Evaluation of applied cases of thrombolytic therapy against ultra-acute ischemic stroke
– Using the Japanese Standard Stroke Registry Database –

Hiroyuki SHIOTSUKI[*,***], Yoichi OGUSHI[**],
Kiyohide FUSHIMI[*] and Shotai KOBAYASHI[***]
for the Japanese Standard Stroke Registry Study (JSSRS) Group

[*]Tokyo Medical and Dental University, Graduate School of Medicine and Dentistry
[**]Department of Medical Informatics, Tokai University School of Medicine
[***]Department of Neurology, Hematology & Rheumatology, School of Medicine, Shimane University

Background: A retrospective evaluation was made concerning thrombolytic therapy for ultra-acute ischemic stroke patients, using a recombinant tissue plasminogen activator (rt-PA), which is not yet approved as a drug for brain infarction in Japan. The evaluation was implemented using the database of patients that suffered acute strokes as collected by the Japanese Standard Stroke Registry Study (JSSRS).

Methods: The thrombolytic therapy group, selected from among the registered 6,090 cases of brain infarction patients, was divided into two groups, namely, a group of patients who were admitted in the hospital within 3 hours of the onset (86 cases, average age 69.6) and the other group who were admitted after 3 hours from the onset (28 cases, average age 66.8). Using a Multiple Logistic Regression Analysis adapted for modified Rankin scale (mRS) regarding each group, the clinical effects of thrombolytic therapy for functional outcome and presence or absence of dementia at the time of hospital discharge were examined. Among the 467 cases of patients (average age 74) who were admitted within 3 hours of the onset and for whom the NIH Stroke Scale (NIHSS) was between 6 and 29 at the time of admission, intravenous or intra-arterial thrombolytic therapy was conducted in 88 cases. Then, a case-control study and Multiple Logistic Regression Analysis was implemented for subject groups matched according to the gender, age and severity at the time of admission, and the effects on early-admitted patients were examined. Also, for two rehabilitation patient groups: one whose rehabilitation started within 7 days (216 cases; average age 73) and the other whose rehabilitation started after 7 days (56 cases, average age 76), the effects of early rehabilitation were examined using Multiple Logistic Regression Analysis. Moreover, the effects of thrombolytic therapy on a group of patients who were admitted early and for whom rehabilitation started early (215 cases; average age 73) were examined in the same way.

Results: In the comparison between the thrombolytic therapy groups, the functional outcome of the group of patients admitted within 3 hours of the onset at the time of discharge (mRS 0-1) was significantly better compared with that of the group after 3 hours from the onset (OR 2.79, 95%CI: 1.06-7.32). Regarding the comparison between the early admitted patients, the frequency of poor functional outcomes (mRS 2-6) at the time of discharge was significantly lower in the thrombolytic therapy group (OR 0.55, 95%CI 0.31-0.98), and the frequency of dementia was also significantly lower (OR 0.37, 95%CI 0.17-0.86). In the case control study, a significant difference was noted for the presence of dementia. In the group rehabilitation was started early, the frequency of poor functional outcomes was significantly lower (OR 0.33, 95%CI 0.11-0.98), and the frequency of dementia was also significantly lower (OR 0.41, 95%CI 0.19-0.89). As for the comparison of the groups admitted early and for which rehabilitation started early, the frequency of poor functional outcomes at the time of discharge was significantly lower in the thrombolytic therapy group (OR 0.38, 95%CI 0.16-0.86).

Hiroyuki SHIOTSUKI, Tokyo Medical and Dental University, Graduate School of Medicine and Dentistry, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan   TEL/FAX: +81-3- 5283-5788

Department of Medical Informatics, Tokai University School of Medicine, Bohwseidai, Isehara, Kanagawa 259-1193, Japan   TEL: +81-463-93-1121 ext.2143   FAX: +81-463-93-5418   E-mail: shiohci@tmd.ac.jp

Conclusions: From the present analysis, in spite of being a retrospective analysis based on comparatively small number of patient cases from the stroke database, it is concluded that the clinical application of thrombolytic therapy for ultra-acute ischemic strokes was effective.
Moreover, it was demonstrated that, if it is possible to start rehabilitation early, a dramatic improvement of the effects might be expected.

Key words : acute ischemic stroke, rt-PA, thrombolytic therapy, case control study, multivariate statistical analysis, rehabilitation.

INTRODUCTION

In recent years in Japan, thrombolytic therapy, which is a treatment for ultra-acute ischemic cerebrovascular disease, is drawing increasing attention. In 1995, the effectiveness [1] of intravenous thrombolytic therapy for ultra-acute ischemic stroke patients, when administered within 3 hours of the onset, and where the recombinant tissue plasminogen activator (rt-PA) is used, was reported by the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. Since that time, acute ischemic cerebrovascular disease has been called "Brain Attack", and the importance of ultra-acute treatment has gained recognition, as in the case of coronary artery disease. Thrombolytic therapy using rt-PA was already approved and is being established as an initial treatment for brain infarction in nations such as Canada, Germany, etc. as well as in the United States, but in Japan, though there are some practical exceptions, it is still not approved [2]. In Japan, too, an rt-PA open clinical trial has been completed, and it is in the stage of application, but it is expected to take some more time before approval is granted. However, it is reported in the aggregate calculation of Japanese Standard Stroke Registry Study (JSSRS) that the therapy was already applied in a considerable number of cases [3].

Accordingly, this study makes a statistical analysis of thrombolytic therapy as the treatment for ultra-acute ischemic stroke using the JSSRS database of patients who have had an acute stroke. Based on this multi-center database, we evaluate retrospectively the effects of the therapy in terms of functional outcome and the presence of dementia at the time discharge as after-effects of a stroke. This evaluation is considered especially significant in light of Japan's demographic trends, in which aging population is rapidly advancing, and nursing care is becoming an increasingly high priority. Moreover, an evaluation of the effects according to rehabilitation starting time was also conducted.

MATERIALS AND METHODS

Objects of Evaluation

The patient data is sourced from "Japanese Standard Stroke Registry, (JSSR)" (Chief researcher: Shotai Kobayashi), in which 8,125 cases (In the year 2001, age 68.92 ± 24.33, female 3,335 examples, male 4,790 examples) were gathered from 42 facilities across the country, and which was implemented as a nationwide registration of a "Stroke database" that is accessible as a stand-alone type computer base at each hospital.

The following items are used as data categories;

Hospital, gender, age, date of admission, time of admission, onset day of stroke, onset day of the week of stroke, onset time of stroke, condition at the onset time of stroke, method of transportation to the hospital, time between onset and admission to hospital, department in charge, hospitalization days, provisional diagnosis of stroke, onset type, systolic arterial pressure at the time of admission, diastolic blood pressure at the time of admission, previous history of strokes, progress after admission, recurrence after admission, family history of strokes, history of alcohol consumption, smoking history, AF (atrial fibrillation), high blood pressure, diabetes, hyperlipemia, cardiac disease, anticoagulant/antiplatelet therapy, renal disease, date of discharge, systolic arterial pressure at the time of discharge, diastolic blood pressure at the time of discharge, confirmed diagnosis, modified Rankin (mRS) at the time of discharge, presence of dementia at

the time of discharge, type of imaging diagnosis used for presence of infarction, size of infarction, image diagnosis, size of bleeding, presence of hemorrhagic infarction, white mater lesion, cardiovascular check, result of cardiovascular check, cerebrovascular check, result of cerebrovascular check, content of acute therapy, starting time, number of days, rehabilitation starting time, presence of surgery, content of surgery, JSS at the time of admission, JSS at the time of discharge, NIHSS at the time of admission, NIHSS at the time of discharge, (not necessarily in this order).

Note that each patient's privacy was fully protected in the analysis and reporting. Items underlined above were used as input data for this analysis.

The types of brain infarction were classified according to NINDS-III cerebrovascular disease classifications, as follows: transient ischemic attack (TIA), atherothrombotic infarction, cardiogenic brain embolism, lacunar infarction, and other brain infarction. Moreover, atherothrombotic embolism cases were further divided for evaluation.

Dementia diagnosis was made according to the DSM-III R diagnostic criteria for dementia, and as for degree of severity, mild case or heavier wad included in the diagnosis.

The essential features of diagnostic criteria were 1) Disorder of memory, 2) either one or more of abstract thinking disorder, disorder of judgment, disorder of other higher cortical function, or personality distortion, 3) Any disorders that tend to cause considerable hindrance to daily social activities, etc. [4].

Research Method
Data arrangement
The data set was arranged in advance as follows to enable statistical processing.
1. Encoding: Since statistical processing cannot be made if data is registered with characters, encoding was made. Gender, for example, was encoded as "1: Male 2: Female", and other data of binary nature is encoded as "0: Absent 1: Present".
2. Category integration: Since data is descriptive, synonyms are used, and also Latin-type letters (one-byte characters) are mixed with Japanese characters (double-byte characters), these were integrated and standardized. There were also multiple categories for similar items that were unified and standardized.

For example, under the 'condition at the onset', "When trying to move" and "In action", or "During sleep" and "While taking a nap", etc. were registered in the database, and these were integrated. For other items, too, the same procedure was taken. Also, lack of data input or "Unknown" were in combined use, and "Unknown" was treated as 'lack of data input'.
3. Binarization: In order to apply the Multiple Logistic Regression Analysis, data of factors (independent variables) must be expressed in interval ratio scale or as binary data, and data of results (dependent variable) must be as binary data. Therefore, we binarized categorical (nominal scale) data and ordinal data or expressed them as dummy variables (quantifiable). For example, "during sleep", "during bed rest", "while in action", "on rising", "during surgery", "while taking a bath" were used for "Condition at onset time", but these were quantified by three newly created dummy variables: "during bed rest", "while in action", "bedtime", with "Others" taken as the base value. The presence of thrombolytic therapy was binarized as "0: Absent, 1: Present" (=t-PA selected intra-arterial injection, t-PA by intravenous drip infusion, UK (Urokinase) selected intra-arterial injection, intravenous bolus of 300 thousand UK units).
4. Ordinal data conversion: Since data input was descriptive, categories of items that can be treated as ordinal data were arranged and quantified. For example, "Rankin 0-1", "Rankin 2", "Rankin 3", "Rankin 4-5", "Rankin 6", and 'no data input' had been used for "mRS at the time of discharge", but this was converted to, 1: Rankin 0-1, 2: Rankin 2, 3: Rankin 3, 4: Rankin 4-5, 5: Rankin 6, and 'no data input'.

Statistical methods
1. Comparison between the middle-level thrombolytic therapy group and high-level thrombolytic therapy

As the thrombolytic therapy evaluated at this time is retrospective and not a proactive clinical trial, it includes a variety of different medications and dosages. Therefore, these were divided into a high reliability level group, equivalent to t-PA clinical trial conducted in the United States and a middle level one, of a slightly lower reliability level

compared to the other group, and comparative review was made to check if there is any difference between the respective groups. In view of thrombolytic therapy, middle level thrombolytic therapy was defined as intravenous bolus of 300 to 420 thousand UK units and high level was defined as t-PA by selected intra-arterial injection, t-PA by intravenous drip, UK selected intra-arterial injection.

For comparing these two groups, we constructed a case-control study, in which the case group was the high-level thrombolytic therapy group (n=52: Female 13 patients, male 39 patients), and the control group consisted of patients selected from among the middle-level thrombolytic therapy group (n =36: Female 14 patients, male 22 patients), namely patients with the same NIHSS (NIH stroke scale) [5, 6] rank, gender, age bracket and disease type as that of a case group patient (n=23: Female 4 patients, male 19 patients: number of cases=number of controls). As for NIHSS rank, NIHSS at the time of admission was divided into 4 sections by percentage quartile, and age brackets were classified by 10-year intervals. When a fact-finding survey is conducted using a database such as a hospital records for strokes, bias such as selective bias, etc. is apt to occur to analysis results. In order to avoid such bias as much as possible, this method enabling matching with gender, age, degree of severity, etc. and random extraction of patients was adopted. Mann Whitney-U was used for the testing method, and SPSS for Windows version 10.1.3J was used as statistical analysis software application.

As a result, no significant difference between the two groups was found [3] regarding hospital days, presence of dementia, changes in NIHSS, changes in Japan Stroke Scale (JSS) [7], mRS (modified Rankin scale) [8] at the time of discharge. Therefore, in this analysis, with consideration to the limited number of available cases, middle-level thrombolytic therapy group and high-level thrombolytic therapy were recombined and examined together as a single thrombolytic therapy group.

2. Comparison between the onset time and admission time in the thrombolytic therapy

From among the patients with brain infarction (n=6,090), those suffering cardiogenic brain embolism (n=103), atherothrombotic infarction (n=22), and atheroembolic infarction based on the NINDS-III diagnosis criteria for stroke (n= 3), respectively in moderate or serious condition with their NIHSS being between 6 and 29, and for whom thrombolytic therapy was applied, were selected for analysis. While those who had the stroke onset during sleep (n=14) were removed from this sample, the following analysis was made on those admitted within 3 hours of the onset (n= 86: Age 69.6±20.1) and those admitted after 3 hours (n=28: Age 66.8 ± 18.2). According to NINDS's clinical trials concerning t-PA, in the case of patients who experienced the onset during sleep, the last minute, e.g. the time just prior to sleep, was calculated as onset time [1, 9], but in this analysis, such cases were treated as "onset time unknown". This comparison between thrombolytic therapy groups include the patients treated after 3 hours from the onset.

(1) A Multiple Logistic Regression Analysis was made on the mRS at the time of admission, in which the binarized mRS at the time of discharge (n=114: Age 68.9 ± 19.7, female 36 patients, male 78 patients), namely binarized as "0: Rankin 0-Rankin 1, 1: Rankin 2-Rankin 6" was assigned as the dependent variable, and while those with the onset during sleep were removed, the patients admitted within 3 hours of the onset (n =86) and those admitted after 3 hours (n= 28) [0: Those after 3 hours, 1: Those within 3 hours] were taken for the independent variable. Gender, age bracket and NIHSS at the time of admission were assigned as covariates.

(2) The Multiple Logistic Regression Analysis was made on the presence of dementia at the time of discharge, in which the presence of dementia; "0: Absent, 1: Present" (n=82: Age 69.1 ± 17.9, female 25 patients, male 57 patients) is used as the dependent variable, and while those with the onset during sleep were removed, the patients admitted within 3 hours of the onset (n=60) and those admitted after 3 hours (n=22) were taken for the independent variable. Gender, age bracket and NIHSS at the time of admission were assigned as covariates.

3. Comparison between the thrombolytic therapy group and the non-thrombolytic

Table 1 Background Factor of Cases and Controls

	No.
Gender	
Female	27
Male	57
Age bracket (y)	
≧49	1
50-59	11
60-69	25
70-79	32
80≦	15
Subtype	
Atherothrombotic infarction	7
Atheroembolic infarction	1
Cardiogenic brain embolism	76
NIHSS at the time of admission*	
6-9	14
10-14	19
15-19	20
20-29	31

*NIHSS at the time of admission was divided into 4 sections by percentage quartile.

therapy group in the early admitted patients

From among the patients with brain infarction (n=6,090), those with the onset during sleep were removed, and those admitted within 3 hours of the onset and suffering cardiogenic brain embolism (n=344: Age 74.1±21.1, female 143 patients, male 201 patients), atherothrombotic infarction (n=98: Age 73.2±21.2, female 32 patients, male 66), and atheroembolic infarction (n=25: Age 71.9 ± 17.5, female 6 patients, male 19 patients), respectively in their moderate or serious condition with their NIHSS between 6 and 29 at the time of admission were selected for the data set, and the following analysis was made on these subjects (n=467: Age 73.8 ± 21.0, female 181 patients, male 286 patients). This comparison between the early-admitted patients does not include the cases after 3 hours from the onset.

(1) A case-control study was made, in which the case group was the complete thrombolytic therapy group (n=88: Female 27 patients, male 61 patients), and the control group were selected from among the non-thrombolytic therapy group (n=379: Female 154 patients, male 225 patients), namely patients with the same NIHSS rank, gender, age bracket and disease type as that of a case group patient (n=84: Female 27 patients, male 57 patients: number of cases=number

of controls. NIHSS rank was divided into 4 sections by percentage quartile, and age bracket was classified by 10 year intervals (Table 1) Regarding testing method, Mann Whitney-U was used, in which gender, age bracket, NIHSS at the time of admission, disease type, hospital days, presence of dementia at the time of discharge, changes in NIHSS, changes in JSS, and mRS at the time of discharge were assigned for test variables, and the presence of thrombolytic therapy was assigned for grouping variable.

The changes in NIHSS and changes in JSS were tabulated as the difference in NIHSS score between the time of admission and the time of discharge, and as the difference in JSS score between the time of admission and the time of discharge, respectively.

(2) The Multiple Logistic Regression Analysis was made on the mRS at the time of discharge, in which the binarized mRS (0: Rankin 0-Rankin 1, 1: Rankin 2-Rankin 6) at the time of discharge (n=459: Age 73.8± 21.0, female 182 patients, male 277 patients), was assigned as the dependent variable, and the presence of thrombolytic therapy "0: Absent, 1: Present" was taken as the independent variable. Gender, age bracket and NIHSS at the admission time were assigned as covariates.

(3) The Multiple Logistic Regression Analysis

was based on the presence of dementia data at the time of discharge, in which the presence of dementia; "0: Absent, 1: Present" (n =334: Age 73.7 ± 20.5, female 126 patients, male 208 patients) is the dependent variable, the presence of thrombolytic therapy is the independent variable. Gender, age bracket and NIHSS at the admission time were assigned as covariates.

4. Verification of the effects of early start of rehabilitation on patients admitted early

From among the patients with brain infarction (n=6,090), those with the onset during sleep were removed, and those admitted within 3 hours of the onset and suffering cardiogenic brain embolism (n=204), atherothrombotic infarction (n=61), and atheroembolic infarction (n=15), respectively in moderate or serious condition and with their NIHSS between 6 and 29 at the time of admission were selected for analysis. Those for whom, for some reason, rehabilitation could not be started were removed from the sample, and the following analysis was made on the remaining subjects (n=280: Age 73.7 ± 20.8, female 108 patients, male 172 patients).

When binarization was made on the rehabilitation starting time (0: After 3 days, 1: Within 3 days), a similar analysis was conducted but no statistically significant result was obtained. Therefore, the data was re-divided by the threshold of within 7 days as the starting time of rehabilitation.
(1) The Multiple Logistic Regression Analysis was made on the mRS at the time of discharge, in which the binarized mRS (0: Rankin 0-Rankin 1; 1: Rankin 2-Rankin 6) at the time of discharge (n=272: Age 73.7 ± 21.0, 106 female patients, 166 male patients) was used as the dependent variable, and the binarized rehabilitation starting time (0: After 7 days, 1: Within 7 days) was taken as the independent variable. Gender, age bracket and NIHSS at the time of admission were assigned as covariates.
(2) The Multiple Logistic Regression Analysis was made on the presence of dementia at the time of discharge, in which the presence of dementia; "0: Absent, 1: Present" (n=212: Age 73.8 ± 20.4, female 80 patients, male 132 patients) is the dependent variable, and the rehabilitation starting time is the independent variable. Gender, age bracket and NIHSS at the admission time were assigned as covariates.

5. Comparison between the thrombolytic therapy group and non-thrombolytic therapy group in the patients that were admitted early and started early rehabilitation

From among the patients with brain infarction (n=6,090), those with the onset during sleep were removed, and those admitted within 3 hours of the onset and suffering cardiogenic brain embolism (n=163: Age 73.93 ± 21.3, female 71 patients, male 92 patients), atherothrombotic infarction (n= 49: Age 71.1 ± 21.2, female 14 patients, male 35 patients), and atheroembolic infarction (n=11: Age 72.4 ± 16.5, female 4 patients, male 7 patients), respectively in moderate or serious condition with their NIHSS between 6 and 29 at the time of admission, and who started early rehabilitation within 7 days of the onset were selected as the sample group, while those for whom, for some reason, rehabilitation could not be started were removed, and the following analysis was made on these subjects (n=223: Age 73.2 ± 21.1, female 89 patients, male 134 patients).
(1) The Multiple Logistic Regression Analysis was made on the mRS at the time of discharge, in which the binarized mRS (0: Rankin 0-Rankin 1, 1: Rankin 2-Rankin 6) at the time of discharge (n=215: Age 73.1 ± 21.3, female 87 patients, male 128 patients) was used as the dependent variable, and the presence of thrombolytic therapy "0: Absent, 1: Present" was taken as the independent variable. Gender, age bracket, NIHSS at the admission time, rehabilitation starting time were assigned as covariates.
(2) The Multiple Logistic Regression Analysis was made on the presence of dementia at the time of discharge, in which the presence of dementia; "0: Absent, 1: Present" (n=168: Age 73.3 ± 20.3, female 65 patients, male 103 patients) was used as the dependent variable, and the presence of thrombolytic therapy was taken as the independent variable. Gender, age bracket and NIHSS at the admission time, rehabilitation starting time were assigned as covariates.

RESULTS

Comparison of the onset-to-admission time in the thrombolytic group
(1) From the result of the Multiple Logistic
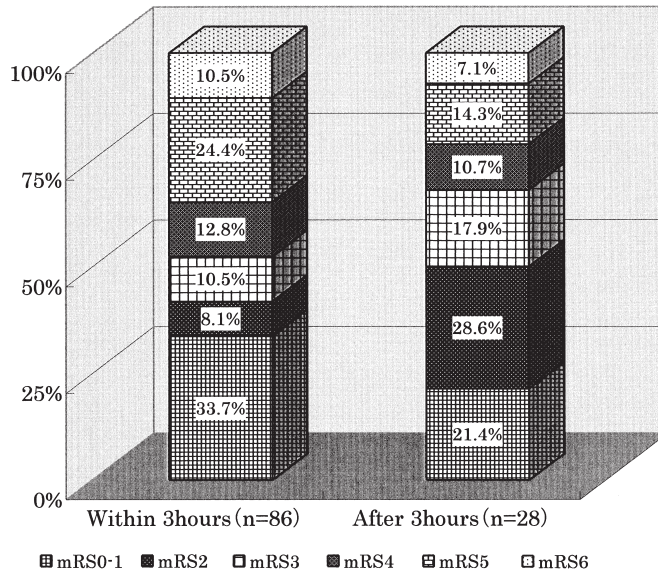
Fig. 1 Comparison within thrombolytic therapy group by time between onset and hospital admission (n=114)
In the thrombolytic therapy group, the outcome at the time of discharge was significantly better in the patients admitted within 3 hours of the onset compared with those admitted after 3 hours (p < .05).
The death rate (mRS6) was 10.5% for the former group and 7.1% for the latter group (NS).

Table 2 The odds ratios of a poor outcome (mRS 2-6) and of dementia at the time of discharge between the group admitted within 3 hours and the group admitted after 3 hours from the onset in the thrombolytic therapy (Evaluation on the 59.8th day (average) after the onset, Multiple Logistic Regression Analysis, covariates: gender, age bracket, NIHSS at the time of admission).

| Dependent variable	OR	95%CI	P
mRS2-6	2.79	1.06-7.32	.037
Dementia at the time of discharge	3.91	0.92-16.63	.065

This shows that the probability of poor outcome at the time of discharge was 2.8 times greater for the group admitted after 3 hours from the onset (p < .05).
Also, the probability of dementia remaining at the time of discharge tended to increase in the group of patients admitted after 3 hours from the onset.

Regression Analysis made on the mRS at the time of discharge for the thrombolytic group, the odds ratio of admission after 3 hours from the onset versus the outcome at the time of discharge was 2.79 (95%CI: 1.06-7.32), and the mRS at the time of discharge was high (mRS 2-6). In other words, it was noted that, even if thrombolytic therapy was given to patients after 3 hours from the onset, the chance of disability continuing into later life increased by 2.8 times (p < .05) (Table 2).

The death rate (mRS 6) was 10.5% for the group of patients admitted within 3 hours from the onset, and 7.1% for the group admitted after 3 hours (NS) (Fig. 1).
(2) Also, from the result of the Multiple Logistic Regression Analysis made on the presence of dementia at the time of discharge for the thrombolytic group, it was noted that the chance of no dementia tended to increase in the group of patients admitted within 3 hours of the onset (p < .1) (Table 2).

☐ With dementia present at the time of discharge
■ With no dementia present at the time of discharge
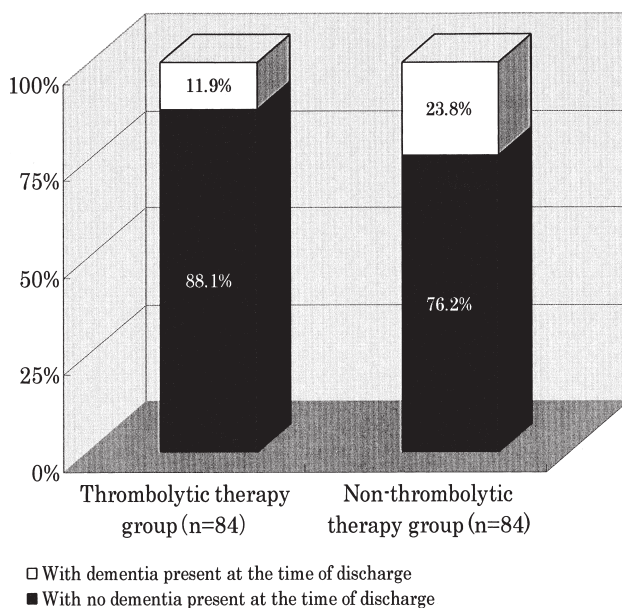
Fig. 2 Frequency of dementia at the time of discharge in the thrombolytic therapy group and the non-thrombolytic therapy group.
The presence of dementia was significantly lower in the thrombolytic therapy group (p < .05).

Table 3 Comparison between the thrombolytic therapy group and non-thrombolytic therapy group by Case-Control Study (Evaluation on the 50th day (average) after the onset, Mann Whitney-U Test).

		Hospitalization days[1]	Dementia at the time of discharge[2]	Changes in NIHSS[3]	Changes in JSS[4]	mRS at the time of discharge[5]
Thrombolytic therapy	Given	52.21	0.17	−6.88	−6.57	0.62
	Not given	46.73	0.33	−5.73	−4.44	0.72
	P	NS	< .05	NS	.094	NS

The presence of dementia at the time of discharge was significantly lower in the thrombolytic therapy group compared with the non-thrombolytic therapy group, thus indicating that the therapy was effective (p < .05). The changes in JSS also tended toward greater improvement in the thrombolytic therapy group compared with the non-thrombolytic therapy group (p < .1). There was no significant difference observed for hospitalization days, changes in NIHSS, or mRS at the time of discharge (p < .05).

1): Average hospitalization days (day)
2): Average of the presence of dementia at the time of discharge (0: absent, 1: present)
3): Average difference between NIHSS scores at the time of admission and at the time of discharge
4): Average difference between JSS scores at the time of admission and at the time of discharge
5): Average value of mRS at the time of discharge   (where 0: Rankin 0-Rankin 1, 1: Rankin 2-Rankin 6)

Comparison between the thrombolytic group and non-thrombolytic group
(1) From the result of the case-control study, compared with the non-thrombolytic group, the presence of dementia was significantly lower in the thrombolytic group, and the effectiveness of the thrombolytic therapy was observed (p<.05) (Fig. 2). Also, it was noted that the changes in JSS tended to be greater compared with the non-thrombolytic group, and the thrombolytic group was more likely to have the positive effects of thrombolytic therapy (p < .1). On the other hand, no significant differences in hospitalization days, changes in NIHSS, or mRS at the time of discharge were noted by this analysis (Table 3).
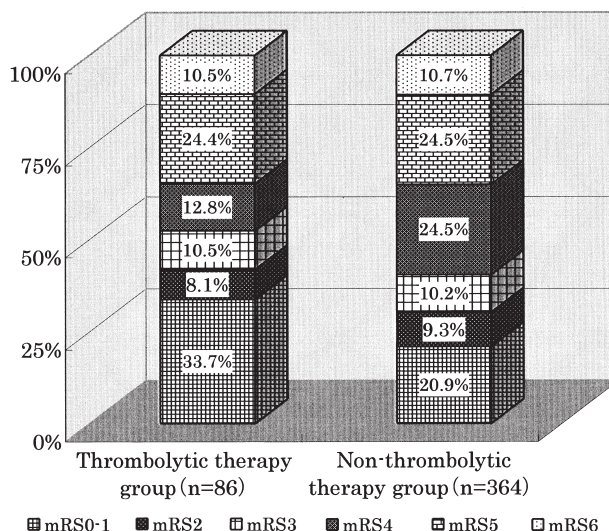
Fig. 3 Comparison of mRS at the time of discharge between the thrombolytic therapy group and the non-thrombolytic therapy group (n =450)
The outcome at the time of discharge was significantly better in the thrombolytic therapy group (p < .05).
The death rate (mRS6) was 10.5% for the thrombolytic therapy group and 10.7% for the non-thrombolytic therapy group (NS).

Table 4 The odds ratio of a poor outcome (mRS 2-6) and dementia at the time of hospital discharge, according to the presence of thrombolytic therapy (Evaluation on the 51.4th day (average) from the onset, Multiple Logistic Regression Analysis, covariates: gender, age bracket, NIHSS at the time of admission).

Dependent variable	OR	95%CI	P
mRS2-6	0.55	0.31-0.98	.041
Dementia at the time of discharge	0.37	0.17-0.80	.012

This shows that the probability of poor outcome at the time of discharge was 45% less for the thrombolytic therapy group (p < .05). Also, it shows that the probability of dementia remaining at the time of discharge was 63% less (p < .05).

(2) As the result of the Multiple Logistic Regression Analysis made on the mRS at the time of discharge, the odds ratio of thrombolytic therapy against the outcome at the time of discharge was 0.55 (95%CI: 0.31-0.98), and the mRS at the time of discharge was higher (mRS 2-6). In other words, the effectiveness of thrombolytic therapy was observed to reduce the chance of disability to continue into later life after the time of discharge by about 50% (p < .05) (Table 4).

The death rate (mRS 6) was 10.5% for the thrombolytic therapy group, and 10.7% for the non-thrombolytic therapy group (NS) (Fig. 3).

(3) Also, from the result of the Multiple Logistic Regression Analysis made on the presence of dementia at the time of discharge, the odds ratio of thrombolytic therapy against the presence of dementia was 0.37 (95%CI: 0.17-0.80), and the effectiveness of thrombolytic therapy was observed to reduce the occurrence of dementia at the time of discharge by about 60% (p<.05) (Table 4) (Fig. 4).

Verification of the effects of early rehabilitation started for patients admitted early
(1) As the result of the Multiple Logistic Regression Analysis made on the mRS at the
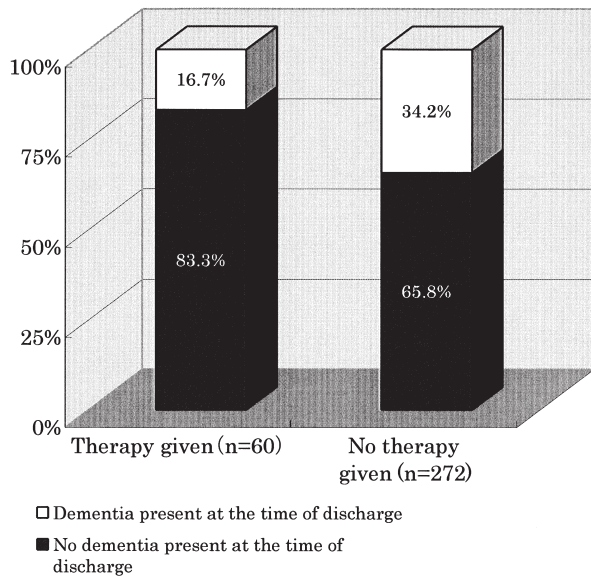
Fig. 4 Thrombolytic therapy and the presence of dementia (n=332: data missing=2).
The presence of dementia was significantly lower in the thrombolytic therapy group (p < .05).
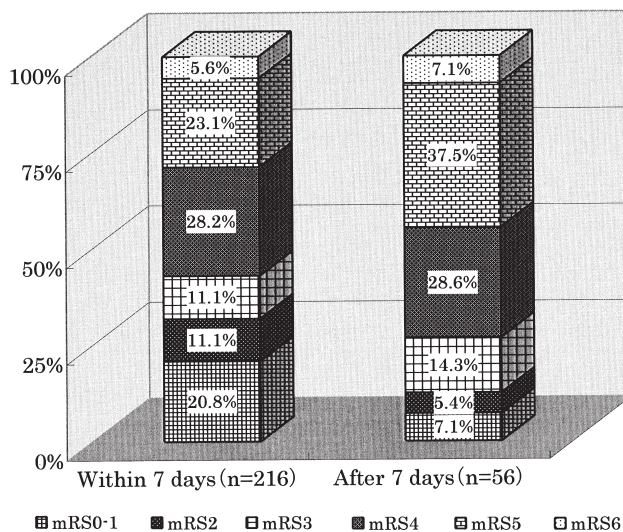
Fig. 5 Effects of early start of rehabilitation on the patients that were admitted early (n=272).
The outcome at the time of discharge was significantly better in the patients for whom rehabilitation was started within 7 days compared with those for whom it was started after 7 days. The death rate (mRS6) was 5.6% in the former group and 7.1% in the latter group (NS).

Table 5 Effects of early start of rehabilitation on the patients that were admitted early, the odds ratio of poor outcome (mRS 2-6) and dementia at the time of hospital discharge in the group of patients admitted within 3 hours of the onset and for whom rehabilitation was started within 7 days, compared with those admitted within 3 hours from the onset and for whom rehabilitation was started after 7 days (Evaluation on the 56.9 day (average) from the onset, Multiple Logistic Regression Analysis, covariates: gender, age bracket, NIHSS at the time of admission)

Dependent variable	OR	95%CI	P
mRS2-6	0.33	0.11-0.98	.045
Dementia at the time of discharge	0.41	0.19-0.89	.024

These results show that the probability of poor outcome at the time of discharge was 67% less for the thrombolytic therapy group (p < .05). Also, it shows the probability of dementia remaining at the time of discharge was 58% less (p < .05).

Table 6 The odds ratio of poor outcome (mRS 2-6) and dementia at the time of hospital discharge, among the patients admitted early and for whom rehabilitation was started early, according to the presence of thrombolytic therapy (Evaluation on the 56.4 day (average) from the on-set, Multiple Logistic Regression Analysis, covariates: gender, age bracket, NIHSS at the time of admission).

Dependent variable	OR	95%CI	P
mRS2-6	0.38	0.16-0.86	.020
Dementia at the time of discharge			NS

This shows that the probability of poor outcome at the time of discharge was 62% less for the thrombolytic therapy group (p < .05). There was no significant difference concerning dementia.
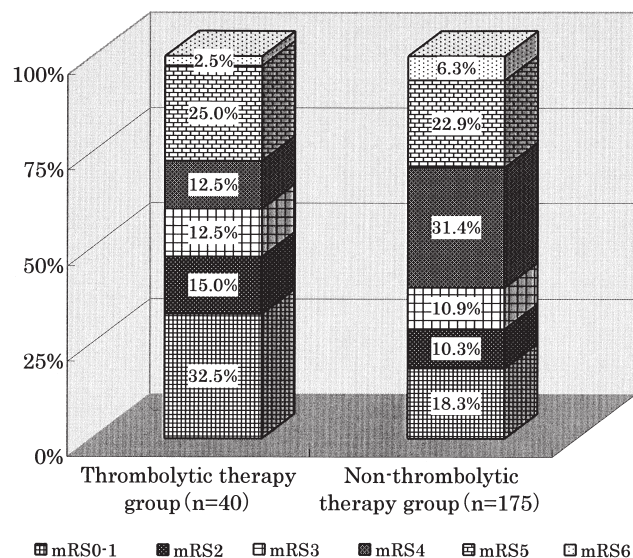
Fig. 6 Comparison between the thrombolytic therapy group and the non-thrombolytic therapy group in the patients who were admitted early and for whom rehabilitation was started early (n=215). The outcome at the time of discharge was significantly better in the thrombolytic therapy group (p < .05). The death rate (mRS6) was 2.5% for the former group and 6.3% for the non-thrombolytic therapy group (p < .01).

time of discharge of the group for which rehabilitation was started early, the odds ratio of rehabilitation started within 7days against the outcome at the time of discharge was 0.33 (95%CI: 0.11-0.98), and the mRS at the time of discharge was higher (mRS 2-6). In other words, the chance of disability continuing into later life at the time of discharge was observed to be reduced by about 70% (p <.05) (Table 5). The death rates (mRS 6) were 5.65% for the group in which rehabilitation was started within 7 days and 7.1% for the group in which rehabilitation was started after 7 days (NS) (Fig. 5).
(2) Also, from the results of the Multiple Logistic Regression Analysis made on the presence of dementia at the time of discharge, the odds ratio of rehabilitation started within 7days against the presence of dementia was 0.41 (95%CI: 0.19-0.89), and the effectiveness was observed to reduce the occurrence of dementia at the time of discharge by about 60% (p < .05) (Table 5).

Comparison between the thrombolytic therapy group and the nonthrombolytic therapy group among the patients that were admitted early and started early rehabilitation
(1) From the results of the Multiple Logistic Regression Analysis made on the mRS at the time of discharge, the odds ratio of thrombolytic therapy against the outcome at the time of discharge was 0.38 (95%CI: 0.16-0.86), and the mRS at the time of discharge was high (mRS 2-6). In other words, the effectiveness was observed to reduce the chance of disability continuing into later life at the time of discharge by about 60% (p<.05) (Table 6). The death rate (mRS 6) was 2.5% for the thrombolytic therapy group, and 6.3% for the non-thrombolytic therapy group (p<.01)

(Fig. 6).

(2) Also, from the results of the Multiple Logistic Regression Analysis made on the presence of dementia at the time of discharge, no significant difference was observed.

DISCUSSION

According to Japanese mortality statistics, the death rate from stroke (cerebrovascular disease), which used to rank first, started to decrease after hitting a peak in the period during 1970 through 1975, and currently it ranks third next to cancer (malignant neoplasm) and heart disease (cardiac disease). However, as the main cause for requiring basic functional aid or monitoring for elderly persons in need of nursing care, stroke represents 34.1%, the largest factor of all [10]. Thus, physical function disorder and dementia as aftereffects of stroke must be considered as important issues from a viewpoint of the current domestic trend that assumes that nursing care should be supported by the whole society.

The result of this analysis show that thrombolytic therapy has potential improvement effects against dementia as well as functional disorder at the time of discharge. In our country, since dementia is the largest cause at 13.8% of the overall sum of reasons for requiring basic functional aid and monitoring [10], this result may be considered significant from a social point of view.

Regarding the aftereffects of stroke, although the time to start rehabilitation and its method are believed to be important factors, there is not yet sufficient ground to support this hypothesis. However, there is a widespread consensus among experts that early application is needed [11, 12]. There is a report that early start of rehabilitation leads to higher ADL independence and lower death rate [13-15]. In contrast, it is said that the longer the time is from onset to rehabilitation start, disuse muscle atrophy remarkably increases [16]. This analysis also shows that, if rehabilitation is started within 7 days from the onset, it is effective in preventing or reducing functional disorder at the time of discharge and dementia. Moreover, it was suggested that, if a patient is admitted early and thrombolytic therapy is given, and rehabilitation can be started early, functional disorder at the time of discharge and death rate can be improved 1.4 times and 4.2 times respectively.

There is a report concerning the relation between the time from the onset until the start of general treatment, that the functional outcome of patients who received treatment after six hours from the onset was poor [17]. In the clinical trials for rt-PA conducted in Europe on brain infarction within 6 hours of the onset, it is reported that the frequency of mRS 0-1 after 3 months had no significant difference from the placebo [18]. The ATLANTIS test [19] conducted in the United States on brain infarction within 3 to 5 hours from the onset had similar results, and therefore, it is a generally accepted view that therapeutic window of thrombolytic therapy based on rt-PA is within 3 hours of the onset. Previous study showed 1 hour as the time necessary between arrival time and the possibility of effectively beginning treatment [20]. In the current analysis of the thrombolytic therapy group, significant improvement in the functional outcome of mRS at the time of discharge was noted for the group of patients admitted within 3 hours of the onset, compared with the group of patients admitted after that. Therefore, the result of this analysis depends on the strict standard further. However, it is pointed out that patients with milder symptoms for which larger therapeutic effects can be expected may be admitted later [20, 21], and factor analysis on late admission has been made [22]. The evidence from these studies are indicative that early start of therapy is crucial for enhancing the effects of this therapy.

Further rt-PA Stroke Study Group confirm the view that prompt and sufficient communication system and protocol must be established within 3 hours from the onset in order to ensure effective treatment for the ultra-acute disease [23]. Moreover, the necessity of creating specialized hospital wards such as stroke care units is also emphasized [24, 25]. According to a report by Yamaguchi in which a large scale research was made on thrombolytic therapy in Japan, of the total number of cases for which thrombolytic therapy is applicable, the therapy was actually implemented in only 2.5% of the cases [2]. However, considering Japan's present situation in which intravenous injection of rt-PA for brain infarction is not yet approved for health insurance treatment, the results

show that thrombolytic therapy including selective intra-arterial administration is actually adopted as treatment more widely than expected. In the United States, which is advanced in thrombolytic therapy, the present frequency of application is as small as 4.6% for those admitted within 3 hours from the onset. However, it is reported that it reaches 58.6% for those admitted within 60 minutes, for which the therapy is known to work most effectively [26]. In Germany, in order to administer rt-PA treatment, 20 stroke centers jointly established a data bank, and under the name of "German Stroke Data Bank", they conduct a centralized outcome follow-up study by telephone after 3 months and again after one year [27].

This data bank made an analysis of 6,234 patients with brain stroke, and reportedly rt-PA treatment was conducted for 4% of them, but the rate of patients with cerebral hemorrhage was as low as 8.8% and mRS 0-1 after 3 months was 35%.

Some sources report that while the use of thrombolytic drug does significantly improve the functional outcome, it is also has a demerit of increasing the frequency of intracranial hemorrhage [28, 29]. It is necessary to fully understand the benefits and risks of implementing this therapy, which should always be applied in strict conformance to the criteria established by the American Heart Association's guidelines [30].

With the decrease in serious cerebral hemorrhage cases, is it observed that the death rate of stroke itself has declined, but the present situation is that the occurrence rate of stroke has not showed any decline, and the death from serious cardiogenic brain embolism is conversely on the rise. This is attributable to the present situation in which non-valvular disorder-based atrial fibrillation is increasing with the aging of the population in Japan [31]. For ultra-acute cardiogenic brain embolism, thrombolytic therapy can be applied effectively, and it is considered as an essential treatment in a rapidly aging country like Japan. From the present analysis, in spite of being a retrospective analysis based on comparatively small number of patient cases from the stroke database, it is concluded that the clinical application of thrombolytic therapy for ultra-acute ischemic strokes was effective. From these results, it may be expected that, if rt-PA is newly approved for coverage by health insurance as a treatment for ischemic stroke in our country, treatment results of ultra-acute ischemic stroke will be dramatically improved.

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APPENDIX

42 facilities across the country where registration in hospital records for cerebral strokes was implemented (not necessarily in this order)

Nakamura Memorial Hospital Department of Outpatient Treatment for Cerebral Stroke, Research Institute for Brain and Blood Vessels Akita Department of Outpatient Treatment for Cerebral Stroke, Iwate Medical University Neurosurgery, Kohnan Department of Outpatient Treatment for Cerebral Stroke, Southern TOHOKU Research Institute for Neuroscience Neurosurgery, Kanto Medical Center NTT EC Neurosurgery, Keio University School of Medicine Neurology, Dokkyo University School of Medicine Neurology, Saiseikai Central Hospital Neurology, Tokai University Oiso Hospital Neurology, Tokai University Hospital Neurology, Hiratsuka Kyosai Hospital Cerebral Surgery, Osaka University Faculty of Medicine First Department of Internal Medicine, National Cardiovascular Center Department of Cerebrovascular Disease, Hoshigaoka Koseinenkin Hospital Neurology, Kyoto Second Red Cross Hospital Neurology, Okayama Kyokutou Hospital Department of Cerebrovascular Disease, National Okayama Medical Center Neurology, Okayama University Neurology, Kajikawa Hospital Neurology, Oota Memorial Hospital Neurology Oota Memorial Hospital Neurology, Shimane University School of Medicine Third Department of Internal Medicine, Shimane Prefectural Central Hospital Neurosurgery, Ohda Municipal Hospital Neurology, University of Fukui Faculty of Medical science Second Department of Internal Medicine, Matsue Red Cross Hospital Neurology, Hyogo Brain and Heart Center Neurology, Yamaguchi University School of Medicine Neurosurgery, Tokushima University School of Medicine Neurosurgery, Ehime University School of Medicine Neurosurgery, Kagawa Medical Center for Adult Disease Internal Medicine, Chikamori Hospital Neurology, Kyusyu University Faculty of Medicine Second Department of Internal Medicine, Kyushu Medical Center Department of Cerebrovascular Disease, St. Mary's Hospital Cerebral Stroke Center, Fukuoka Red Cross Hospital Neurology, Fukuoka Tokushukai Medical Center Neurology, Iizuka Hospital Neurology, Saiseikai Kumamoto Neurology, Kumamoto City Hospital Neurology, Oita ALMEIDA

Hospital Neurosurgery, University of the Ryukyu Faculty of Medicine Third Department of Internal Medicine.

REFERENCES

1) The NINDS rt-PA Stroke Study Groupe: Tissue plasmminogen activator for acute ischemic stroke. N Engl J Med 333: 1581-1587, 1995.

2) Yamaguchi T: National Cardiovascular Center, Osaka: Acute stroke managements in Japan: present and future perspective. Jpn J Stroke 23: 261-268, 2001.

3) Kobayashi S: The Japanese Standard Stroke Registry Study (JSSRS) Group. Health Science General Research Program, 2002 Research Report, 2002.

4) DSM-III-R Classification of psychic disturbance and Guidance of diagnosis, second edition. The American Psychiatric Association, Takahashi S (Translation). Tokyo: Igaku-Shoin, 71-73, 1988.

5) Brott T, Adams Jr. HP, Olinger CP, *et al*: Measurements of acute cerebral infarction: a clincal examination scale. Stroke 20: 864-870, 1989.

6) Goldstein LB, Bertels C, Davis JN, *et al*: Interrater reliability of the NIH stroke scale. Arch Neurol 46: 660-662, 1989.

7) The Japan Stroke Society, Stroke Scale Committee: The Japan Stroke Society, Official announcement of Japan Stroke Scale (JSS). Jpn J Stroke 19: 2-5, 1997.

8) Bonita R, Beaglehole R: Recovery of motor function after stroke. Stroke 19: 1497-1500, 1988.

9) Hoshino H, Takagi M, Tsuchiya H, *et al*: Factors delaying CT examination, and antithrombotic therapy after onset in acute stroke. Jpn J Stroke 20: 480-488, 1998.

10) The Ministry of Health, Labour and Welfare, Minister's Secretariat, Statistics and Information Dept., Household research of Nursing service 2000 24: 2001.

11) Hirshberg GG: Rehabilitation: a manual for the care of the disable and elderly. 2nd ed. Philadelphia: J.B Lippincott; 1972. 219-256.

12) Ozer MN, Materson RS, Caplain LR (eds.): Management of persons with stroke. St, Louis: Mosby; 1994.

13) Evans RL, Connis RT, Hendricks RD, *et al*: Multidisciplinary rehabilitation versus medical care: a meta-analysis. Soc Sci Med 1995; 40: 1699-1706.

14) Stroke Unit Traialists'Collaborative systematic review of the randmised trials of organized inpatient (stroke unit) care after stroke. BMJ1997; 314: 1151-1159.

15) Langhorne P, Ducan P: Dose the organization of postacute stroke care really matter? Stroke 2001; 32: 268-274.

16) Okawa Y, Ueda S: The Disuse Muscle Atrophy in the Hemiplegic Patients: The Muscle Weakness in the "UNAFFECTED" Extreamities. Jpn J Rehabili Med 1988; 25: 143-147.

17) Davalos A, Castillo J, Martinez-Vila E: Delay in ueurological attention and stroke outcome. Stroke 26: 2233-2237, 1995.

18) Hacke W, Kaste M, Fieschi C, *et al*: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 352: 1245-1251, 1998.

19) Clark WM, Wissman S, Albers GW, *et al*: Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 282: 2019-2026, 1999.

20) Azzimondi G, Bassein L, Fiorani L, *et al*: Variables associated with hospital arrival time after stroke. Effect of delay on the clinical efficiency of early treatment. Stroke 28: 537-542, 1997.

21) Jorgensen HS, Nakayama H, Reith J, *et al*: Factors delaying hospital admission in acute stroke: The Copenhagen Stroke Study. Neurology 47: 383-387, 1996.

22) Koga M, Kimura K, Minematsu K, *et al*: Factors influencing delayed arrival of acute stroke patients. Jpn J Stroke 22: 301-306, 2000.

23) NINDS rt-PA Stroke Study Groupe: A system approach to immediate evaluation and management of hyperacute stroke. Experience at eight centers and implications for community practice and patienta care. Stroke 28: 1530-1540, 1997.

24) Strand T, Asplund K, Eriksson S, *et al*: A nonintensive stroke unit reduces functional disability and the need for long-term hospitalization. Stroke 16: 29-34, 1985.

25) Jorgensen HS, Nakayama H, Raaschou HO, *et al*: The effect of a stroke unit: reductions in mortality, discharge rate to nursing home, length of hospital stay, and cost. A community-based study. Stroke 26: 1178-1182, 1995.

26) Rosamond W: Paul Coverdell pilot prototypes -Wave II- preliminary data from year one. 29th International Stroke Conference, Feb. 6, 2004.

27) Schenkel J, Weimar C, Knoll T, *et al*: R1-systemic thrombolysis in German stroke units--the experience from the German Stroke data bank. J Neurol 250: 320-324, 2003.

28) Wardlaw JM, del Zoppo G, Yamaguchi T, *et al*: Thrombolysis for acute ishaemic stroke (Cochrane Review).In: The Cochrane Library-2001. Oxford, Update Software, 2001.

29) Otsubo Y, Minematsu K, Kobayashi S, for Japanese Standard Stroke Registration Study (JSSRS) Group: Hemorrhagic infraction and its predisposing factors in acute ischemic stroke. Jpn J Stroke 23: 227-233, 2001.

30) Adams Jr HP, Brott TG, Crowell RM, *et al*: Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Circulation 90: 1588-601, 1994.

31) Minematsu K: Ischemic stroke, Transient ischmic attack and Fibrillation atrial. Stroke Data Bank. Tokyo: Nakayamashoten, p32-33, 2003.