Introduction

Ischemic stroke is well recognized as a leading cause of death and disability worldwide. In Japan, the incidence of ischemic stroke is 260–357 per 100,000 person-years, corresponding to a mortality rate of 45–68 per 100,000 person-years [1]. Moreover, in patients who survive a first ischemic stroke, the risk of recurrence is high; 4.83% for Japanese patients enrolled in the REACH registry [2] and 24.5% in Japanese patients with mild strokes [3] within 2 years. Therefore, administration of antiplatelet agents is essential for the secondary prevention of ischemic stroke [4].

The antiplatelet agent clopidogrel is a thienopyridine agent that inhibits platelet aggregation by selectively and irreversibly inhibiting the binding of adenosine diphosphate to its platelet receptor P2Y12 [5]. In a large, predominantly Caucasian population at risk of ischemic events due to atherosclerotic vascular disease (manifested as ischemic stroke, myocardial infarction, or symptomatic peripheral arterial disease), clopidogrel 75 mg once daily was shown to be more effective than aspirin 325 mg once daily for the prevention of ischemic events [6]. On the basis of these and other results, clopidogrel 75 mg once daily has been licensed for more than 10 years in Western countries for the prevention of atherothrombotic events in patients with ischemic cerebrovascular, coronary, or peripheral arterial disease [7, 8].

Studies conducted in Japan among patients with a history of ischemic stroke have demonstrated that clopidogrel 75 mg once daily is better tolerated than ticlopidine 200 mg once daily, and shows noninferior efficacy with regard to the secondary prevention of vascular events [9, 10]. However, any bleeding adverse events requiring attention were observed with a higher incidence among patients receiving clopidogrel who were aged ≥75 years (vs. <75 years) or weighed <50 kg (vs. ≥50 kg) [9]. Consequently, in Japan, clopidogrel is licensed for oral use at a dose of 75 mg once daily, but, depending on the patient's age and body weight, a dose of 50 mg once daily is recommended.

Thus, the present postmarketing study compared the safety and efficacy of clopidogrel 50 and 75 mg for the secondary stroke prevention in Japanese patients, who were aged <75 years and weighed >50 kg.

Materials and Methods

Study Design

This study was a multicenter, single-country, randomized, double-blind, double-dummy phase IV trial (NCT00386191) designed to compare the safety of 50 and 75 mg of clopidogrel for the secondary stroke prevention in Japanese patients. The primary safety endpoint was the incidence of bleeding adverse events. The secondary safety endpoints included the incidence of serious adverse events (SAEs), serious bleeding adverse events, and prespecified adverse events of interest comprised of leukopenia, neutropenia, thrombocytopenia, and hepatic dysfunction. The incidence of vascular events was used to compare the efficacy of the two clopidogrel doses.

Patients were recruited to the study from 118 Japanese medical institutions. Patients aged 20–74 years with a body weight >50 kg were eligible for the study if they had experienced an episode of noncardioembolic ischemic stroke at least 8 days prior to randomization and their clinical course preceding randomization was well documented, or if they had experienced an ischemic stroke confirmed at the study institution using diagnostic brain imaging (assessed by CT or MRI) performed <12 weeks before treatment initiation.

The main exclusion criteria for the study were: patients with cardiogenic stroke or disease that could precipitate cardiogenic cerebral thromboembolism, such as atrial fibrillation or valvular heart disease (including valve replacement); patients with a transient ischemic attack occurring after the last episode of ischemic stroke; patients with a serious impairment that would hinder the detection of a new ischemic event (e.g. bedridden, needing total assistance, or dementia); patients with bleeding diathesis, coagulopathy, or hemorrhagic disease; patients with a history of intracranial hemorrhage; patients with diabetic retinopathy; patients with hypertension and insufficient control of blood pressure despite antihypertensive therapy, and patients with malignancy (except complete remission from malignancy <5 years prior to randomization), cardiac disease, serious renal disease or abnormal creatinine levels, leukopenia, neutropenia, thrombocytopenia, severe hepatic dysfunction, or a history of drug allergy.

Within 2 weeks of obtaining informed consent, patients were randomly allocated to receive either clopidogrel 50 or 75 mg. Based on an application from the investigator, a centralized patient registration center confirmed the patient eligibility, and notified his/her registration and an allocation number to identify the study drug among the distributed drugs to the investigator and the sponsor by telephone or facsimile. If a patient was ineligible due to noncompliance with the inclusion and exclusion criteria, the centralized patient registration center notified the fact to the investigator.

Double-blinding was maintained in both treatment groups throughout the course of the study as follows: a controller confirmed the indistinguishability of the study drugs and of their package appearances at the time of randomized allocation and between finalization of all case report forms and the key code breaking. The controller established the key codes and emergency key codes to cope with emergencies. The controller also retained the key codes and emergency key codes in sealed and signed envelopes until the time of key code breaking.

Patients assigned to the 50-mg group received two 25-mg clopidogrel tablets and one 75-mg placebo tablet that was indistinguishable from the 75-mg clopidogrel tablet (3 tablets in total). Those patients assigned to the 75-mg group received two 25-mg placebo tablets that were indistinguishable from the 25-mg clopidogrel tablets and one 75-mg clopidogrel tablet (3 tablets in total). The doses for the 50- and 75-mg groups were administered orally once daily after a meal.

Treatment was continued for 52 weeks and assessments were performed at baseline (day 1) and at weeks 4, 8, 12, 20, 28, 36, 44, and 52. These included assessments of compliance, blood pressure, pulse rate, concomitant drug use, adverse events developed after the last observation, and blood sampling for laboratory tests (hematological and biochemical tests). Additionally, diagnostic brain imaging (CT or MRI) and electrocardiography were performed at baseline and week 52 (or at discontinuation of treatment). Patients were instructed to report any safety-related event occurring within 2 weeks after final study drug intake. Follow-up was performed after 52 weeks until discontinued by the investigator based on an appropriate medical assessment.

Bleeding adverse events were defined as all adverse events with any bleeding, including intracranial hemorrhage, retinal bleeding of the ocular fundus, subcutaneous bleeding, nasal bleeding, intraoral bleeding, hypermenorrhea, and gastrointestinal bleeding. SAEs were defined as any adverse events that met the following criteria: all-cause death, any life-threatening events, hospitalization or prolongation of existing hospitalization, clinically persistent or significant disability/incapacity, or medically important events. Leukopenia was defined as a white blood cell count $<3{,}000/mm^3$, neutropenia as a neutrophil count $<1{,}500/mm^3$, and thrombocytopenia as a platelet count $<100{,}000/mm^3$. Hepatic dysfunction was defined as a change in levels of L-aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, or total bilirubin ≥120% of the upper limit of normal (if levels were normal at baseline) or ≥200% of the baseline value (if levels were abnormal at baseline), or when jaundice was detected. The following frequency distributions of treat-emergent adverse events (TEAEs) were provided by treatment: overview of all TEAEs, serious TEAEs, TEAEs leading to death and TEAEs leading to treatment discontinuation. Vascular events included ischemic stroke, myocardial infarction and other vascular events in heart, extremities, or other organs that did not fit the previous criteria, e.g. transient ischemic attack or angina.

The study was monitored by the Safety/Efficacy Evaluation Committee, whose role was to evaluate safety variables, especially bleeding adverse events, SAEs, and adverse events of interest and efficacy variables (i.e. vascular events).

The study protocol was approved by the Institutional Review Board/Ethics Committee and all patients gave informed consent. The study was conducted in accordance with ethical principles such as the Declaration of Helsinki, together with good clinical practice guidelines, good postmarketing study practice, good vigilance practice, and domestic pharmaceutical laws and regulations.

Statistical Analyses

The target population of this study excluded elderly and low-weight patients with a possible high bleeding risk. From an unpublished study in this population, the incidence of bleeding adverse events for clopidogrel 75 mg over 52 weeks excepting patients aged ≥75 years or with a weight ≤50 kg was calculated as 26.8%. For clopidogrel 50 mg, the incidence of bleeding adverse events was assumed to be 30% lower than with clopidogrel 75 mg, based on the 30% decrease in platelet aggregation inhibitory effect and 30% decrease in incidence of ≥2-fold prolongation of bleeding time in patients receiving the lower dose. Therefore, 541 patients per group (approximately 1,100 in total) were required in order to show a significant difference in safety between clopidogrel 50 and 75 mg, using a log rank test with a 5% two-sided significance level and 80% statistical power. The study was powered for a definitive evaluation of the primary endpoint. The main safety and efficacy analyses were based on the intention-to-treat (ITT) population (all randomized patients) and other safety analyses were based on the all-treated population (all patients who received ≥1 dose of study drug). Incidence curves and corresponding 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. Finally, for all parameters measured, no imputation of missing data was performed.

Results

Study Population

The study was conducted between September 4, 2006 and December 12, 2008. A total of 1,110 patients were randomized to either clopidogrel 50 mg (n = 558) or clopidogrel 75 mg (n = 552) and were, therefore, included in the ITT population (fig. 1). Only 2 patients (both randomized to clopidogrel 50 mg) were not exposed to the study drug, yielding an all-treated population of 1,108 patients.

Similar proportions of patients in the clopidogrel 50-mg group (n = 469, 84.1%) and the 75-mg group (n = 457, 82.8%) completed the 52-week treatment course. The most common reasons for treatment discontinuation were adverse events [n = 53 (9.5%) and n = 67 (12.1%) in the clopidogrel 50- and 75-mg groups, respectively], patient's request [n = 12 (2.2%) and n = 11 (2.0%)], and poor compliance [n = 5 (0.9%) and n = 5 (0.9%)]. Regardless of treatment discontinuation, a high proportion of patients (n = 1,039, 93.6%) were followed up at week 52 [n = 522 (93.5%) of the 50-mg group and n = 517 (93.7%) of the 75-mg group].

The demographics and clinical characteristics of the study participants were well balanced across the two treatment arms (table 1). Most patients were male (80.0%) and the mean age was 62.1 years, with more than a half of patients (55.7%) younger than 65 years of age. In the majority of patients (85.3%), the time from the most recent stroke was later than 30 days from study enrollment, and lacunar stroke (61.9%) was the most common type of recent stroke.

Previous use of antiplatelet drugs was prevalent among the study cohort, with most patients from both treatment groups having previously received aspirin.

Compliance to treatment throughout the study period was high (99% in both groups). All patients exposed to the study drug were therefore compliant, defined as administration of at least 75% of the prescribed dosage regimen.

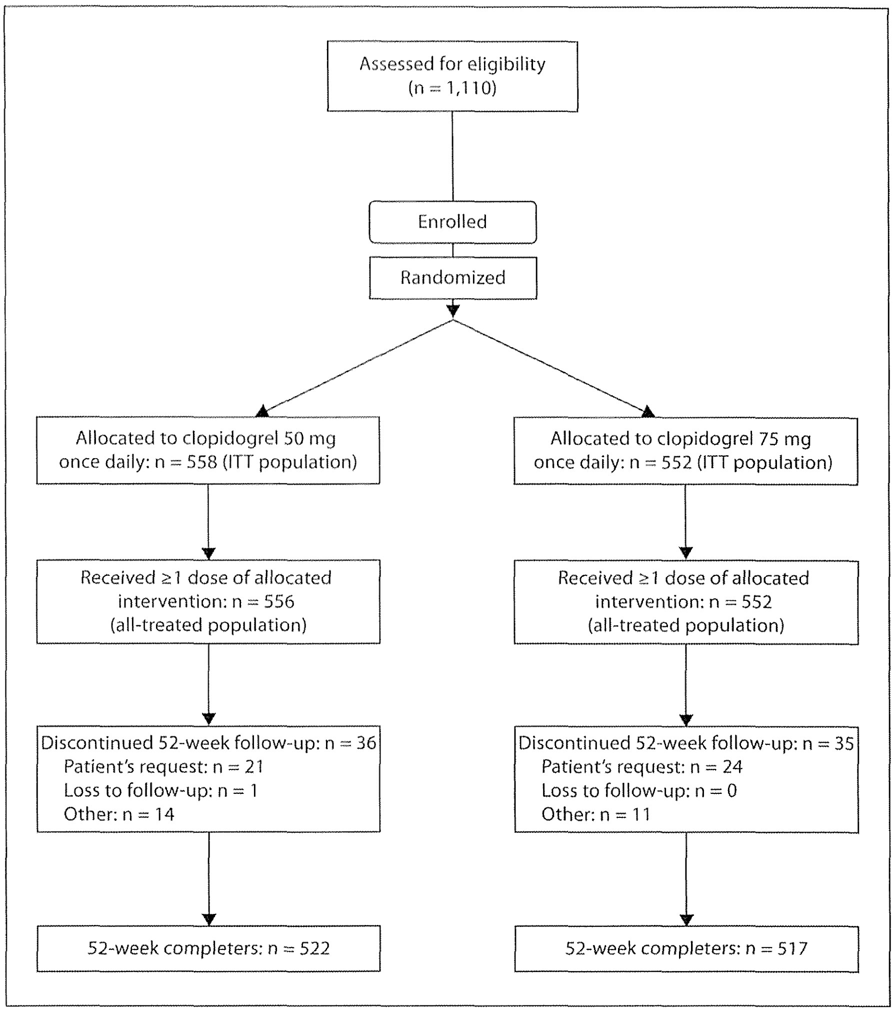


Fig. 1. Patient flowchart of the study.

Cumulative exposure to clopidogrel 50 and 75 mg was 512.3 and 498.9 person-years, respectively, with a mean duration of exposure of 336.5 and 330.1 days. Indeed, most patients in the clopidogrel 50-mg (84.4%) and 75-mg groups (82.6%) received the study drug for ≥1 year.

Safety

No significant difference between the treatment groups was detected with respect to the incidence of bleeding adverse events. Analysis of the time to first bleeding adverse event in the ITT population indicated that bleeding events occurred in 78 of 558 patients and 92 of 552 patients in the clopidogrel 50- and 75-mg groups, respectively (table 2). The cumulative incidences (95% CI) of bleeding at week 52 in the clopidogrel 50- and 75-mg groups were 14.0% (11.1–16.9%) and 16.5% (13.4–19.6%), respectively (fig. 2a; hazard ratio = 0.831, 95% CI = 0.615–1.124, p = 0.2274). Although 2 patients in the 50-mg group did not take the study drug, the time to the first bleeding adverse event in the all-treated population (on-treatment analysis) was consistent with that in the ITT population (50 mg: 13.7%, 95% CI = 10.7–16.6%; 75 mg: 16.0%, 95% CI = 12.9–19.2%; hazard ratio = 0.836, 95% CI = 0.612–1.140, p = 0.2558).

Looking at details of bleeding adverse events, severe intensity in the 50- and 75-mg group was 0.4% (2/558) and 0.4% (2/552), moderate intensity was 2.0% (11/558) and 1.8% (10/552), and mild intensity was 11.6% (65/558) and 14.5% (80/552), respectively (for online suppl. table 1, see www.karger.com/doi/10.1159/000342655). Furthermore, the percentage of gastrointestinal bleeding in the ITT population was low in both groups (50 mg: 2.2%, 12/558; 75 mg: 2.5%, 14/552) (table 3), and bleeding requiring transfusion had not been observed in this study. Importantly, the percentages of intracranial hemorrhage in the 50- and 75-mg groups were 0.18% (1/558) and 0.18%

Table 1. Patient baseline and disease characteristics

Characteristic	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Male, n (%)	444 (79.6)	444 (80.4)
Mean age ± SD, years	62.2 ± 8.0	62.0 ± 8.6
Age ≥65 years, n (%)	251 (45.0)	241 (43.7)
Mean body weight ± SD, kg	64.2 ± 8.9	65.3 ± 9.6
Body weight strata, n (%)		
<60 kg	180 (32.3)	166 (30.1)
≥60 to <70 kg	245 (43.9)	222 (40.2)
≥70 kg	133 (23.8)	164 (29.7)
Mean elapsed time from last ischemic stroke ± SD, days	896 ± 1,216	974 ± 1,366
Time from the most recent onset of ischemic stroke, n (%)		
Median (range), days	343.5 (9–7,334)	252.5 (9–7,941)
8–30 days	83 (14.9)	80 (14.5)
31–364 days	200 (35.8)	218 (39.5)
≥365 days	275 (49.3)	254 (46.0)
Type of last ischemic stroke, n (%)		
Atherothrombotic stroke	218 (39.1)	192 (34.8)
Lacunar stroke	333 (59.7)	354 (64.1)
Other	7 (1.3)	6 (1.1)
Number of infarcts, n (%)		
Single	329 (59.0)	329 (59.6)
Multiple	229 (41.0)	222 (40.2)
Unknown	0	1 (0.2)
Past use of antiplatelet drugs, n (%)		
Clopidogrel	114 (20.4)	107 (19.4)
Ticlopidine	88 (15.8)	82 (14.9)
Aspirin	317 (56.8)	313 (56.7)
Cilostazol	79 (14.2)	76 (13.8)
Other	70 (12.5)	62 (11.2)
None	11 (2.0)	16 (2.9)

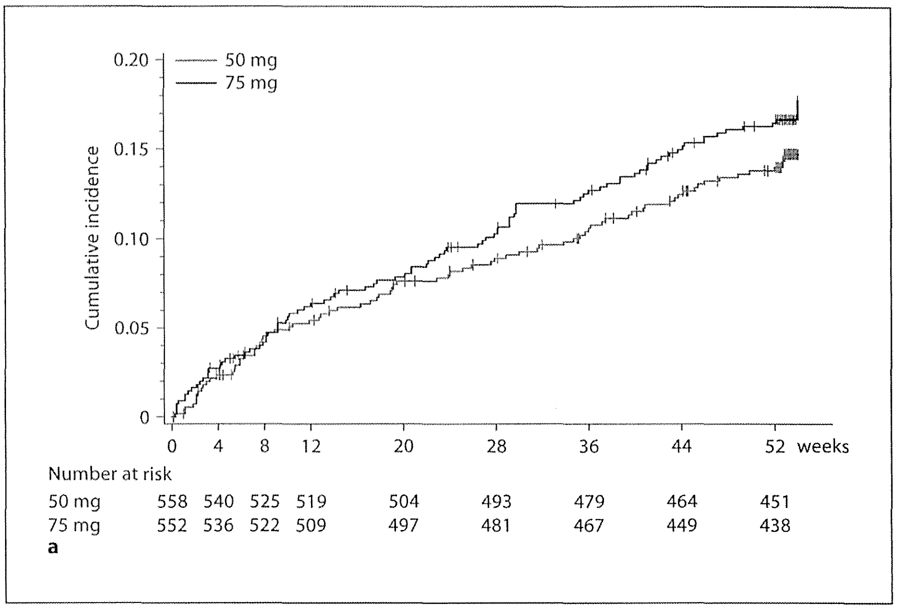
(1/552), respectively. In the all-treated population, a significant drop in hematocrit (more than 15% decrease) was observed in 3 patients of the clopidogrel 50-mg group and in 1 patient of the clopidogrel 75-mg group.

No statistically significant differences between the treatment groups were detected with respect to any of the secondary safety endpoints (table 4). Hence, patients receiving clopidogrel 75 mg were not at greater risk than those receiving clopidogrel 50 mg of experiencing an SAE, a serious bleeding adverse event, or the adverse event of interest. The cumulative incidences of SAEs at week 52 in the clopidogrel 50- and 75-mg groups were comparable (8.6%, 95% CI = 6.3–11.0% vs. 9.5%, 95% CI = 7.0–11.9%; hazard ratio = 0.877, 95% CI = 0.597–1.289; p = 0.5035), as were the cumulative incidences of serious bleeding events (1.7%, 95% CI = 0.6–2.8% vs. 1.5%, 95% CI = 0.5–2.5%; hazard ratio = 1.240, 95% CI = 0.489–3.142; p = 0.6496). The cumulative incidences (95% CI) of adverse events of interest at week 52 were 22.4% (18.9–25.9%) in the clo-

Table 2. Time to first bleeding adverse event in the ITT population

Measure	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Number of events	78	92
Cumulative incidence[a]		
Week 4	0.023 (0.011–0.036)	0.027 (0.014–0.041)
Week 8	0.045 (0.028–0.063)	0.042 (0.025–0.059)
Week 12	0.054 (0.035–0.073)	0.064 (0.043–0.084)
Week 20	0.076 (0.054–0.098)	0.079 (0.056–0.101)
Week 28	0.089 (0.065–0.113)	0.103 (0.077–0.128)
Week 36	0.106 (0.080–0.132)	0.127 (0.099–0.155)
Week 44	0.125 (0.097–0.153)	0.150 (0.120–0.180)
Week 52	0.140 (0.111–0.169)	0.165 (0.134–0.196)
log rank test p value	0.2274	–
Hazard ratio[b]	0.831 (0.615–1.124)	–

Figures in parentheses indicate 95% CIs.
[a] Kaplan-Meier method and Greenwood's formula.
[b] Cox regression model.



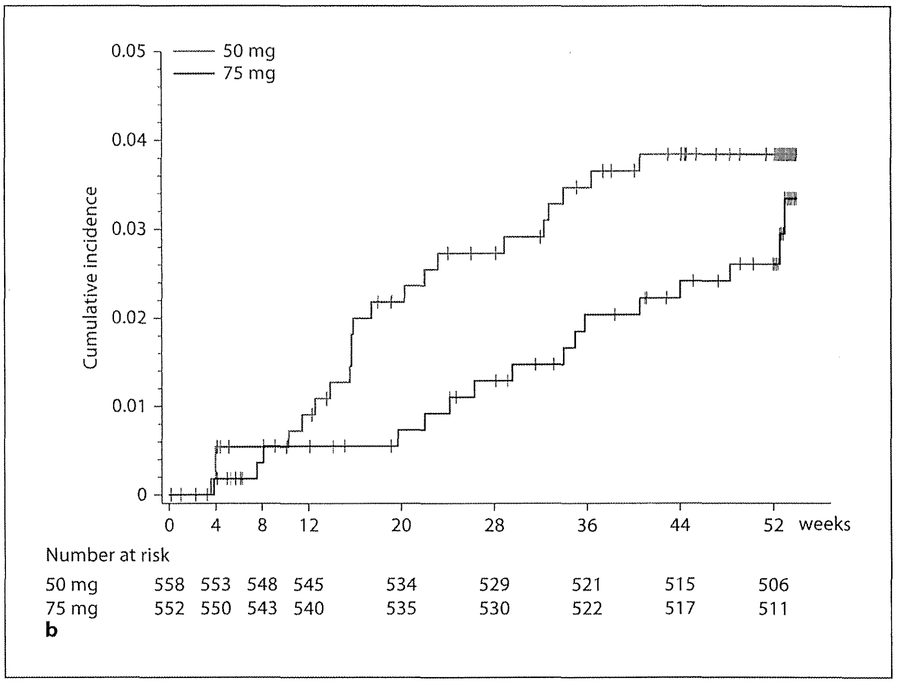


Fig. 2. Kaplan-Meier cumulative incidence curves for (**a**) time to first bleeding adverse event among the ITT population and (**b**) time to vascular event among the ITT population.

pidogrel 50 mg and 23.8% (20.2–27.4%) in the clopidogrel 75-mg group (hazard ratio = 0.935, 95% CI = 0.735–1.190; p = 0.5834) and there were no intergroup differences in the individual incidences of these 4 safety variables.

In the all-treated population, most patients reported a TEAE but there were no clinically meaningful differences between the groups regarding the percentages, nature, or severity of events (table 5). Overall, 83.3% (463/556) of patients in the 50-mg group and 86.4% (477/552) of patients in the 75-mg group reported at least 1 TEAE during the course of the study. The most frequently observed TEAEs were increased eosinophil count [clopidogrel 50 mg: 8.5% (47/556); clopidogrel 75 mg: 9.2% (51/552)]; increased γ-glutamyl transpeptidase [clopidogrel 50 mg: 8.6% (48/556); clopidogrel 75 mg: 7.8% (43/552)]; increased alanine aminotransferase [clopidogrel 50 mg:

5.6% (31/556); clopidogrel 75 mg: 6.2% (34/552)], and nasopharyngitis [clopidogrel 50 mg: 20.9% (116/556); clopidogrel 75 mg: 22.3% (123/552)]. Several TEAEs were more frequent in the 75-mg group, including abnormal liver function test [clopidogrel 50 mg: 2.0% (11/556); clopidogrel 75 mg: 4.2% (23/552)]; bronchitis [clopidogrel 50 mg: 1.4% (8/556); clopidogrel 75 mg: 2.9% (16/552)], and pruritus [clopidogrel 50 mg: 1.4% (8/556); clopidogrel 75 mg: 2.9% (16/552)].

The number of patients with serious TEAEs was also similar in both groups [clopidogrel 50 mg: 9.9% (55/556); clopidogrel 75 mg: 9.8% (54/552)]. There was no significant difference in the types of serious TEAEs between the two treatment groups; however, two classes of serious TEAEs [unspecified, benign and malignant neoplasms (including cysts and polyps) and cardiac disorders] were observed more frequently (≥2-fold) in the 50-mg group than in the 75-mg group.

Two patients experienced a TEAE which led to death in the 50-mg group, but none were reported for the 75-mg group. However, for both these patients, there was no causal relationship between the events leading to death and the study drug.

Finally, fewer patients discontinued treatment due to TEAEs in the 50-mg group than in the 75-mg group [9.4% (52/556) and 12.0% (66/552), respectively].

Efficacy

Vascular events occurred in 21 of 558 patients and 16 of 552 patients in the clopidogrel 50- and 75-mg groups, respectively (table 6). The cumulative incidence of vascular events at week 52 was slightly lower in the clopidogrel 75-mg group, although no statistically significant difference was detected (clopidogrel 50 mg: 3.8%, 95% CI = 2.2–5.5%; clopidogrel 75 mg: 2.6%, 95% CI = 1.3–4.0%). Furthermore, the log rank test revealed that patients receiving clopidogrel 50 mg were no more likely to have a vascular event than counterparts receiving clopidogrel 75 mg (fig. 2b; hazard ratio = 1.312, 95% CI = 0.685–2.514, p = 0.4118). Ischemic stroke was observed in 10 patients (1.8%) in the clopidogrel 50-mg group and 12 patients (2.2%) in the clopidogrel 75-mg group. Furthermore, 2 patients from the 75-mg group had cardiogenic cerebral thromboembolism due to arterial fibrillation and patent foramen ovale, despite patients with disease that could precipitate cardiogenic cerebral thromboembolism being excluded from the study. Myocardial infarction was observed in 2 patients (0.4%) in the clopidogrel 50-mg group and 1 patient (0.2%) in the clopidogrel 75-mg group. Other vascular events (e.g. peripheral arterial diseases, transient ischemic attack) were observed in 9 patients (1.6%) in the clopidogrel 50-mg group and 5 patients (0.9%) in the clopidogrel 75-mg group. Finally, there was 1 death due to a vascular event (peripheral arterial disease) in the clopidogrel 50-mg group (table 7).

Table 3. Number (%) of patients experiencing gastrointestinal bleeding adverse events presented by preferred term in the ITT population

Preferred term	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Number of events	12 (2.2)	14 (2.5)
Occult blood	0	4 (0.7)
Occult blood positive	0	3 (0.5)
Colon cancer	1 (0.2)	2 (0.4)
Hematochezia	2 (0.4)	1 (0.2)
Duodenal ulcer hemorrhage	0	1 (0.2)
Gastrointestinal hemorrhage	0	1 (0.2)
Esophageal hemorrhage	0	1 (0.2)
Rectal cancer stage 0	0	1 (0.2)
Gastric ulcer hemorrhage	3 (0.5)	0
Melena	2 (0.4)	0
Feces discolored	1 (0.2)	0
Gastric cancer	1 (0.2)	0
Hemorrhoidal hemorrhage	1 (0.2)	0
Large intestine carcinoma	1 (0.2)	0
Rectal cancer	1 (0.2)	0

Discussion

Clopidogrel 75 mg has been approved since 2006 in Japan for 'the reduction of recurrence after ischemic cerebrovascular disorder (excluding cardiogenic brain embolism)'. In addition to the recommended dose of 75 mg, a lower dose (50 mg) is also available for use in Japanese patients who are aged ≥75 years or weigh <50 kg and may have an increased bleeding risk at the standard dose. This is based on data that demonstrate a reduction in the incidence of bleeding events with clopidogrel 50 mg (vs. clopidogrel 75 mg), while a significant level of platelet aggregation inhibition is maintained. The aim of this phase IV randomized controlled study was to satisfy the risk-to-benefit ratio of clopidogrel 75 mg versus clopidogrel 50 mg in Japanese patients with noncardioembolic ischemic stroke who were aged <75 years and weighed >50 kg.

The COMPASS study indicates that treatment with clopidogrel 75 mg is not associated with a significant in-

Table 4. Time to first SAE, serious bleeding event, and other predefined adverse events in the ITT population

Measure	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Serious adverse event		
Number of events	49	55
Cumulative incidence[a]		
Week 4	0.004 (0.000–0.009)	0.007 (0.000–0.014)
Week 8	0.009 (0.001–0.017)	0.009 (0.001–0.017)
Week 12	0.013 (0.003–0.022)	0.013 (0.003–0.022)
Week 20	0.027 (0.014–0.041)	0.029 (0.015–0.044)
Week 28	0.044 (0.027–0.061)	0.039 (0.022–0.055)
Week 36	0.057 (0.037–0.076)	0.063 (0.042–0.083)
Week 44	0.073 (0.051–0.095)	0.074 (0.052–0.096)
Week 52	0.086 (0.063–0.110)	0.095 (0.070–0.119)
log rank test p value	0.5035	–
Hazard ratio[b]	0.877 (0.597–1.289)	–
Serious bleeding adverse event		
Number of events	10	8
Cumulative incidence[a]		
Week 4	0.000 (0.000–0.000)	0.000 (0.000–0.000)
Week 8	0.002 (0.000–0.005)	0.002 (0.000–0.005)
Week 12	0.002 (0.000–0.005)	0.002 (0.000–0.005)
Week 20	0.004 (0.000–0.009)	0.007 (0.000–0.015)
Week 28	0.005 (0.000–0.012)	0.007 (0.000–0.015)
Week 36	0.005 (0.000–0.012)	0.007 (0.000–0.015)
Week 44	0.011 (0.002–0.020)	0.007 (0.000–0.015)
Week 52	0.017 (0.006–0.028)	0.015 (0.005–0.025)
log rank test p value	0.6496	–
Hazard ratio[b]	1.240 (0.489–3.142)	–
Time to first neutropenia, leukopenia, thrombocytopenia, and hepatic dysfunction		
Number of events	130	135
Cumulative incidence[a]		
Week 4	0.005 (0.000–0.012)	0.013 (0.003–0.022)
Week 8	0.038 (0.022–0.054)	0.062 (0.042–0.082)
Week 12	0.078 (0.056–0.100)	0.102 (0.077–0.128)
Week 20	0.122 (0.094–0.149)	0.137 (0.108–0.166)
Week 28	0.140 (0.111–0.169)	0.167 (0.136–0.198)
Week 36	0.186 (0.154–0.219)	0.199 (0.165–0.232)
Week 44	0.205 (0.171–0.239)	0.229 (0.193–0.264)
Week 52	0.224 (0.189–0.259)	0.238 (0.202–0.274)
log rank test p value	0.5834	–
Hazard ratio[b]	0.935 (0.735–1.190)	–

Figures in parentheses indicate 95% CIs.
[a] Kaplan-Meier method and Greenwood's formula.
[b] Cox regression model.

crease in the risk of bleeding adverse events in the ITT population compared with clopidogrel 50 mg. The trend for cumulative incidence of bleeding adverse events in the all-treated population was consistent with that in the ITT population, a fact which suggests robustness of the study results and denies our hypothesis that clopidogrel 75 mg increases the risk of bleeding adverse event by approximately 30%, as compared to 50 mg. Moreover, the rate of gastrointestinal bleeding in the clopidogrel 75-mg group was similar to that in the clopidogrel 50-mg group and no bleeding events requiring transfusion were identified. During the on-treatment period, 3 patients in the clopidogrel 50-mg group and 1 patient in the clopidogrel 75-mg group experienced a significant drop in hematocrit. The drops in the clopidogrel 50-mg group were due to surgery for arteriosclerosis obliterans, ascending colon cancer and gastric ulcer hemorrhage; however, in the clopidogrel 75-mg group, a cause of the drop could not be specified since it recovered to normal without any treatment or study drug discontinuation. Furthermore, patients treated with clopidogrel 75 mg are not at increased risk of experiencing an SAE, a serious bleeding adverse event or adverse events of interest. Taking into consideration the above facts, the safety profile of clopidogrel 75 mg is thought to be comparable to that of clopidogrel 50 mg.

As regards efficacy, the COMPASS study showed a numerically lower cumulative incidence of vascular events in the group treated with clopidogrel 75 mg (2.6%, 95% CI = 1.3–4.0% vs. 3.8%, 95% CI = 2.2–5.5%; p = 0.4118). Although the standard dose (75 mg) is not associated with a significant reduction in the incidence of vascular events in this clinical trial setting, vascular events defined in this study were considered as life-threatening or serious events. Taking into consideration the facts that 2 patients suffering vascular events in the clopidogrel 75-mg group would have primarily been excluded from the study and standard dose has a comparable safety profile to lower dose of clopidogrel, this numerical difference might mean potential benefit of the standard dose of clopidogrel. In other words, the study may present a medically important risk of the low-dose clopidogrel for patients without bleeding risk, even in the absence of a statistically significant difference. It should also be noted that this study was not powered to detect a difference in efficacy.

The incidences of bleeding adverse events and other adverse events in the present study are comparable to previous clinical trials with clopidogrel. In the pivotal phase III studies in Japan, major hemorrhagic adverse drug reactions were rare following treatment with clopidogrel 75 mg for 52 weeks, occurring in <2% of Japanese stroke patients [9]. The same study showed an incidence of hepatic dysfunction of approximately 13.4%, with the incidences of leukopenia, neutropenia and thrombocytopenia <2.5%. The PRoFESS study investigated clopidogrel 75 mg versus aspirin and dipyridamole in stroke patients [7, 11]. Here, the incidence of major hemorrhagic events was 3.6% in the clopidogrel arm, while any hemorrhagic events occurred in 4.9% of patients. Adverse events leading to treatment discontinuation occurred at a similar frequency in the PRoFESS study (10.6%) to the present study (12.0%).

The incidence of vascular events in the present study (2.6%) was also similar to that found previously in two separate studies with clopidogrel 75 mg in Japanese patients (3.6 and 4.4%, respectively) [9, 10]. Vascular events in both studies were infrequent compared with those reported in non-Japanese populations. For example, the incidence of ischemic stroke, myocardial infarction or vascular death was 5.32% in the clopidogrel 75 mg arm of the CAPRIE study and the incidence of stroke, myocardial infarction or vascular death was 13.1% in the PRoFESS study [6, 11]. However, cross-study comparisons are often unreliable due to subtle differences in study protocols and distinct patient populations. Indeed, the recurrence of myocardial infarction has been shown to be lower in patients from Japan compared with the rest of the world, which could have had an impact on these results [12].

The main strengths of this study lie in its design as a randomized, double-blind, double-dummy trial and the fact that following randomization, the patient characteristics in the two treatment arms were very similar. The study also had a high completion rate, with similar proportions of patients from both groups completing the 52-week course, in addition to a high follow-up rate, with 93.6% of patients completing the study undergoing follow-up assessments.

However, there are also several potential limitations to the current study. First, the incidence of bleeding adverse events in the 75-mg group (16.5%) was lower than that estimated during the sample size collection (26.8%), thereby reducing the power of the study to determine a statistically significant difference between the two treatment groups. Second, the trial had many exclusion criteria because the COMPASS study was a postmarketing clinical trial in which patients with off-label use and/or with impairments that may hinder detection of efficacy and safety variables cannot be enrolled. Actually, in Ja-

Table 5. Number (%) of TEAEs among the all-treated population

Type	Clopidogrel 50 mg (n = 556)	Clopidogrel 75 mg (n = 552)
Any TEAE	463 (83.3)	477 (86.4)
Any serious TEAE	55 (9.9)	54 (9.8)
Any TEAE leading to death	2 (0.4)	0
Any TEAE leading to treatment discontinuation	52 (9.4)	66 (12.0)

Table 6. Time to first vascular event

	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Number of events	21	16
Cumulative incidence[a]		
Week 4	0.005 (0.000–0.012)	0.002 (0.000–0.005)
Week 8	0.005 (0.000–0.012)	0.004 (0.000–0.009)
Week 12	0.009 (0.001–0.017)	0.005 (0.000–0.012)
Week 20	0.022 (0.010–0.034)	0.007 (0.000–0.015)
Week 28	0.027 (0.014–0.041)	0.013 (0.003–0.022)
Week 36	0.035 (0.019–0.050)	0.020 (0.008–0.032)
Week 44	0.038 (0.022–0.055)	0.024 (0.011–0.037)
Week 52	0.038 (0.022–0.055)	0.026 (0.013–0.040)
log rank test p value	0.4118	–
Hazard ratio[b]	1.312 (0.685–2.514)	–

Figures in parentheses indicate 95% CIs.
[a] Kaplan-Meier method and Greenwood's formula.
[b] Cox regression model.

Table 7. Number (%) of vascular events

	Clopidogrel 50 mg (n = 558)	Clopidogrel 75 mg (n = 552)
Vascular events	21 (3.8)	16 (2.9)
Ischemic stroke	10 (1.8)	12 (2.2)
Myocardial infarction	2 (0.4)	1 (0.2)
Other vascular event	9 (1.6)	5 (0.9)
Peripheral vascular disease	1 (0.2)[a]	2 (0.4)
Coronary artery stenosis	1 (0.2)	1 (0.2)
Angina pectoris	2 (0.4)	0
Transient ischemic attack	5 (0.9)	2 (0.4)

[a] One patient died due to a vascular event (peripheral arterial disease).

pan, clopidogrel 50 mg has been recommended for patients with higher bleeding risk such as patients aged ≥75 years and/or with a body weight ≤50 kg. That would have resulted in a study population with a small rate of female gender and atherothrombic stroke. Taking into account that mean body weight (SD) in Japanese people in their 60s was 64.2 (9.4) kg in men and 53.3 (8.4) kg in women when the study was conducted, many of the female patients would have been likely to be excluded from the study [13]. Furthermore, it can be speculated that some of the patients with atherothrombic stroke had been excluded because of being bedridden, needing total assistance, or having dementia, which may impede efficacy and safety evaluation considering its larger ischemic area as compared to lacunar stroke. Third, efficacy had been evaluated during 52 weeks of treatment. Nevertheless, the primary objective of the COMPASS study was safety evaluation in terms of bleeding adverse events. In addition, neither new findings nor increasing of the concerned bleeding frequency beyond week 52 had been predicted.

Furthermore, as described in the section of statistical analyses, 541 patients per group (approximately 1,100 in total) were thought to be adequate to show a significant difference in bleeding adverse events during 52 weeks between the 50- and 75-mg group. Therefore, 52 weeks was thought to be an appropriate duration for the postmarketing commitment study for safety evaluation. Lastly, our disclosed relationship with the sponsor would be a potential risk for the interpretation of the study results. However, major endpoints of the study were adjudicated by a third party not related to both authors and sponsor under blinded condition. Thorough evaluation of clopidogrel 50 mg versus 75 mg over 52 weeks for the management of ischemic stroke in Japanese patients aged <75 years and weighing >50 kg demonstrated that there were no statistically significant differences between the two dosages in any safety analyses, and no clear difference in the incidence of vascular events, although this was numerically higher in the low-dose group. Considering the balance between the seriousness of clinical outcomes associated with vascular events and bleeding severity, the benefit of clopidogrel 75 mg in reducing vascular risk could potentially outweigh the risk engendered by a bleeding adverse event. Namely, clopidogrel 75 mg provides a clinically acceptable safety profile and is expected to be of better clinical benefit as compared to clopidogrel 50 mg for the secondary prevention of ischemic stroke in Japanese patients who are <75 years old with a body weight >50 kg.

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Intravenous Recombinant Tissue Plasminogen Activator Thrombolysis in Acute Ischemic Stroke due to Middle Cerebral Artery Dissection

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Beneficial effect of recombinant tissue plasminogen activator (rtPA) in cerebral arterial dissection is controversial. We experienced a 45-year-old man with acute ischemic stroke due to middle cerebral artery dissection, who was treated with rtPA. Characteristic vascular findings indicating dissection became evident only in subsequent angiographic examinations. Our case indicates that serial angiographic examinations should be essential after acute thrombolytic therapy, especially in young patients who are at a high risk of cerebral arterial dissection. **Key Words:** Acute thrombolysis—acute brain infarction—spontaneous cerebral arterial dissection—magnetic resonance angiography.

Although intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) is effective in carefully selected patients with acute ischemic stroke,[1] the beneficial effect of rtPA in patients with cerebral arterial dissection remains controversial[2,3]. Furthermore, it is often difficult to distinguish spontaneous cerebral artery dissection from atherothrombotic or embolic infarction when the culprit artery is occluded. We report a patient with acute ischemic stroke due to middle cerebral artery (MCA) dissection who was treated with rtPA.

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Case Report

A right-handed, 45-year-old man presented with sudden onset of left-sided motor deficit and dysarthria, but no complaint of headache. He arrived in our emergency room 30 minutes after the onset of symptoms exhibiting hemiparesis, right conjugate deviation, and dysarthria, corresponding to a National Institutes of Health Stroke Scale score of 15. Magnetic resonance imaging (MRI) detected acute ischemic lesions in the right basal ganglia and corona radiata (Fig 1A). The anterior branches of the right MCA were not identified on magnetic resonance angiography (MRA) (Fig 1B). Although IV rtPA infusion (0.6 mg/kg) was started by 98 min after stroke onset, no neurologic improvements were observed. MRA revealed an occlusion at the superior trunk of the right MCA insular segment (M2) at 24 hours after initiation of thrombolytic treatment. MRA as well as 3D- digital subtraction angiography (3D-DSA) on day 7 revealed an aneurysmal-like pouch from the right M2 origin (Fig 1C1, C2). Subsequent MRA examination showed partial recanalization of the M2 from its origin on day 23 (Fig 1D), and complete recanalization with the pearl-and-string sign 6 months after stroke onset (Fig 1E1,

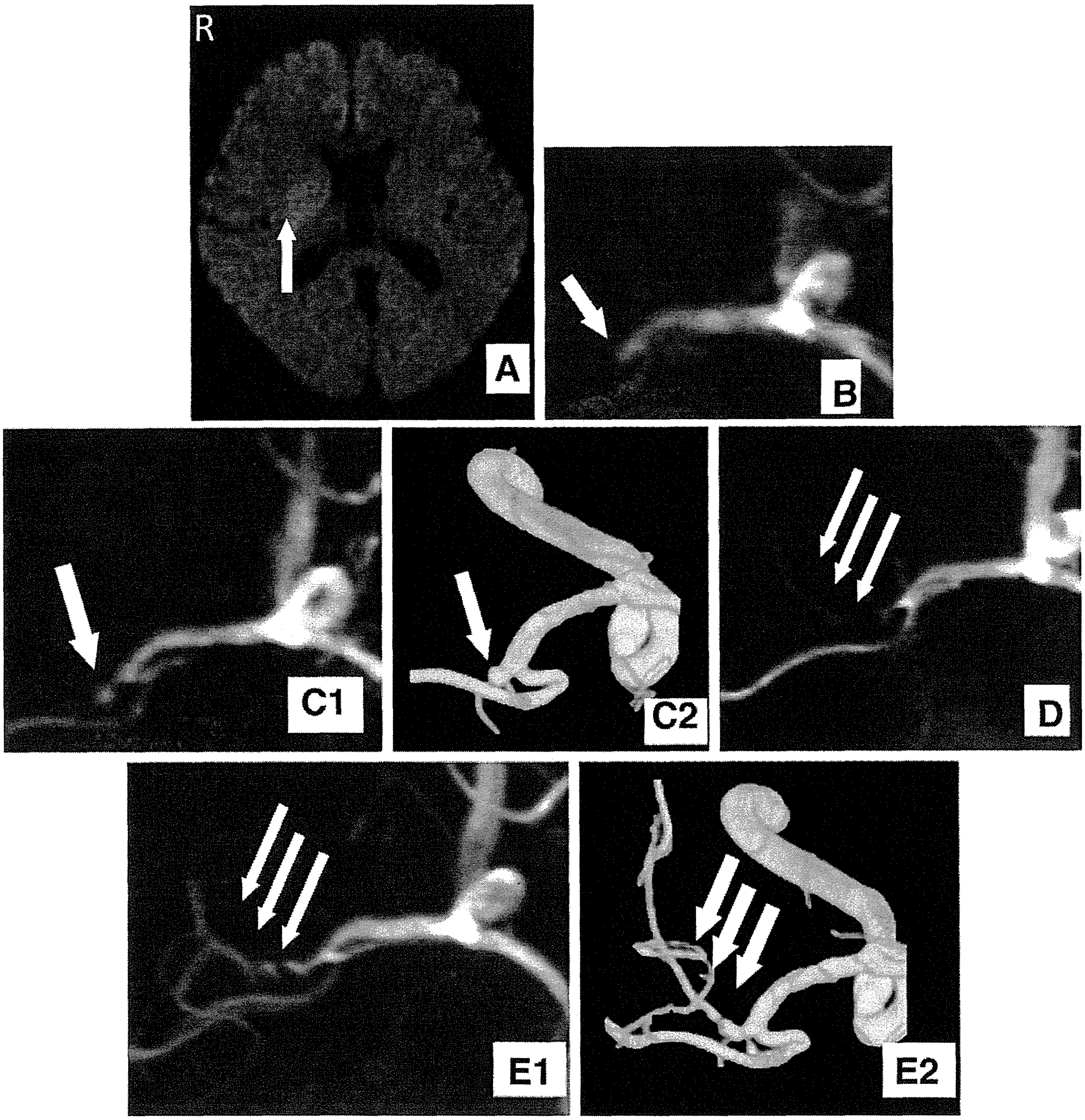

Figure 1. *Magnetic resonance imaging (MRI) and 3D-digital subtraction angiography (3D-DSA). (A) Diffusion-weighted MRI showing the area of hyperintensity in the right basal ganglia and corona radiata (arrow). (B) Magnetic resonance angiography (MRA) performed on admission showing an obstruction of the insular segment of the right MCA (arrow). (C) A bulge-like change in the obstructing stump (arrow) observed on day 7 of MRA (C-1) as well as 3D-DSA (C-2). (D) A partial recanalization (arrows) from the obstructing stump detected on day 23. (E) Complete recanalization with the pearl-and string sign (arrows) were seen 6 months later on MRA (E-1) and 3D-DSA (E-2).*

E2). We finally arrived at a diagnosis of ischemic stroke due to spontaneous MCA dissection.

Discussion

Our patient had no definite evidence of arterial dissection or other limitations against IV thrombolysis during the therapeutic time window. Characteristic vascular findings indicating dissection became evident only on subsequent MRA examinations. Although thrombolysis did not trigger aneurysmal formation or intracranial bleeding in this patient, subarachnoid hemorrhage is not a rare occurrence after intracranial artery dissection.[4]

Although the use of thrombolysis for extracranial carotid artery dissection has been well studied,[2] the efficacy and safety of rtPA in patients with intracranial arterial dissection remains controversial.[3] Even in Japan, where intracranial vertebral artery dissection is relatively frequent,[5] spontaneous MCA dissection has been rarely documented.[6] Accumulation of data on the management of intracranial artery dissection would be of great value for the future prognosis of such patients.

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<原　著>

わが国における「脳卒中急性期インディケーター案」の検証：ウェブ登録研究報告

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要旨：普遍的かつ正確な統合型脳卒中地域医療評価システムの構築を目的とし，科学的根拠に基づく「脳卒中急性期インディケーター案」が策定された．2010年7～9月の任意の2カ月間，発症3日以内に入院した脳卒中1686例を前向きに登録した．全協力施設を人口密度で2群，登録患者数，病床数，脳卒中従事医師数で3群に分け，施設毎の各インディケーター実施率を調査した．インディケーター実施率と人口密度，病床数，脳卒中従事医師数との関連は認めず，頭部CT/MRI，脳血管評価，抗血栓療法，脂質/血糖検査の施行率は90％以上の高い施行率であった．登録患者数の最多群において，理学療法評価の施行率が高値であり（p=0.026），最少群において，抗血栓療法施行率が高値であった（p=0.0046）．今後，全国規模でインディケーター実施率を評価し，施設へフィードバックを行うシステムの構築が必要と考える．

Key words: evidence, stroke, clinical indicators, audit, diagnosis procedure combination
（脳卒中 34: 289–297, 2012）

はじめに

脳卒中医療では，救命救急・急性期治療から回復期リハビリテーション，さらには在宅介護にいたるまで，継ぎ目のない医療・介護（シームレスケア）が提供されることが望まれる．そのためには，行政の支援に加え，脳卒中医療の質を全体的かつ客観的に評価する体制を構築する必要がある．その手段として，脳卒中医療の全体像が反映されるようなインディケーターの開発が求められる．インディケーターは，科学的裏づけ（エビデンス）とclinical audit（臨床監査）によって，地域差を超越した普遍性とデータの信頼性担保とがなければならない．すでに，英国では12項目，デンマークでは8項目のインディケーターを選定し，国家規模で監査を行っている[1,2]．しかし，わが国には，これまで脳卒中治療成績を客観的かつ総合的に評価，監視するシステムは存在しなかった．

普遍的かつ正確な統合型脳卒中地域医療評価システムを構築することを目的として，厚生労働科学研究費補助金による「脳卒中地域医療におけるインディケーターの選定と監査システム開発に関する研究」班（主任研究者：峰松一夫）が結成された[3)]．同研究班は，文献レビュー等による科学的根拠に基づいたわが国の医療事情に即した「脳卒中急性期インディケーター案」を策定した（Table 1）[4,5)]．今回われわれは，循環器病研究開発費22–4-1「新しい脳卒中医療の開拓と均てん化のためのシステム構築に関する研究」班（主任研究者：峰松一夫）を組織し，この「脳卒中急性期インディケーター案」の検証を行った．

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（2012年2月1日受付，2012年3月7日受理）

Table 1　脳卒中急性期インディケーター案[4)]

I. Process

1. 初診医が脳卒中診療担当医であった率
2. Stroke unit 治療率
3. 入院後 24 時間以内に頭部 CT もしくは MRI 施行を施行した率
4. 入院期間中に頸動脈エコー，MR angiography，もしくは CT angiography による脳血管（頸動脈）病変を評価した率
5. rt-PA 静注療法を施行した率
6. 来院から rt-PA 静注療法開始までが 1 時間以内であった率
7. 入院後 48 時間以内に抗血栓療法を施行した率
8. 退院時にワルファリンを使用した率
9. 入院後 24 時間以内に嚥下機能評価を施行した率
10. 入院後 3 日以内に理学療法の評価を施行した率
11. 入院後 7 日以内に多職種でカンファレンスを施行した率
12. 入院期間中に脂質（T-chol，LDL-chol，HDL-chol，TG）・血糖検査を施行した率
13. 入院中に深部静脈血栓症の予防を行った率

II. Outcome

1. 入院患者数（発症後 3 日以内入院例）
2. 入院期間
3. 入院時 National Institutes of Health Stroke Scale（NIHSS）
4. 退院時 modified Rankin Scale（mRS）
5. rt-PA 静注療法施行患者の退院時（または 30 日目）mRS

・初診医が脳卒中診療担当医であった率，頭部 CT/MRI 施行率，脂質・血糖検査施行率：分母は発症後 3 日以内に入院した脳梗塞，脳出血，くも膜下出血および TIA 患者
・脳血管（頸動脈）病変評価施行率，抗血栓療法施行率：分母は発症後 3 日以内に入院した脳梗塞，および TIA 患者
・rt-PA 静注療法施行率：分母は発症後 3 時間以内に来院した脳梗塞患者
・来院から rt-PA 静注療法開始までが 1 時間以内であった率：分母は rt-PA 静注療法を施行した脳梗塞患者
・退院時ワルファリン使用率：分母は発症後 3 日以内に入院した Af を有する脳梗塞，および TIA 患者
・Stroke unit 治療率，嚥下機能評価施行率，理学療法評価施行率，多職種によるカンファレンス施行率，深部静脈血栓症の予防施行率：分母は発症後 3 日以内に入院した脳梗塞，脳出血，くも膜下出血患者

対象と方法

本研究遂行にあたり，分担研究者の所属する 6 施設において，倫理委員会の承認を得た．対象は，分担研究者の所属する 6 施設と，選定された各地域の協力施設である．調査地域として分担研究者所属施設所在地の 6 府県（秋田県，神奈川県，京都府，大阪府，福岡県，熊本県）と研究協力者所属施設所在地の鹿児島県の計 7 府県を選定した．これら 7 府県の平成 21 年 10 月現在の推計人口は計 3003.7 万人，日本総人口の 23.6% に相当した．調査対象施設は，平成 19 年度第 5 次医療法改正により各都道府県が公表した脳卒中急性期診療を担う医療機関の中から，各医療機関の所在する二次医療圏の人口密度に基づき選定した．人口密度は，厚生労働統計資料の二次医療圏別人口から抽出し[6)]，府県のホームページに記載されている二次医療圏の面積から算出した．対象施設選定にあたり，各対象府県の二次医療圏を人口密度の高い順に並べ，最上位と最下位の人口密度を有する二次医療圏内の施設に同時に研究協力を依頼した．各二次医療圏内から 5 施設の協力が得られた場合，その時点で施設選定を終了した．5 施設未満であった場合は，その次に上位（または下位）の人口密度を有する二次医療圏の施設に研究協力を依頼した．内

諾の得られた各施設に対して研究資料提供契約を締結し，正式な協力施設とした．対象例は，2010年7月より同年9月までの3カ月のうち，任意の2カ月間に発症3日以内に入院した急性期脳卒中患者(脳梗塞，脳出血，くも膜下出血，一過性脳虚血発作)である．当該施設で，対象例を連続的にウェブ登録した．人口密度は，当該施設における二次医療圏の人口密度数とした．病床数は，インターネット上に公表された総病床数とし，脳卒中従事医についても同様に，インターネット上に公表された各施設の脳神経外科，脳血管内科，神経内科のいずれかに所属する医師の総数とした．

インディケーター案の各項目の定義に関して，「脳卒中診療担当医」とは，脳卒中診療経験3年以上(初期研修は含まない)の神経内科，脳血管内科，脳神経外科医など，脳卒中診療を主たる業務としている医師とした．また，入院直後は救急医が対応し，脳卒中診療担当医と連絡をとって診療が始まる場合を勘案し，入院時刻から3時間以内に脳卒中診療担当医が診療を開始したとき，初診医が脳卒中診療担当医であったと定義した．「Stroke unit」とは，他職種からなる専属の脳卒中チームが配属され，他疾患と明確に区別された脳卒中専用の病棟(病床)とした．脳卒中ケアユニット入院医療管理料算定のための施設基準を概ね満たす場合には，管理料算定がなくとも，Stroke unitとした．「抗血栓療法」には，アスピリン，チクロピジン，クロピドグレル，シロスタゾール，ワルファリン，ヘパリン，アルガトロバン，オザグレルナトリウム投与が含まれる．「嚥下機能評価」とは，医師，言語聴覚士または看護師が，反復唾液嚥下や水飲みテストなどによって評価を行った記録がカルテに記載されていること，「理学療法の評価」は，理学療法士が保険点数を請求して行ったこととした．「多職種カンファレンス」に関しては，カルテにカンファレンスを実施した日付の記載があること，会議には最低限，医師，看護師と最低1人のリハビリスタッフまたはmedical social worker(MSW)が参加し，参加者の名前と職種の記載があること，医師により患者の診断，治療方針，予後予測が述べられること，と定義した．「深部静脈血栓症の予防」は，弾性ストッキング，あるいは，間欠的空気圧迫装置を用いて計画的な医療管理を行い，肺血栓塞栓症予防管理量を算定した場合とした．

協力施設の二次医療圏の人口密度，登録患者数，病床数，脳卒中従事医師数，入院時NIHSSスコア(National Institutes of Health Stroke Scale)の分布を調べた．人口密度は，高密度群(high群)と低密度群(low群)の2群に分けた．登録患者数，病床数，脳卒中従事医師数は3分位に分け，各々small群(S群)，medium群(M群)，large群(L群)とした．脳梗塞，脳出血，くも膜下出血において，重症例をNIHSSスコア25点以上と定義した．各インディケーター案の実施率を施設毎に算出し，人口密度，登録患者数，病床数，脳卒中従事医師数，重症度との関連を調べた．3群の同時比較にはKruskal-Wallis検定を，2群間の比較としてMann-WhitneyのU検定を用いた．$p<0.05$を有意差ありとした．

結　果

秋田県3施設，神奈川県6施設，京都府5施設，大阪府12施設，福岡県12施設，熊本県8施設，鹿児島県9施設の計55施設(分担研究6施設を含む)の協力を得た．このうち有効回答の得られた44施設(80%，1686例)を対象とした(Table 2)．地域別の登録患者数は，秋田県72人(2施設)，神奈川県185人(4施設)，京都府117人(4施設)，大阪府428人(8施設)，福岡県377人(12施設)，熊本県259人(7施設)，鹿児島県248人(7施設)であった．病型別では，脳梗塞1182例(70.1%)，脳出血305例(18.2%)，くも膜下出血73例(4.3%)，一過性脳虚血発作126例(7.4%)であった．Stroke unit治療率が0%であった施設は，11施設(25%)あり，いずれも本調査で定義した「Stroke unit」を有していない施設であった．理学療法士は，全施設に配置されていた．登録期間中のrt-PA静注療法施行率が0%であった施設は18施設(40.9%)あり，うち4施設では，発症3時間以内の対象患者の来院がなかった．入院後24時間以内の頭部CT/MRI，入院期間中の脳血管評価(頸動脈エコー，MR angiography，CT angiography)，入院後48時間以内の抗血栓療法，入院期間中の脂質・血糖検査の施行率は，いずれも90%以上であった(Fig. 1，Table 3)．

施設の分布は，人口密度別ではlow群(65.4–4000人/km^2)34施設，high群(4001–11330人/km^2)10施設(中央値2000：4分位657–3407人/km^2)，登録患者数別では，S群(1–26人)14施設，M群(27–43人)15施設，L群(44–123人)15施設(中央値35人)，病床数別では，S群(60–329人)14施設，M群(330–550人)16施設，L群(551–1354人)14施設(中央値403人)，

Table 2　本研究の研究協力施設一覧

秋田県	山本組合総合病院，秋田県立脳血管研究センター
神奈川県	済生会横浜市東部病院，独立行政法人労働者健康福祉機構横浜労災病院，聖マリアンナ医科大学病院，聖マリアンナ医科大学東横病院
京都府	京都第二赤十字病院，京都府立医科大学附属病院，京都第一赤十字病院，公立南丹病院
大阪府	国立循環器病研究センター，りんくう総合医療センター市立泉佐野病院，医療法人医誠会 医誠会病院，独立行政法人国立病院機構大阪医療センター，国家公務員等共済組合連合会大手前病院，医療法人寿会 富永病院，大阪鉄道病院，弘善会 矢木脳神経外科病院
福岡県	九州大学病院，独立行政法人国立病院機構九州医療センター，福岡県済生会福岡総合病院，福岡赤十字病院，公立学校共済組合九州中央病院，独立行政法人国立病院機構福岡東医療センター，福岡大学筑紫病院，社会医療法人 雪の聖母会 聖マリア病院，医療法人天神会 新古賀病院，大牟田市立総合病院，新日鉄八幡記念病院，医療法人社団陽明会 小波瀬病院
熊本県	熊本大学医学部附属病院，独立行政法人国立病院機構熊本医療センター，熊本市立熊本市民病院，熊本赤十字病院，済生会熊本病院，健康保険人吉総合病院，社団法人天草郡市医師会立天草地域医療センター
鹿児島県	医療法人慈風会 厚地脳神経外科病院，公益財団法人慈愛会 今村病院分院，独立行政法人国立病院機構鹿児島医療センター，鹿児島市立病院，いちき串木野市医師会立脳神経外科センター，県民健康プラザ鹿屋医療センター，鹿児島県立大島病院

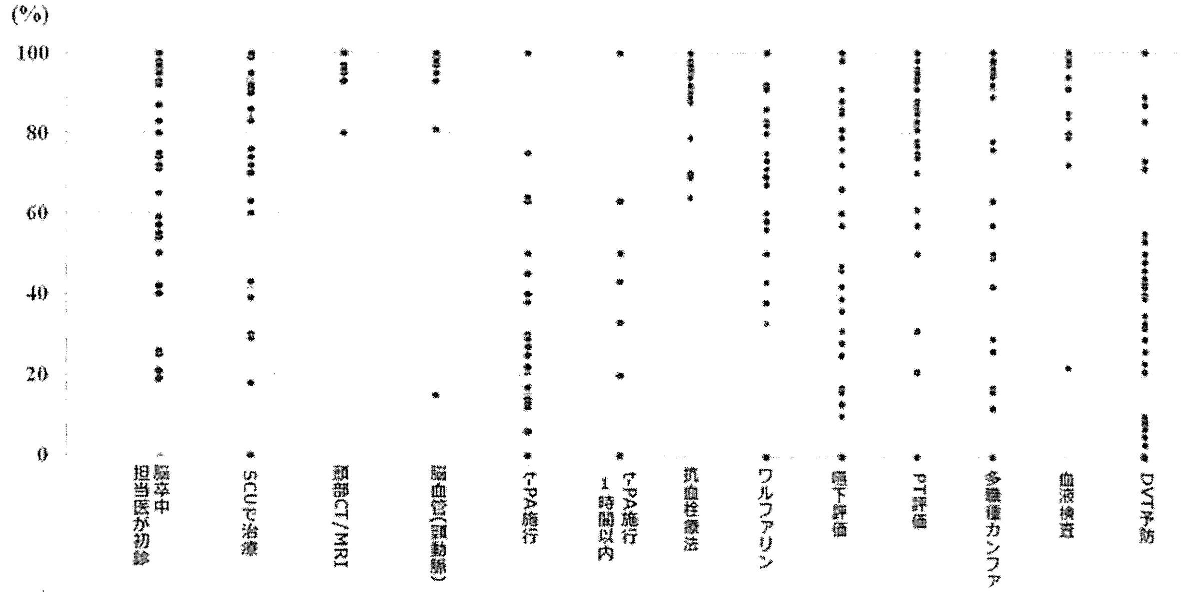

Fig. 1　脳卒中急性期インディケーター実施率の分布
ドットは，各協力施設のインディケーターの実施率を示す．

脳卒中従事医師数別では，S群（1–3人）12施設，M群（4–7人）18施設，L群（8–39人）14施設（中央値5人）であった（Fig. 2）．

人口密度，病床数，脳卒中従事医師数の多寡と各インディケーター案の実施率に関連はなかった．また，登録患者数の最多群（L群）において，入院後3日以内の理学療法評価の施行率が高値であり（S群：70.1±26.5％，M群：81.3±19.4％，L群：88.4±11.0％，p=0.026），最少群（S群）では，入院後48時間以内の抗血栓療法の施行率が高値であった（S群：98.5±2.4％，M群：90.5±11.0％，L群：93.1±7.6％，p=0.0046）（Fig. 3）．リハビリテーション関連のインディケーター案では，重症例で入院後24時間以内の嚥下機能評価（0–24：65.4％ vs 25–42：36.3％，p<0.0001），

Table 3　脳卒中急性期インディケーター案の項目別の実施率

	全国平均
初診医が脳卒中診療担当医であった率（%）	80.3 (78.3–82.1)
Stroke unit治療率（%）	67.1 (64.7–69.4)
頭部CT/MRI施行率（%）	98.7 (98.0–99.1)
脳血管（頸動脈）病変評価率（%）	97.9 (96.9–98.5)
rt-PA静注療法施行率（%）	20.4 (16.3–25.2)
rt-PA静注療法までが1時間以内の率（%）	40.6 (29.5–52.9)
抗血栓療法施行率（%）	92.7 (91.2–94.0)
退院時ワルファリン使用率（%）	77.8 (72.8–82.1)
嚥下機能評価施行率（%）	60.0 (57.5–62.3)
理学療法評価施行率（%）	83.8 (81.9–85.5)
多職種によるカンファレンス施行率（%）	75.3 (73.1–77.4)
脂質・血糖検査施行率（%）	95.1 (94.0–96.1)
深部静脈血栓症の予防施行率（%）	36.8 (34.4–39.2)
在院日数	17 (10–29)
入院時NIHSS	4 (2–12)
退院時mRS	2 (1–4)
rt-PA静注療法施行患者の退院時（または30日目） mRS	3 (1–4)

入院時 NIHSS，退院時 mRS，在院日数は中央値(IQR)，その他は平均値(95% CI)を示す．

入院後3日以内の理学療法評価(0–24：86.4% vs 25–42：62.8%，p<0.0001)の施行率が低く，入院中の深部静脈血栓症予防の施行率が高かった(0–24：30.5% vs 25–42：56.4%，p<0.0001)．重症例の割合は，人口密度，登録患者数，病床数，脳卒中従事医師数の群間比較において，いずれも有意差はなかった．

考　察

本調査では，人口密度，病床数，脳卒中従事医師数の多寡と各インディケーター案の実施率に関連はなかった．入院後24時間以内の頭部CT/MRI，入院期間中の脳血管評価(頸部エコー，CTA，MRA)，入院期間中の脂質/血糖検査の施行率のばらつきは小さく，いずれも90%以上の高い施行率であった．CT/MRI施行率は，英国では70.5% (95%CI 58.6–79.7%)[7]，デンマークで71.2% (95%CI 68.4–73.9%)[2]であり，いずれも今回のわれわれの調査に比べて低値であった．嚥下機能評価の施行率は，英国において84.1% (95% CI 75.5–94.2%)であり[7]，本調査と比較して高い水準であった(Table 3)．今回の協力施設が，脳卒中急性期診療を担う医療機関の中から選定されたことから，CT/MRI施行率は高値であったが，一方で，嚥下機能に関する評価が不十分であるというわが国の現状が示された結果であった．

登録患者数の最多群(L群)において，3日以内の理学療法評価の施行率が高値であった．これは多くの症例を診療する施設では，リハビリテーションの診療スタッフや実施体制が充実しているためと推察される．今後，リハビリテーション関連のスタッフ数，休日のリハビリテーション実施の有無についての検討が必要であろう．また，登録患者の最少群(S群)において，48時間以内の抗血栓療法の施行率が高値であった．抗血栓療法の施行率が最も低値であったM群は，他の2群に比して施行率のばらつきが大きかった．急性期における抗血栓療法は，重症例では出血性梗塞を懸念し，控える場合があるが，本調査では重症脳梗塞患者の割合は，3群間の比較で有意差はなかった．

脳梗塞，脳出血，くも膜下出血患者において，重症例の嚥下機能評価，理学療法評価の施行率が低かったのは，重症度が高い急性期では症状が安定するまでの間，リハビリテーションを見合わせた患者

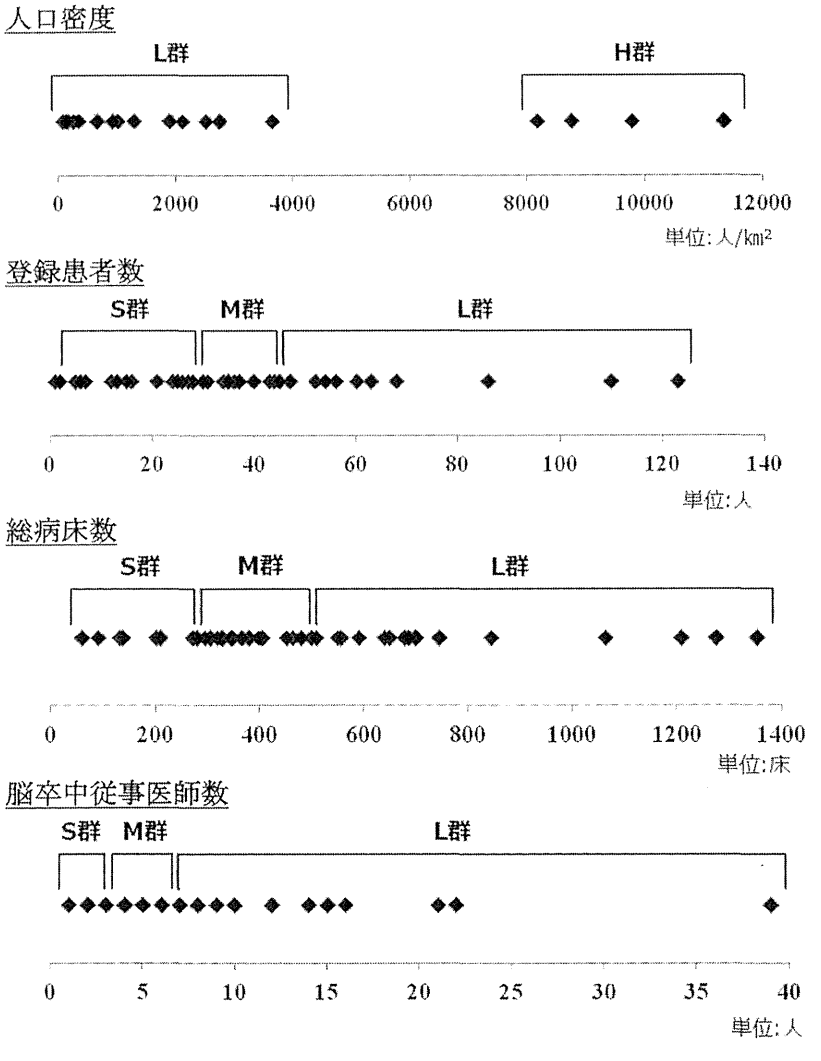

Fig. 2 各施設の地域人口密度，登録患者数，総病床数，脳卒中従事医師数の分布
ドットは，対象施設を示す．人口密度を2群，登録患者数，総病床数，脳卒中従事医師数は3分位に分けた．

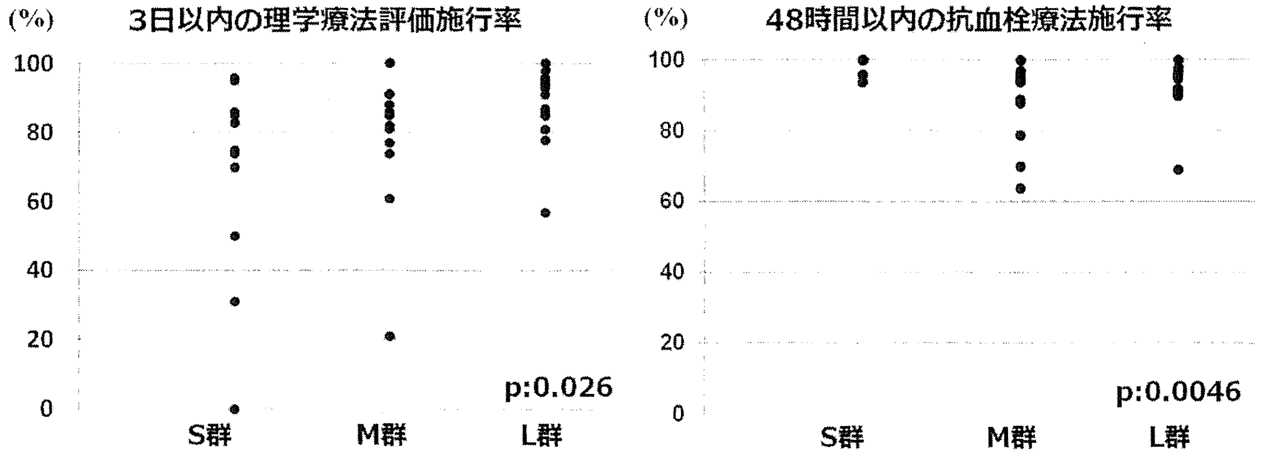

Fig. 3 登録患者数とインディケーター実施率の関係
理学療法評価率は登録患者数の最多群（L群）で高値であり，抗血栓療法施行率は最少群（S群）で高値であった．

が含まれているためと推察した．深部静脈血栓症予防に関しては，重症例では，離床困難な場合が多く施行率が高かったものと思われる．

今回の調査は，協力施設の自己申告によりインディケーターの実施率が入力されている．今後，インディケーターを用いた医療の質の評価を客観的かつ継続的に行うためには，DPC(diagnosis procedure combination)やレセプトからのデータの抽出と，これを利用した監査などを検討すべきであろう．DPC対象病院は，全一般病院の18.0%であり[8]，必ずしも全ての病院を網羅するものではないが，インディケーターの実施率を自動的に算出し，経時的な評価を実施することが可能になると考える．一方で，DPCのデータは，日単位の情報であり，厳密な時間単位の情報が得られない．このため，入院後の時間を設定したインディケーター測定の際には，抽出の精度を見直す必要がある．加えて，週末入院患者における脳卒中の重症度，死亡率が上昇するとの報告があり[9]，入院曜日，あるいは入院時間帯によるインディケーターの解析も重要な点と考えられる．

本インディケーター案の中で，現行のDPC，レセプトからは得られない情報として，「初診医が脳卒中担当医である率」，「来院からrt-PA投与までが1時間以内であった率」，「入院後24時間以内の嚥下機能評価施行率」，「入院後7日以内の多職種カンファレンス施行率」，「入院時NIHSSスコア」が含まれている．今後，これらのデータ抽出を可能とするために，定義を明確にし，円滑なデータ抽出システムを構築することが求められる．測定施設数が少なく，かつ施行頻度にも大きなばらつきがみられた「来院からrt-PA投与までが1時間以内であった率」に関しては，American Heart Associationのガイドラインに基づいている．すなわち，同ガイドラインでは病院到着後10分以内に臨床評価を行い，45分以内にCTの読影を完了させ治療の適応を判断，1時間以内にrt-PA静注療法を開始するよう推奨されている[10]．また，rt-PA静注療法を病院到着から60分以内で施行した患者群において，院内死亡率，症候性頭蓋内出血の頻度が低かったとする報告もある[11]．その一方で，わが国におけるrt-PA承認後3年目の調査より，rt-PA静注療法の実施状況には，一定の地域格差が存在することが示された．すなわち，全国358の二次医療圏においてrt-PA使用が10例未満の医療圏が119カ所(33%)，うち1例も使用経験がない医療圏は67カ所あったという[12]．到着後1時間以内のrt-PA静注療法の施行率の向上は，患者転帰の改善につながりうることから，「来院からrt-PA投与までが1時間以内であった率」は「rt-PA静注療法の施行率」とともに，達成目標とすべきである．「入院時NIHSSスコア」は，退院時転帰へ最も寄与する因子であり，退院時転帰を評価する際の調整因子として，データ抽出が必須となろう．

既に諸外国では，脳卒中医療の質の評価および改善を図る取り組みの周知と活用によって，rt-PA静注療法施行率の上昇[13]，院内肺炎発症率の減少など[14]，脳卒中医療のレベルアップにつながることが明らかにされている．今後，わが国においても脳卒中急性期インディケーターの積極的な運用に向けて，DPCやレセプトデータの検証，円滑な自動データ抽出システムの構築，インディケーター実施率の評価と各医療機関へのフィードバックシステムの構築が不可欠である．

結　語

脳卒中急性期インディケーター案の各項目の実施率と，人口密度，病院の規模，脳卒中従事医師数には関連がなかった．画像診断や血液検査に関する施行率は高い水準であった一方で，海外のインディケーターと比較して，嚥下機能評価の施行率は低値であった．登録患者数の最多群(L群)において，理学療法評価の施行率が高値であったこと，最少群(S群)での抗血栓療法施行率が高値であったことについては，その原因を明らかにしていく必要がある．今後，脳卒中急性期インディケーターの積極的な運用とともに，その実施率を高めるための脳卒中診療体制の整備を含めた取り組みが重要である．

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