, but that specialists in Japan have largely implemented this more aggressive approach in everyday clinical practice even in the absence of recommendations. This highlights an urgent need for RCTs designed specifically to address several unanswered questions. What is the optimal time frame for initiation of antihypertensive treatment? At what BP levels should antihypertensive treatment be initiated? (It appears that specialists are already intervening at levels below those suggested in current guidelines.) What is the optimal target value (range) for BP reduction? Does this target value (range) differ for patients with hemorrhagic or ischemic stroke? Which efficacy variable is more prognostic: SBP, DBP or MBP? Are certain drug classes/drug combinations more effective than others? Over the next 5 years we anticipate that more clinical evidence will accumulate which will help answer some of these important questions. This should assist physicians in the management of patients with acute stroke with the ultimate goal of improving treatment outcomes; most notably reducing the risk of recurrences and stroke-related mortality.

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Key issues

- Challenge–Stroke was an observational study intended to collect information about the use of antihypertensive therapy in everyday practice in patients with acute stroke and, more specifically, about the efficacy and safety of candesartan in this therapeutic setting.
- A total of 84 institutions across Japan participated in the study that involved 869 patients (445 with brain hemorrhage [BH], 415 with brain infarction [BI] and nine with other cerebrovascular diseases) treated with candesartan from November 2006 to September 2009.
- Candesartan treatment was initiated before day 3 after the initial stroke in 79.6% of BH patients and before day 7 in 60.2% of BI patients, and at lower blood pressures (BPs) than those stated in current guidelines, indicating that Japanese specialists currently employ an aggressive approach to BP management in these patients.
- Good control of BP throughout the 1-year study and low incidences of recurrent stroke (2.7%), cardiovascular events (0.2%) and adverse drug reactions (7.0%) support the efficacy and safety of candesartan in patients with acute stroke.
- No significant differences in terms of the incidence of recurrent stroke were found between patient subsets based on the timing of candesartan treatment (0–2 days or 3+ days after BH; 0–6 days or 7+ days after BI) although this may have been related to the low number of recurrent strokes during the study (12 in the BH group and 11 in the BI group) and the high rate of patient withdrawals.
- A significant correlation between final systolic BP and risk of recurrent stroke was found in the BH group (<130 mmHg vs ≥150 mmHg; hazard ratio: 6.807; $p = 0.004$), suggesting that strict management of systolic BP may be important for the secondary prevention of stroke after BH.
- Study limitations include its observational design, potential differences in baseline stroke severity between patients treated 'early' or 'late' with candesartan, and the high number of patients lost to follow-up.
- The results of this study alone are not sufficient to establish criteria for antihypertensive therapy in patients with acute stroke; however, they provide valuable insight into everyday clinical practice and can guide the design and conduct of future randomized controlled trials.

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特集

Therapeutic Window を広げる

脳梗塞急性期治療の行方

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超急性期脳梗塞に対するアルテプラーゼ静注療法承認までの歴史的経緯を述べた．その治療可能時間は 3 時間以内であるが，2008 年に報告された ECASSⅢの結果より，欧米ではすでに 4.5 時間以内が推奨されはじめている．更なる治療可能時間延長のために，新しい血栓溶解薬による 9 時間以内の治療，Merci などの血管内治療デバイスを用いた 8 時間以内の治療が試みられているが，その治療効果のエビデンスを得るのは容易ではない．プロトコル，治療指針を遵守し，これらの取り組みに臨むことが重要である．

Key Words
アルテプラーゼ（alteplase），拡散強調画像（DWI），血管内治療（intravascular therapy），ペナンブラ（penumbra）

はじめに

超急性期脳梗塞患者に対する遺伝子組み換え組織型プラスミノーゲン・アクチベータ（recombinant tissue-type plasminogen activator：rt-PA）であるアルテプラーゼの静注療法が 2005 年 10 月に国内承認されてから，丸 5 年が経過した．最近の報告では，承認後 4 年間の全国のアルテプラーゼ静注療法実施症例数は推計 22,491 例に達している．すなわち年平均 5,000 例以上となり，かつ使用症例数は年々増加しているという[1]．2009～2010 年にかけて，市販後臨床研究や国内登録調査研究の結果が，あいついで国内外の一流誌に報告された．アルテプラーゼ静注療法は，脳卒中専門医療機関ではもはや一般医療のレベルに達したといっても過言ではない．と同時に，診療現場でのアルテプラーゼ静注療法の有効性や限界も明らかになりつつある．

筆者は，本誌 2008 年 7 月号に総説「rt-PA 血栓溶解薬の使用の現状と今後への展望」を発表した．そこでは，最初の線溶薬ストレプトキナーゼの登場（1950 年代末）から，National Institute of Neurological Disorders and Stroke（NINDS）rt-PA Stroke Study[2]による発症 3 時間以内のアルテプラーゼ静注療法の有効性の証明（1995 年），米国での本薬承認（1996 年），国内第Ⅲ相治験 Japan Alteplase Clinical Trial（J-ACT）[3]の実施（2002～2003 年），2005 年の国内薬事承認，そして 2008 年当時までのアルテプラーゼ静注療法に関する国内外の動きを概説した．

その直後の 2008 年 9 月には，欧州で実施された大規模ランダム化比較試験（randomized controlled trial：

RCT) European Cooperative Acute Stroke Study (ECASS) Ⅲ[4]の結果が発表され，発症後 3～4.5 時間におけるアルテプラーゼ静注療法の有効性，安全性が確認された．欧州では，2008 年に発表されたばかりの急性虚血性脳卒中および一過性脳虚血発作の診療ガイドライン[5]が，ECASSⅢの公表を受けて，2009 年 1 月に「発症後 4.5 時間以内の rt-PA 静注療法を推奨する（Class Ⅰ, Level A）」と再改訂された．米国でも，これを支持する科学報告（Science Advisory）がなされた（Class Ⅰ, Level of Evidence B）[6]．最初の血栓溶解薬ストレプトキナーゼの開発から，アルテプラーゼによる発症 3 時間以内までの time window 確立に 35 年以上，これが 4.5 時間まで延長するのに，さらに 13 年を要したことになる．

さて，今回の本誌の特集は，「Therapeutic Window を広げる」である．ほかの筆者にはより具体的な執筆テーマが与えられており，それぞれ rt-PA 治療を軸にして治療効果をさらに高める具体的な工夫，提案がなされている．しかしながら，筆者に与えられた執筆課題は，「有効性が限定的な rt-PA 治療を核とした現状をどう発展させるか」という漠然としたものであった．そこで，これまでの歴史的経緯を振り返ることに重点を置くこととし，そのうえで，現役世代，そして次世代の医療者が肝に銘じて取り組むべき課題を論じることとする．すなわち，温故知新である．

1 13 年前へのタイムトラベル… 治療の time window

アルテプラーゼ静注療法の一般臨床応用が米国ではじまったばかりの 1997 年 10 月，筆者は，ある国内雑誌に「治療の time window」[7]と題した総説を発表した．そこに書いたサマリーを，以下に再掲する．

「ペナンブラ領域は血行再開により回復しうるが，その可逆性は虚血の「程度」と「持続時間」に依存する．超急性期血栓溶解療法の成功により，治療可能時間（therapeutic window of time）は臨床的に重要な概念となっている．この window は固定的なものではなく，治療法を含めた多くの要因によって異なりうる．現在多くの脳保護薬が検討中であり，可逆性判定法としての diffusion MRI も注目されている．より多くの患者の超早期治療を可能とする救急医療システム構築も急務である．…」

このときの総説では，それまで実験的概念にすぎなかった「虚血早期の治療可能性」が，アルテプラーゼ静注療法の米国内承認により「臨床現場での現実」となったことを強調したうえで，①虚血性ペナンブラ（ischemic penumbra）と therapeutic time window の理論，②血栓溶解療法における therapeutic time window の考え方，③脳保護療法や抗血栓療法による治療可能性，④SPECT，PET，diffusion MRI によるペナンブラの画像化の問題を論じた．この時点では，ペナンブラ領域の可逆性が時間とともに失われるメカニズムとして，拡延性抑制（spreading depression：SD），興奮性アミノ酸の過剰放出，Ca チャンネルの活性化などが議論されていた．また，これらの生化学的プロセスの抑制，修飾による治療の可能性が検討され，実験レベルで数百種類以上，また臨床試験で検討中の薬（脳保護薬）は少なくとも 31 種類あった．

残念ながら，検討された脳保護薬の臨床試験はことごとく失敗し，ペナンブラの正確な画像化にもいまだ成功していない．また，アルテプラーゼ静注療法の日本国内承認が 8 年も先になるとは，その当時は夢にも思っていなかった．

2 更なるタイムトラベル…20 年前へ… なぜ，3 時間以内だったのか？

最近，とある新聞社（全国紙）の記者から，「アルテプラーゼ静注療法の治療可能時間が，海外で 3 時間から 4.5 時間に延びた」ことに関するインタビュー取材を受けた．このとき，「そもそも，米国の試験ではなぜ 3 時間以内とされたのか，その経緯をご存じでしたら教えてください」との質問を受け，新鮮な驚きを感じた．米国の臨床試験の結果が発表されてから，はや 15 年……．もはや「3 時間以内」は科学的事実として定着し，専門家は「なぜ 3 時間以内なのか？」との疑問を発しなくなっていたからである．

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study，すなわち NINDS Study は，今でこそ完璧な RCT，脳卒中急性期治療の金字塔と信じられているが，紆余曲折が結構あった試験である．その一端は，1994 年 4 月（すなわち NINDS Study 発表の 1 年半前）に奈良市で開催された国際学会 The 3rd International Symposium on Thrombolytic Therapy in Acute Ischemic

Stroke（会長：山口武典，事務局長：峰松一夫）[8]で報告された．その経緯をかいつまんで説明すると，以下の通りとなる．

1980～1990年代の多くの動物実験成績は，再開通療法（いったん閉塞した脳動脈を再開通させる治療法）の効果が期待できるのは，せいぜい2～3時間以内であることを示していた．NINDS Studyも，いきなり3時間以内・600例以上のRCTをはじめたわけではない．すなわち1987年2月～1989年9月に発症後90分以内の症例を対象とする予備試験が，さらに1988年12月～1989年12月には91～180分の症例を対象とする第二予備試験が実施され，薬物量や治療可能時間が慎重に検討された[9][10]．その結果，当然のことながら，治療開始が早いほど効果も良好であることが示唆された．以上の結果を受け，0.9 mg/kgで180分（3時間）以内という条件での本試験が1990年10月にスタートした．試験はまず300例の予定で実施された．その結果は確実性に乏しく，当局より追加試験の実施が要請された．

筆者がNINDS Studyグループの一人であるPatrick Lyden教授から直接聞いた話では，費用も時間もかかる追加試験を実施すべきか否かについて，研究グループ内で大変もめたという．そのころわが国で実施された6時間以内の血栓溶解療法（米国とは異なるrt-PAの，デュテプラーゼを使用）の試験成績が比較的良好であったとの情報が研究グループに伝わった．また欧州でも，発症6時間以内を対象とする大規模試験ECASS（アルテプラーゼを使用）が進行中であった．こうした日欧の研究動向とその結果情報を参考にプロトコルが一部修正され，300例以上の症例を上積みする本試験が再開された．その結果が1995年に発表されたNINDS Studyである．

わが国で実施されたRCTは，治療可能時間を6時間以内に設定し，治療前後に全例に脳血管撮影を実施するという難易度のきわめて高い試験であった．症例数が少なく（約100例），統計的に有意な臨床的効果は示せなかった[11]．ただし，閉塞血管の再開通率は実薬群で有意に高率で，症候性頭蓋内出血の増加は認められなかった．再開通率の有意な上昇という情報が，NINDS Study再開の判断を決定づけたという．残念ながら国内試験薬のデュテプラーゼは，特許権をめぐる国際訴訟に敗れ，本薬の製造販売，そして薬事への承認申請も断念された．

欧州の試験ECASS[12]（6時間以内で約600例）の結果も1995年に発表されたが，「有効性はあるが，安全上の懸念もある」との結果であった．用量を米国と同じ0.9 mg/kgに減らして，6時間以内の症例を対象に実施されたECASSⅡ[13]も確実な有効性を証明できなかった．

要は，米国のほうが理論的に，かつ短いtime windowから段階を追って試験を実施し，かつ3時間以内の症例を600例以上も試験に組み込むことを可能とする国力があったということになる．

3 今日に戻る

アルテプラーゼ静注療法は，その後世界各国で承認されたが，その唯一の根拠はNINDS Studyであった．しかしながら，海外で実施されたいくつかの臨床試験のメタアナリシス[14]では，本療法の治療可能時間は4.5時間目まで延長できる可能性が示された．それを証明すべく実施されたのがECASSⅢ[4]であり，結果的にtime windowを4.5時間目までに伸ばすことに成功した．

さて，わが国である．2005年にやっとアルテプラーゼ静注療法が国内承認となったわが国では，その後さまざまな市販後登録調査や臨床試験が実施された．その結果，使用用量が欧米の2/3の0.6 mg/kgと少量であるにもかかわらず，欧米での成績とほぼ同等の好成績を収めていることが明らかとなった[15]～[18]．ただし，内頸動脈閉塞や中大脳動脈のごく近位部での閉塞（閉塞断端までの長さが5 mm未満）の場合，再開通率や転帰良好の比率が不良であることも判明した[15][19]．

アルテプラーゼ静注療法の承認は診療現場に大きな影響を及ぼした．すなわち，発症3時間以内の受診率向上のための市民啓発，救急隊との連携，診療体制の再構築，SCUや脳卒中センターの整備など，脳卒中診療を取り巻く環境は激変しつつある．アルテプラーゼ静注療法では，適応患者を迅速かつ適切に選別し，治療開始までの時間をできるだけ短縮させることが重要である．不適切な患者選択，治療開始時間の遅れ，治療指針からの逸脱は，効果の減弱のみならず，転帰を悪化させる危険性があるからである．

国立循環器病研究センターを受診した発症7日以内の急性期脳卒中患者のうち，アルテプラーゼ静注療法を実施された患者は10%前後であった[15]．全国平均では，わずか2～3%程度と推計されている．さらに，頸動脈～

表❶ Merci リトリーバー適正治療指針
（一般社団法人日本脳卒中学会ホームページ[20]より）

平成 22 年 5 月

日本脳卒中学会会員各位
Merci リトリーバー使用者各位

一般社団法人日本脳卒中学会　　理事長　小川　彰
同 脳卒中医療向上・社会保険委員会委員長　峰松 一夫

Merci リトリーバー適正治療指針について

Merci リトリーバーについて

Merci リトリーバー（以下 Merci）は，遠位端にらせんループを有するワイヤー状の医療機器で，マイクロカテーテル内に誘導することにより頭蓋内動脈に到達可能であり，欧米では急性脳動脈閉塞の原因となっている血栓を回収する目的で使用されています．これまでの欧米での臨床研究により，原則として発症後 8 時間以内の急性期脳梗塞において，遺伝子組み換え組織型プラスミノーゲン・アクチベータ（rt-PA，アルテプラーゼ）静注療法の治療適応外，または rt-PA 静注療法でも血流再開が得られなかった患者を対象とした場合に，本機器を用いた血栓摘除治療が有効であることが示唆されてきました．しかしながら，本療法の有効性および安全性は，まだ十分に確認されている訳ではありません．

社団法人日本脳卒中学会は，本機器による脳卒中急性期治療が適正に実施され，以て本療法の有効性が発揮されることを大いに期待しています．そのために，以下に述べる適正治療指針が遵守されることを，本学会会員，ならびにすべての Merci リトリーバー使用者に求めます．

適正治療指針のまとめ

1　rt-PA 静注療法の適応例に対しては，これを優先すること．
2　「Merci を用いた再開通療法が有効である」との科学的根拠は十分ではないことに留意すること．
3　Merci 使用者は，その添付文書，実施基準を遵守し，所定の訓練を経て正しい操作方法および使用方法を身につけたうえで実施すること．
4　Merci 使用者は，その市販後調査や臨床研究に積極的に協力し，本療法の効果や問題点を明らかにすることに協力すること．

解　説

1　rt-PA 静注療法の適応例に対しては，これを優先すること．

急性脳動脈閉塞に対する再開通療法としては，rt-PA 静脈内投与が認可されており，これまでの科学的根拠の蓄積に基づき，発症 3 時間以内に治療可能な虚血性脳血管障害のうち，除外項目を有しない適応患者に対して強く推奨されている．脳卒中治療ガイドライン 2009，日本脳卒中学会 rt-PA（アルテプラーゼ）静注療法適正治療指針に基づき，適応患者を慎重に選択して rt-PA 静注療法を実施すべきであり，その適応患者に対する Merci の使用は厳に慎まねばならない．

2　「Merci を用いた再開通療法が有効である」との科学的根拠は十分ではないことに留意すること．

カテーテルを用いる局所再開通療法として科学的根拠を有するのは，中大脳動脈の塞栓性閉塞において，症候が中等症以下で，CT 上梗塞巣を認めないか軽微な梗塞にとどまり，発症から 6 時間以内に治療開始可能なものに対する経動脈的局所線溶療法だけである（MELT-Japan）．Merci を用いた再開通療法には前向き登録研究があるのみであり，内科治療や他の再開通療法と比較して有効であるという十分な科学的根拠はないことに留意すべきである．

3　Merci 使用者は，その添付文書，実施基準を遵守し，所定の訓練を経て正しい操作方法および使用方法を身につけたうえで実施すること．

本デバイスの適応や標準的操作方法，使用方法は，添付文書に記載されている．また日本脳卒中学会が日本脳神経外科学会，日本脳神経血管内治療学会とともに取りまとめた 3 学会承認実施基準が定められており，定められた基礎資格を有する者が，所定の訓練を経て Merci を使用する者（実施医）と認定される．これらの規則を遵守し，Merci を用いた再開通療法を実施すること．

4　Merci 使用者は，その市販後調査や臨床研究に積極的に協力し，本療法の効果や問題点を明らかにすることに協力すること．

承認後に実施される市販後調査やその他の臨床研究により，Merci を用いた再開通療法の実態を調査し，その安全性や有効性を明らかにする必要がある．急性脳動脈閉塞のなかでの本治療法の位置づけを含め，これらの調査，研究に協力することが求められる．

以上

中大脳動脈起始部閉塞，治療直前 NIHSS（National Institutes of Health Stroke Scale）スコア高値，高血圧症の存在，比較的広汎な早期虚血性変化の存在などが転帰不良に寄与する．すなわち，アルテプラーゼ静注療法の恩恵を被る患者は必ずしも多くないというのが実情である．

4 今後の展開

わが国でも，「アルテプラーゼ静注療法の治療可能時間を，従来の 3 時間以内から 4.5 時間に延長する」ことを日本脳卒中学会から厚生労働省に要請中であるが，まだこれに対する回答がなされていない（検討中との答え）．欧米でも，ガイドライン上では「4.5 時間以内の治療」を勧告しているものの，添付文書上の治療可能時間は 3 時間以内のままである．この点が，厚生労働省が時間延長を認めていない大きな理由と思われる．グレーな状態はしばらくつづくかもしれない．

現在，発症 3～4.5 時間以内のアルテプラーゼ静注療法の限界を打破すべく，さまざまな試みがなされ続けている．その多くが今回の特集で論じられている．ここでは現在進行中の取り組みを簡単に紹介する．

●1．デスモテプラーゼ静注療法

発症 9 時間以内の脳梗塞症例を対象に，新しい rt-PA の一つで，かつ血栓選択性・特異性の高いデスモテプラーゼ（desmoteplase）静注療法が国際第Ⅲ相臨床試験として 2 件実施中である．わが国はこれらに不参加であるものの，独自の国内第Ⅱ相治験を実施中である．すべてよい結果となれば，国内外で治療可能時間は大幅に延びるであろう．

●2．血管内治療デバイス

急性期脳梗塞治療用医療機器の一つである Merci リトリーバーが 2010 年 4 月 30 日付で承認され，10 月より保険償還も実施されている．アルテプラーゼ静注療法は，原則として発症後 8 時間以内の急性期脳梗塞で，アルテプラーゼ静注療法の適応外，もしくは同療法無効例（血流再開が得られない症例）を対象とし，機械的血行再開による転帰改善を目的としている．血栓溶解薬を使用しないため，「症候性頭蓋内出血などの出血性合併症がかなり抑制されるであろう」との仮説が根拠となっている．

ただし，アルテプラーゼ静注療法の有効性は証明されてはいない．このため，日本脳卒中学会から「適正治療指針」が発表され（表❶）[20]，また市販後 3 年間の全例調査が義務付けられた．類似の急性期脳梗塞治療用医療機器には，血栓吸引装置としての Penumbra などがあり，2011 年以降薬事承認される予定である．エビデンスレベルは高くなく，また死亡率の高い症例群を対象にすることから，おそらく Merci リトリーバーと同様の対策が講じられるであろう．

おわりに

急性期脳梗塞の治療可能時間の延長の問題を，アルテプラーゼ静注療法の承認前後の歴史を振り返りながら論じた．アルテプラーゼ静注療法にさまざまな限界があることは確かであり，その限界を超える新しい治療方法の模索，beyond alteplase への取り組みが本格化している．しかしながら，わずか 3 時間，4.5 時間の治療可能時間のエビデンスを得るのに先人たちが 35 年以上，さらに 13 年の大変な努力を要したことを忘れてはならない．その道は容易ではない．しかしいつか必ず目的地に達するであろう．

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