Temporal Trends in Clinical Characteristics and Door-to-Needle Time in Patients Receiving Intravenous Tissue Plasminogen Activator: A Retrospective Study of 4 Hospitals in Japan

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Temporal Trends in Clinical Characteristics and Door-to-Needle Time in Patients Receiving Intravenous Tissue Plasminogen Activator: A Retrospective Study of 4 Hospitals in Japan

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Background: Intravenous recombinant tissue plasminogen activator (rt-PA) has become a common treatment for acute ischemic stroke and has highly time-dependent benefits. We aimed to clarify temporal trends regarding the frequency and characteristics of patients receiving rt-PA and explore factors associated with door-to-needle time (DNT) in Japanese emergency hospitals. *Methods:* Consecutive patients who received intravenous rt-PA for acute ischemic stroke from October 2005 to December 2015 were retrospectively registered from 4 hospitals. Temporal trends in the frequency and characteristics of patients receiving rt-PA and factors associated with DNT were investigated. *Results:* A total of 750 patients, including 688 (420 men, median 75 years old) with out-of-hospital stroke, were registered. The frequency of patients receiving intravenous rt-PA for acute ischemic stroke continuously increased from 1.8% in 2005 to 9.5% in 2015. The proportion of patients who were elderly or had prestroke disability increased over time, while pretreatment stroke severity declined. The DNT gradually decreased (median 105 minutes in 2005, 61 minutes in 2015). According to multivariate regression analysis with correction for multiple comparisons, activation of a code stroke system (standardized partial regression coefficient (β) −.50, $P < .001$, $q < .001$), onset-to-door time (β −.15, $P < .001$, $q < .001$), pretreatment with antithrombotic agents (β .12, $P < .001$, $q = .001$), and year of treatment (β .11, $P = .007$, $q = .011$) were associated with DNT. *Conclusions:* Intravenous rt-PA was widely adopted in Japanese emergency hospitals. Characteristics of patients receiving intravenous rt-PA have changed over the past decade. Several factors, including the year of treatment, were associated with DNT, which has shortened over time.

Key Words: Thrombolysis—temporal trends—door-to-needle time—stroke

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Introduction

Intravenous recombinant tissue plasminogen activator (rt-PA) is a proven treatment for acute ischemic stroke to reduce mortality and improve functional outcomes. In Japan, intravenous rt-PA was approved in October 2005 and the percentage of patients treated with intravenous rt-PA was 5.2% in hospitals with a stroke unit and .6% in those without.[1] According to the recent Japan Standard Stroke Registry,[2] intravenous rt-PA is administered to approximately 5% of all patients with acute ischemic stroke. Previous studies have demonstrated an increase in the number of patients with acute ischemic stroke who receive intravenous rt-PA,[3-8] especially in patients aged >85 years, non-white patients, and patients with milder strokes.[5] However, data on temporal trends in the clinical characteristics of patients receiving intravenous rt-PA are relatively scarce.

Because the benefit of rt-PA is highly time dependent,[9] many guidelines recommend a door-to-needle time (DNT) of under 60 minutes.[10,11] Previous studies showed that there were various patient-related or hospital system-related factors associated with the DNT[12-15] and that a successful emergency medical service (EMS)-based and hospital-based performance-improvement initiative effectively shortened the DNT.[16-18] However, most of these studies were conducted over a relatively short term and temporal trends in the DNT and its related factors have not been well studied.

Given this context, we aimed to clarify temporal trends regarding the frequency and clinical characteristics of patients receiving intravenous rt-PA for acute ischemic stroke since its approval and to investigate factors associated with DNTs in Japanese emergency hospitals.

Materials and Methods

Study Design

This multicenter, retrospective observational study was conducted at 4 affiliated hospitals, all of which are urban hospitals with a stroke unit. Saiseikai Fukuoka General Hospital and Iizuka Hospital are tertiary-level emergency facilities for the Fukuoka and Iizuka areas, respectively, including both cities and surrounding small cities and towns. Fukuoka City Hospital and Kokura Memorial Hospital are secondary-level facilities for Fukuoka and Kitakyushu areas, respectively. Each facility has 24/7 availability of CT, MRI, and neurologists and/or neurosurgeons to provide stroke care. The cohort comprised consecutive patients who received intravenous rt-PA for acute ischemic stroke between October 1, 2005 and December 31, 2015. Trained specialized stroke physicians in each hospital performed emergency evaluations, including imaging, and made decisions about administration of rt-PA and endovascular therapy alongside thrombolysis. All patients received intravenous administration of .6 mg/kg alteplase (the recommended dose in Japanese guidelines[11] and the approved labeling). Endovascular therapy accompanied by thrombolysis was performed for eligible patients.

Patients' clinical information was recorded in a web-based Research Electronic Data Capture database hosted at Kyushu University Hospital.[19] For calculation of the annual rate of intravenous thrombolysis among acute ischemic stroke patients, the total number of patients with acute ischemic stroke admitted to each hospital during the study period was identified from the hospital discharge record of the Diagnosis Procedure Combination. The Diagnosis Procedure Combination is a mixed-case patient-classification system that includes principal diagnosis, coded according to the International Classification of Diseases and Injuries, 10th revision (ICD-10), which is linked to a hospital financing system.[20] We identified patients hospitalized for acute ischemic stroke by using ICD-10 diagnosis codes related to ischemic stroke (I63.0-9), excluding patients with scheduled admission. This study was approved by the ethics committee of Kyushu University Hospital (29-111) and by each facility (Saiseikai Fukuoka General Hospital, Fukuoka City Hospital, Iizuka Hospital, and Kokura Memorial Hospital). Written informed consent was waived because of the retrospective study design.

Study Patients

The following clinical information was systematically collected from medical records: age; sex; the presence of hypertension, diabetes mellitus, dyslipidemia, or atrial fibrillation; and pretreatment with antithrombotic agents, including antiplatelet and anticoagulant medications. Severity of stroke symptoms was assessed with the National Institutes of Health Stroke Scale (NIHSS) score, which was obtained before administration of rt-PA. Prestroke functional status was estimated with the modified Rankin Scale (mRS); prestroke disability was defined as mRS more than or equal to 3. Arrival time was classified as daytime working hours (from 8:00 AM to 4:59 PM) or night hours (from 5:00 PM to 7:59 AM), and weekdays (from Monday to Friday) or weekends (Saturday or Sunday). In hospitals with a code stroke system for earlier administration of rt-PA, whether the code stroke system was activated was assessed for patients with out-of-hospital stroke. The brain imaging modality before administration of rt-PA was classified as follows: CT only, with or without contrast enhancement (CT-based thrombolysis); MRI only (MRI-based thrombolysis); or both CT and MRI. The onset-to-door time (ODT) and the DNT were calculated from emergency medical charts for patients with out-of-hospital stroke. Symptomatic intracerebral hemorrhage was defined as CT evidence of new parenchymal intracerebral hemorrhage associated with neurological deterioration corresponding to an increase of more

than or equal to 4 points from the baseline NIHSS score within 36 hours after treatment.

Statistical Analysis

All statistical analyses were performed with EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[21] Data are expressed as medians and interquartile ranges for continuous variables and as counts and percentages for categorical variables. Clinical characteristics were compared with the Mann-Whitney's *U* test or Cochran-Armitage or Jonckheere-Terpstra test for trend, as appropriate. Linear regression analysis was performed to investigate associations between the rates of intravenous rt-PA and the year of treatment. Multivariate regression analysis was performed to investigate factors associated with the DNT, using stepwise selection with variables entered into the model at a significance level of $\alpha = .10$ and removed at $\alpha = .10$, including all variables in the univariate analysis, in addition to the year of treatment. Because hospital characteristics vary across facilities, variables for each facility were also included. For the sensitivity analysis, DNT values were transformed with the Box-Cox transformation to better approximate a normal distribution and multivariate regression models were constructed in the manner described above. All findings were very similar; thus, for ease of interpretation we present data from the primary analysis only. For the variables included in the multivariate model, adjustment for multiple testing was applied with the Benjamini-Hochberg false discovery rate set at .05. A *P* value with a corresponding q value of less than .05 was considered statistically significant.

Results

Annual Rates of Intravenous rt-PA Among Patients With Acute Ischemic Stroke

A total of 750 patients were registered during the study period. According to the discharge records of the Diagnosis Procedure Combination, a total of 12,559 patients with acute ischemic stroke were admitted during the same period and were included in this analysis. Figure 1 shows annual rates of intravenous rt-PA administration among acute ischemic stroke cases. From the time of approval of rt-PA in October 2005, the rate of intravenous rt-PA use increased continuously, from 1.8% in 2005 to 9.5% in 2015.

Temporal Trends in Characteristics of Patients Receiving Intravenous rt-PA

Of the 750 patients, 62 were excluded, 60 because of in-hospital stroke and 2 because intravenous rt-PA was administered twice during the study period. A total of 688 patients (420 men; median age, 75 [66-82] years) were thus included in the final analysis. Patients' characteristics are listed in Table 1. Among patients receiving intravenous rt-PA, the percentage who were older and with pre-stroke disability increased over time. The proportion of patients aged more than 85 years increased from 6.0% of treated patients in 2005-2007 to 16.0% in 2014-2015 ($P = .010$ for trend). Pretreatment stroke severity declined over time and the proportion of patients with mild stroke (NIHSS score ≤ 4) significantly increased over time (2.0% in 2005-2007 versus 17.7% in 2014-2015, $P < .001$ for trend). Six hundred fifty-five patients (93.5%) were

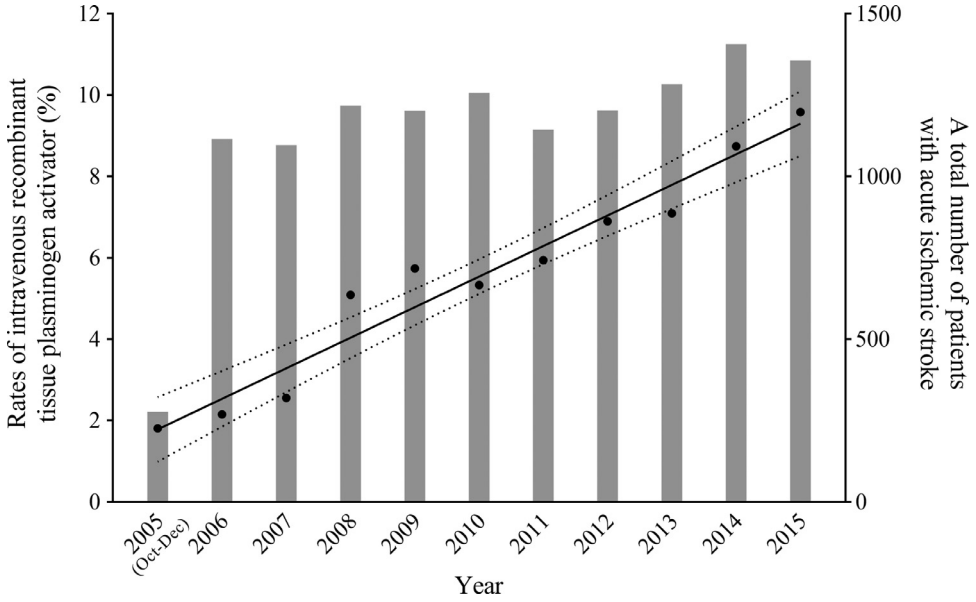

Figure 1. *Annual rates of intravenous recombinant tissue plasminogen activator administration among acute ischemic stroke cases. Linear regression analysis with* $R^2 = .947$ *and* $P < .001$.

Table 1. *Temporal trends in demographics and clinical characteristics of patients receiving intravenous thrombolysis*

	Total n = 688	2005-2007 n = 50	2008-2009 n = 124	2010-2011 n = 121	2012-2013 n = 161	2014-2015 n = 232	*P* value
Sex, male*	420 (61.0)	34 (68.0)	78 (62.9)	62 (51.2)	101 (62.7)	145 (62.5)	.990
Age in years†	75 (66-82)	71 (62-78)	72 (64-80)	78 (66.5-84)	75 (68-81.5)	76 (66-84)	.006
Age >85*	101 (14.7)	3 (6.0)	7 (5.7)	25 (20.7)	29 (18.0)	37 (16.0)	.010
Prestroke disability*	51 (7.4)	3 (6.0)	2 (1.6)	8 (6.6)	13 (8.1)	25 (10.8)	.005
Hypertension*	453 (65.8)	34 (68.0)	82 (66.1)	86 (71.1)	104 (64.6)	147 (63.4)	.325
Dyslipidemia*	185 (26.9)	11 (22.0)	35 (28.2)	31 (25.6)	42 (26.1)	66 (28.4)	.547
Diabetes mellitus*	157 (22.8)	17 (34.0)	20 (16.1)	20 (16.5)	45 (28.0)	55 (23.7)	.510
Atrial fibrillation*	349 (50.7)	28 (56.0)	67 (54.0)	71 (58.7)	73 (45.3)	110 (47.4)	.052
Pretreatment with antithrombotics*	266 (38.7)	22 (44.0)	50 (40.3)	52 (43.0)	62 (38.5)	80 (34.5)	.106
Antiplatelets*	185 (26.9)	15 (30.0)	30 (24.2)	32 (26.4)	52 (32.3)	56 (24.1)	.802
Anticoagulants*	103 (15.0)	8 (16.0)	25 (20.2)	24 (19.8)	18 (11.2)	28 (12.1)	.027
Arriving in night hours*	302 (43.9)	23 (46.0)	60 (48.4)	51 (42.1)	77 (47.8)	91 (39.2)	.177
Arriving in weekend*	186 (27.0)	11 (22.0)	36 (29.0)	26 (21.5)	45 (28.0)	68 (29.3)	.339
Patients treated under code stroke*	162 (23.5)	0 (0)	10 (8.1)	16 (13.2)	25 (15.5)	111 (47.8)	<.001
Imaging before thrombolysis*							<.001
Both CT and MRI	495 (71.9)	30 (60.0)	106 (85.5)	90 (74.4)	119 (73.9)	150 (64.7)	
CT-based thrombolysis	113 (16.4)	19 (38.0)	14 (11.3)	7 (5.8)	13 (8.1)	60 (25.9)	
MRI-based thrombolysis	80 (11.6)	1 (2.0)	4 (3.2)	24 (19.8)	29 (18.0)	22 (9.5)	
ODT†	55 (35-90)	49.5 (38-75)	43.5 (30-68)	48 (33-64.5)	60 (36.5-99)	68 (38.5-120)	<.001
DNT†	75 (59-93)	69 (61.5-88.5)	75.5 (65-93)	85 (70-103.5)	75 (61.5-93.5)	65 (41-90)	<.001
DNT <60 min*	193 (28.1)	12 (24.0)	23 (18.5)	14 (11.6)	39 (24.2)	105 (45.3)	<.001
Preadministration NIHSS score†	15 (8-20)	16.5 (12-21)	16 (10-21)	15 (8-21.5)	14 (8-19)	13 (6-20)	<.001
NIHSS score ≤4*	69 (10.0)	1 (2.0)	7 (5.6)	5 (4.1)	15 (9.3)	41 (17.7)	<.001
Endovascular therapy*	110 (16.0)	4 (8.0)	2 (1.6)	11 (9.1)	32 (19.9)	61 (26.3)	<.001
sICH*	20 (2.9)	1 (2.0)	5 (4.0)	6 (5.0)	2 (1.2)	6 (2.6)	.420

Abbreviations: DNT, door-to-needle time; NIHSS, National Institutes of Health Stroke Scale; ODT, onset-to-door time; sICH, symptomatic intracerebral hemorrhage.
Data are presented as n (%) or median (interquartile range).
*Cochran–Armitage test for trend.
†Jonckheere–Terpstra test for trend.

ambulance-transported admissions. Two of the 4 hospitals developed and implemented a code stroke system during the study period. The system was implemented in May 2009 at Saiseikai Fukuoka General Hospital and in January 2014 at Kokura Memorial Hospital. Code stroke systems at these 2 hospitals were not identical, but both consisted of prearrival notification and activation of the entire stroke team, rapid laboratory testing, and an rt-PA toolkit. At EMS prenotification or at self-presented arrival, if the attending emergency department doctor identified patients with suspected acute ischemic stroke within the time window for intravenous rt-PA, he called the following staff immediately: an emergency room (ER) nurse, stroke physicians, a stroke unit chief nurse, and technologists (CT and MRI room, angiography room, and clinical laboratory). As laboratory tests that affect treatment decisions, point-of-care international normalized ratio and glucose measurements were performed in the ER (international normalized ratio was adopted at both facilities in 2014). A standardized rt-PA treatment kit, including rt-PA, required documents, and vascular access route set, was kept in a fixed location in the ER to allow for immediate retrieval and use. Among 209 patients who received intravenous rt-PA at these 2 hospitals after code-stroke-system implementation, 162 (77.5%) were treated under the code stroke system; the remaining 47 patients were treated without code-stroke-system activation, despite implementation. Among patients admitted after May 2009, patients treated under a code stroke system had shorter DNT than other patients (median 54 [33-69] minutes versus 82 [68-103] minutes, $P < .001$). The median DNT shortened over the study period and the proportion of patients with DNT less than 60 minutes almost doubled (24.0% in 2005-2007 versus 45.3% in 2014-2015, $P < .001$ for trend). The proportion of patients who received endovascular therapy alongside thrombolysis increased from 8.0% in 2005-2007 to 26.3% in 2014-2015 ($P < .001$ for trend).

Temporal Trends in DNT and Factors Associated With DNT

Temporal trends in the DNT are shown in Figure 2. DNT shortened more markedly among patients treated under a code stroke system than among other patients. Multivariate regression analysis with correction for multiple comparisons (Table 2) revealed that activation of a code stroke system (standardized partial regression coefficient (β) −.50, $P < .001$), the ODT (β −.15, $P < .001$), pretreatment with antithrombotic agents (β .12, $P < .001$), and the year of treatment (β .11, $P = .007$) were associated with the DNT. Patients who underwent CT only (CT-based thrombolysis, β −.27, $P < .001$) or MRI only (MRI-based thrombolysis, β −.13, $P < .001$) had shorter DNTs, compared with those who underwent both CT and MRI. Similar results were observed when antithrombotic agents were divided into antiplatelet and anticoagulant medications (unstandardized partial regression coefficient (B) 2.65, standard error 1.09, β .08, t = 2.43, $P = .015$; and B 3.55, standard error 1.33, β .08, t = 2.66, $P = .008$, respectively).

Discussion

This study clarified temporal trends over the past decade regarding clinical characteristics of patients who received intravenous rt-PA in Japanese emergency hospitals with a stroke unit. The rate of intravenous rt-PA use

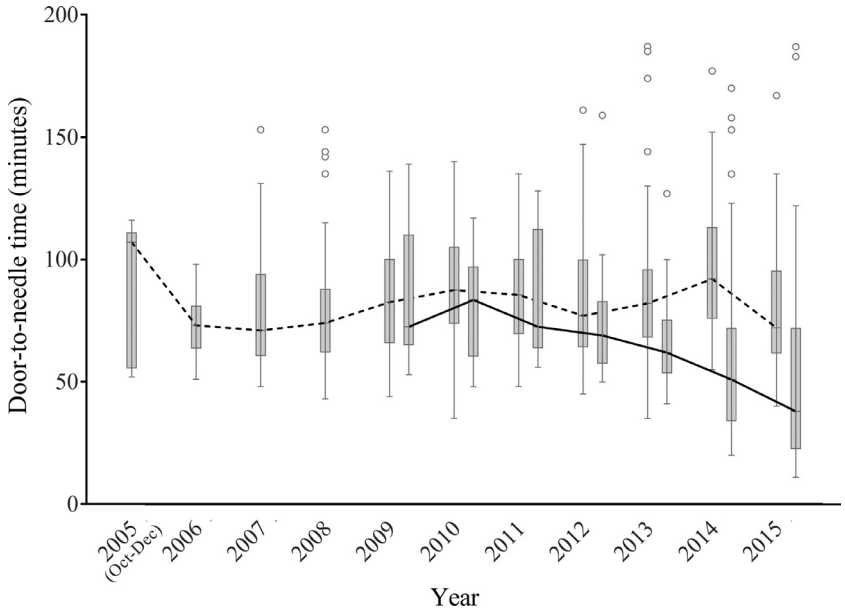

Figure 2. *Temporal trends in door-to-needle times among patients treated with versus without code-stroke-system activation. Lines connect median values. The solid line represents patients treated under a code stroke system; the dotted line represents those treated without code-stroke-system activation.*

Table 2. *Multiple regression analysis of door-to-needle time*

	Unstandardized		Standardized			
	B	SE	β	*t* value	*P* value	*q* value
No code stroke system (reference)						
Code stroke system implemented but not activated	−2.75	2.42	−.05	−1.13	.257	.257
Activation of code stroke system	−17.66	1.77	−.50	−9.99	<.001	<.001
CT and MRI before thrombolysis (reference)						
CT-based thrombolysis	−11.19	1.39	−.27	−8.04	<.001	<.001
MRI-based thrombolysis	−5.99	1.75	−.13	−3.43	<.001	.001
ODT, 1 min increase	−.11	.02	−.15	−4.58	<.001	<.001
Pretreatment with antithrombotics	3.70	.99	.12	3.75	<.001	.001
Arriving in night hours	1.91	.96	.06	2.00	.046	.062
Sex, male	−1.90	.98	−.06	−1.56	.053	.064
Year of treatment, 1 year past from 2005	1.18	.44	.11	−2.72	.007	.011
Adjusted R^2	.331					

Abbreviations: ODT, onset-to-door time; SE, standard error.
The model was adjusted for the facility variable.

for acute ischemic stroke continued to increase during the 10 years after its approval in October 2005. In the United States, rt-PA was approved in 1996. However, the use of rt-PA began to increase only in the early 2000s at high-volume academic hospitals and in 2006 at community hospitals.[4,7] By contrast, in Sweden the frequency of patients receiving intravenous rt-PA rapidly increased after its approval in 2003.[3] A similar rapid increase was observed in the present study. International evidence of the benefits of rt-PA reported during the period before drug approval in Japan might explain the rapid increase in rt-PA use after its approval in 2005.

This study showed a temporal trend of increased rt-PA use for older patients and those with mild stroke. These findings corroborate those of a previous report from hospitals using the Get With the Guidelines-Stroke program from 2003 to 2011.[5] Moreover, in the October 2012 revision of the Japan Stroke Society's guidelines for the intravenous application of rt-PA,[11] the target population criteria were expanded; several exclusion criteria were removed (eg, ischemic stroke within 3 months, mild stroke deficits, and rapidly improving stroke symptoms) and the upper age limit for intravenous rt-PA administration in selected patients was revised from 75 to 81 years. These revisions of the guidelines might have led to increased administration of rt-PA in elderly patients and patients with mild stroke. Additionally, this study showed an increase in rt-PA use in patients with prestroke disability. Prestroke disability is more common among stroke patients aged more than 75 years[22] and has been associated with the decision not to offer rt-PA.[23] However, rt-PA is beneficial even in patients with severe prestroke disability.[24] Given the aging of the population, vascular neurologists and neurosurgeons will more frequently need to assess the indications for rt-PA in acute stroke patients with prestroke disability.

The median DNT gradually decreased over the study period. Despite the decreasing trend in DNT, later year of treatment was associated with longer DNT in multivariate analysis. There are 2 possible reasons for this finding. First, intravenous rt-PA within 4.5 hours of onset was approved in August 2012; guidelines were revised in October 2012[11] to allow even patients with long DNT to receive rt-PA. Second, some patient characteristics changed over time but were not selected in stepwise selection. Previous reports showed that DNT was longer among older patients and those with lower NIHSS score.[12,15,25] The proportion of patients with these characteristics increased during the study period. Our results support those of a previous report that found that DNT did not decrease much without specific interventions.[26]

Activation of a code stroke system had the most significant impact on shortening the DNT, a finding in accordance with previous reports showing that an EMS- and hospital-based performance-improvement initiative including a code stroke system was effective for shortening the DNT.[16-18,27-29] In the present study, the code stroke system was activated for 77.5% of patients receiving rt-PA in the hospitals where it was implemented. This rate was comparable with that in the previous study from Iglesias Mohedano et al,[29] in which a prehospital code stroke was activated for 88.3% of patients receiving rt-PA. In the present retrospective study, some hospitals had independently implemented code stroke systems while others had not. This study allowed investigation of the effect of implementation and activation of a code stroke system on DNT by comparing hospitals with and without implementation of a code stroke system during the same period.

Pretreatment with antithrombotic agents, both antiplatelet and anticoagulant medications, was associated with longer DNTs, as shown in a previous study.[15]

The most recent guidelines from the American Heart Association recommend intravenous rt-PA for patients taking antiplatelet agents or warfarin who have an international normalized ratio less than or equal to 1.7[10]; Japanese guidelines recommend that rt-PA should be carefully administered in selected patients taking those medications.[11] Because uncertainty about anticoagulation status delays DNT,[14] screening for medical contraindications for rt-PA, measuring prothrombin time in suitable patients, and obtaining informed consent for the increased risk of hemorrhage might prolong the DNT in patients receiving antithrombotic agents.

The age and sex distributions, preadministration imaging modality, and stroke severity of patients in this study were similar to those of the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement rt-PA registry.[30] Although the sample size was small, the population of this study reflects at least in part those in current clinical practice in Japanese emergency hospitals. Some of the factors revealed in this study are modifiable and argue for the introduction of medical resources for the timely administration of rt-PA. One recent study reported that EMS with prehospital notification resulted in shorter DNT and ODT. A shorter onset-to-treatment time was associated with better neurological outcomes.[31] Although the 3-month mRS was not investigated in the present study, the shortening trend in DNT, especially that derived from a code stroke system, may have contributed to improved stroke outcomes.

Our study has several limitations. First, the study has a retrospective design with a small number of patients from limited facilities, which might have created selection bias. Second, because of the retrospective study design, not all factors that have been reported to be associated with the DNT were included (eg, fluctuating neurological deficits, incorrect triage, and other logistic factors). Third, we used ICD-10 diagnosis codes to determine the population with acute ischemic stroke, which was not validated. Moreover, details of patients' background characteristics, including changes in the proportion of patients over 85 years of age or with mild stroke in the overall population of acute ischemic stroke patients, remain unclear. Finally, associations between temporal trends in patients' clinical characteristics and the DNT and clinical outcomes were not investigated.

Conclusions

Since 2005, intravenous rt-PA has become widely adopted for the treatment of acute ischemic stroke in Japanese emergency hospitals with a stroke unit. The administration of rt-PA to older patients, those with prestroke disability, and those with mild stroke has increased. Alongside factors described previously, the year of treatment was associated with DNT, which has shortened over time.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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