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Original Article

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Improvement of Functional Outcomes in Patients with Stroke who Received Alteplase for Over 15 Years: Japan Stroke Data Bank

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Aim: The nationwide verification of intravenous thrombolysis (IVT) was rarely performed after the extension of the therapeutic time window of alteplase or after the expansion of mechanical thrombectomy (MT). We aimed to examine the long-term change in accurate real-world outcomes of IVT in patients with acute ischemic stroke (AIS) using the Japan Stroke Databank, a representative Japan-wide stroke database.

Methods: We extracted all patients with AIS who received IVT with alteplase between October 11, 2005, the approval date for alteplase use for AIS in Japan, and December 31, 2020. Patients were categorized into three groups using two critical dates in Japan as cutoffs: the official extension date of the therapeutic time window for IVT to within 4.5 h of symptom onset and the publication date of the revised guideline, where the evidence level of MT was heightened. We assessed the yearly trend of IVT implementation rates and the secular changes and three-group changes in clinical outcomes at discharge.

Results: Of 124,382 patients with AIS, 9,569 (7.7%) received IVT (females, 41%; median age, 75 years). The IVT implementation rate has generally increased over time and plateaued in recent years. The proportion of favorable outcomes (modified Rankin Scale score of 0–2) increased yearly over 15 years. The results of the changes in the outcomes of the three groups were similar to those of the annual changes.

Conclusions: We revealed that IVT implementation rates in patients with AIS increased, and the functional outcome in these patients improved over 15 years. Therefore, the Japanese IVT dissemination strategy is considered appropriate and effective.

Key words: Acute ischemic stroke, Intravenous thrombolysis, Secular change, Therapeutic time window, Endovascular therapy

Abbreviations: IVT, intravenous thrombolysis; AIS, acute ischemic stroke; J-ACT, Japan Alteplase Clinical Trial; TTW, therapeutic time-window; MT, mechanical thrombectomy; JSDB, Japan Stroke Databank; EVT, endovascular therapy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale

Introduction

In Japan, intravenous thrombolysis (IVT) with a tissue plasminogen activator (rt-PA) for patients with acute ischemic stroke (AIS) within 3 h of symptom onset was approved on the basis of the results of a domestic one-arm trial, the Japan Alteplase Clinical Trial (J-ACT)[1], in 2005. Following the results of the European Cooperative Acute Stroke Study (ECASS) III trial[2] and the meta-analysis of individual patient data from seven randomized trials[3], the therapeutic time window (TTW) for IVT with alteplase was extended from within 3–4.5 h of symptom onset, and alteplase within 4.5 h of AIS onset was covered by

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insurance in Japan in August 2012. Furthermore, the first device for mechanical thrombectomy (MT) for patients with AIS was approved in 2010 in Japan, and the efficacy of MT with stent retrievers was clarified in February 2015. In response to the introduction or change of notable technologies, the Japan Stroke Society published or revised domestic guidelines for the proper use of these techniques[4-8].

After the regulatory approval of alteplase, evidence of the effectiveness and safety of IVT within 3 h of symptom onset was accumulated by J-ACTII[9], the Japan post-Marketing Alteplase Registration Study (J-MARS)[10], and the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry[11]. However, nationwide verification of IVT was rarely performed after the extension of the TTW of alteplase or after the expansion of MT because there is no public registry of patients with stroke in Japan.

Aim

This study aimed to examine the long-term changes in accurate real-world outcomes of IVT in patients with AIS using the Japan Stroke Databank (JSDB)[12-14], a representative nationwide stroke database in Japan. The annual number of stroke cases was estimated to be approximately 290,000 in Japan[15]; however, >10,000 cases are registered in JSDB annually, and the number of registrations has increased in recent years, with approximately 20,000 cases enrolled in 2020.

Methods

Study Design and Participants

JSDB is an ongoing hospital-based multicenter stroke registration database of hospitalized patients with acute stroke and transient ischemic attack in Japan that was initiated in 1999 and supported by a research grant from the Ministry of Health and Welfare. JSDB aims to standardize the acute treatment of stroke and verify and establish evidence for treating Japanese patients with stroke. Over the past 20 years, approximately 230,000 cases have been reported from 123 academic or regional stroke centers across Japan. JSDB is an ongoing long-term registry, and the participating hospitals have changed a little over the years. In recent years, approximately 130 facilities have participated; of these, approximately 120 were primary stroke centers and approximately 60 were particularly primary stroke center core hospitals accredited by the Japan Stroke Society.

For the present analyses, we extracted all patients with AIS who received IVT with alteplase between October 11, 2005, the approval date for alteplase use for AIS in Japan, and December 31, 2020. The system and input items of JSDB were modified to ensure data consistency and promote efficiency in data acquisition in 2016; therefore, the data of the two systems were input into one dataset. Patients were categorized into three groups (Group A, patients registered between October 11, 2005, and August 30, 2012; Group B, between August 31, 2012, and April 30, 2015; and Group C, between May 1, 2015, and December 31, 2020) using two critical dates[5, 7] in Japan as cutoffs: the date for the official extension of TTW for IVT to within 4.5 h of symptom onset (August 31, 2012), and date for publication of the revised guideline, where the evidence level of MT was heightened.

Because of the anonymous nature of the data, the requirement for informed consent was waived, and we provided a means to opt out. Additionally, the protocol of JSDB was approved by the institutional review board or ethics committee at each participating site. This study was approved by the research ethics review board of the National Cerebral and Cardiovascular Center (approval number: M27-090).

Outcome Measures

Data on patients' demographic characteristics, AIS types, stroke history, premorbid antithrombotic drugs (prescription of antithrombotic drugs just before the onset of stroke, regardless of medication adherence), AIS severity, and performance of acute endovascular therapy (EVT) were collected from JSDB. EVT included thrombectomy, percutaneous transluminal angioplasty, stenting, and arterial injection of urokinase. The primary outcome measure was the proportion of patients with favorable functional outcomes at hospital discharge, defined by a modified Rankin Scale (mRS) score of 0–2, following the methods by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[16]. The secondary outcomes were (1) the proportion of patients with excellent functional outcomes, defined by an mRS score of 0–1; (2) the proportion of patients with unfavorable outcomes at

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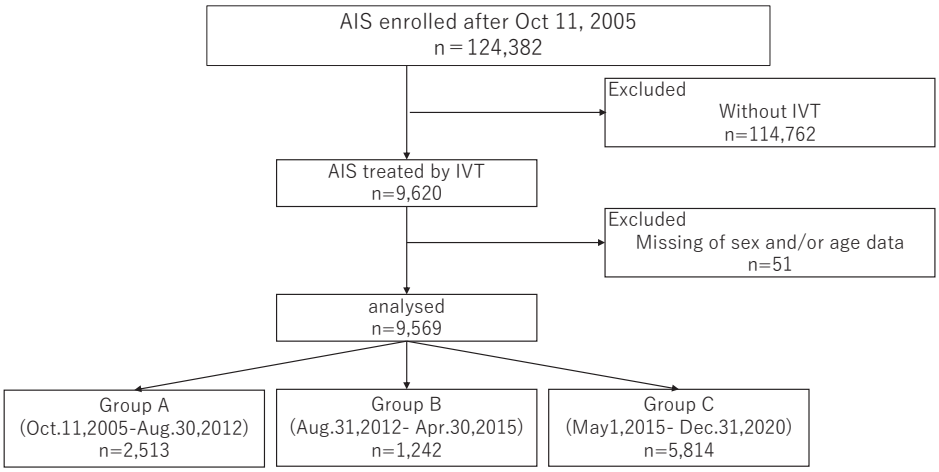

Fig. 1. Flowchart of the study

Group A: Patients who received intravenous thrombolysis (IVT) before the extension of the therapeutic time window of IVT.
Group B: Patients who received IVT after the extension of the therapeutic time window of IVT.
Group C: Patients who received IVT after the establishment of clinical evidence of mechanical thrombectomy for acute ischemic stroke.

hospital discharge, defined by an mRS score of 5–6; and (3) mortality in the hospital.

Statistical Analysis

Continuous variables were presented as mean (standard deviation) or median (interquartile range), whereas categorical variables were presented as numbers (%). Analysis of variance, the Kruskal–Wallis test, and the chi-squared test were used to determine the significance of differences among the three groups for continuous and categorical variables, as appropriate. Mixed-effects univariate and multivariate logistic regression models using institutions as random intercepts were conducted and adjusted for sex, age, baseline National Institutes of Health Stroke Scale (NIHSS) score, atrial fibrillation, premorbid independency corresponding to an mRS score of 0–1, premorbid anticoagulation, stroke history, and EVT to test the secular changes in outcomes at discharge. Patients with a pre-stroke mRS score of ≥ 2 were excluded from the analysis when analyzing for an mRS score of 0–1, and patients with a pre-stroke mRS score of ≥ 3 were excluded when analyzing for an mRS score of 0–2.

Statistical significance was set at $P<0.05$. Statistical analyses were performed using STATA ver16.1 (Stata Corp, College Station, TX, USA).

Results

Of the 124,382 patients with AIS registered in JSDB between October 11, 2005, and December 31, 2020, 114,762 who did not receive IVT and 51 with unavailable data on sex or age were excluded from the study. The remaining 9,569 patients (females, 41%, median age, 75 years) were eligible for this study **(Fig. 1)**.

Fig. 2 shows the yearly trend in IVT implementation rates between October 11, 2005, and December 31, 2020. The IVT implementation rate has generally increased over time and plateaued in the last few years.

The baseline characteristics and index stroke features were compared among the groups and are summarized in **Table 1**. There were statistically significant differences in age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, anticoagulant use at admission, the distribution of AIS type, pre-stroke mRS score of 0–1, baseline NIHSS at admission, and EVT among the groups.

Fig. 3 presents the distribution of mRS as a clinical outcome at discharge. Overall, 42.8% of patients had an mRS score of 0–2, 21% had an mRS score of 5–6, and 6% died. Patients treated with IVT alone had lower mRS scores than those treated with EVT ($P<0.001$). Moreover, mRS scores decreased as time passed among Groups A–C ($P<0.001$).

Table 2 presents the secular changes in the clinical outcomes at discharge. The proportion of favorable outcomes (mRS score of 0–2) increased yearly over 15 years, even after adjusting for sex, age, baseline NIHSS score, atrial fibrillation, premorbid anticoagulant, history of stroke, and EVT. The proportion of patients with excellent functional outcome (mRS score of 0–1) increased yearly without any adjustment overall, but not after adjustment; it

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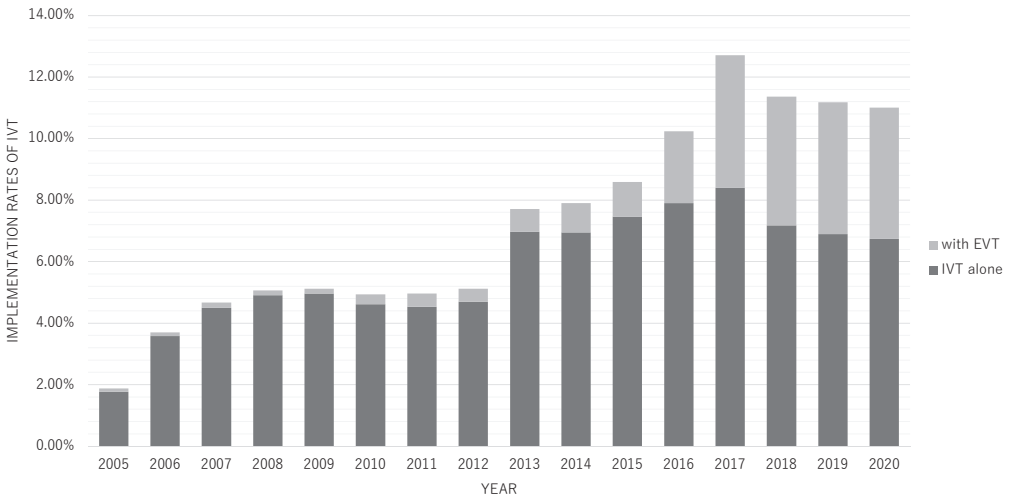

Fig. 2. Implementation rates of intravenous thrombolysis (IVT) only and IVT with endovascular therapy for acute ischemic stroke

In 2012, the implementation rates were 4.72% and 5.99% before and after the expansion of indications for alteplase, respectively. In 2015, the rates were 8.47% and 8.65% before and after the establishment of the evidence of mechanical thrombectomy, respectively.

Table 1. Patient's demographic and clinical characteristics

	Total (n=9,569)	Group A (n=2,513)	Group B (n=1,242)	Group C (n=5,814)	P value
Age, year	74.8 ± 12.3	72.6 ± 11.8	74.9 ± 12.2	75.7 ± 12.4	<0.001
Female sex	3,919 (41.0)	943 (37.5)	524 (42.2)	2,452 (42.2)	<0.001
History of stroke	1,715 (17.9)	446 (17.7)	177 (14.3)	1,092 (18.8)	0.14
Hypertension	6,209 (64.9)	1,588 (63.2)	822 (66.2)	3,799 (65.3)	<0.001
Diabetes Mellitus	1,961 (20.5)	492 (19.6)	256 (20.6)	1213 (20.9)	0.027
Hyperlipidemia	2,851 (29.8)	635 (25.3)	330 (26.6)	1,886 (32.4)	<0.001
Atrial fibrillation	3,477 (36.3)	1,257 (50.0)	472 (38.0)	1,748 (30.1)	<0.001
Smoking	2,289 (23.9)	715 (28.5)	282 (22.7)	1,292 (22.2)	0.50
Premorbid antithrombotic drugs					
Warfarin	373 (3.9)	16 (0.6)	72 (5.8)	285 (4.9)	<0.001
Direct oral anticoagulant	331 (3.5)	0 (0)	0 (0)	331 (5.7)	<0.001
Antiplatelet Agent	3,269 (34.2)	899 (35.8)	404 (32.5)	1,966 (33.8)	0.096
Acute ischemic stroke type					<0.001
Atherothrombotic brain infarction	1,983 (20.7)	538 (21.4)	239 (19.2)	1,206 (20.7)	
Cardioembolic stroke	5,560 (58.1)	1,651 (65.7)	776 (62.5)	3,133 (53.9)	
Lacunar infarction	641 (6.7)	133 (5.3)	76 (6.1)	432 (7.4)	
Others	1,365 (14.3)	190 (7.6)	148 (11.9)	1027 (17.7)	
Pre-stroke mRS 0-1	7,714 (80.6)	2,248 (89.5)	1,023 (82.4)	4,443 (76.4)	<0.001
Baseline NIHSS	12 [6, 20]	14 [8, 20]	12 [6, 20]	11 [5, 20]	<0.001
EVT for AIS	2,226 (23.3)	130 (5.2)	136 (11.0)	1960 (33.7)	<0.001

N (%), mean ± SD, or median [interquartile ratio].
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; EVT, endovascular therapy; AIS, acute ischemic stroke
Group A: Patients who received intravenous thrombolysis (IVT) before the extension of the therapeutic time window of IVT (patients registered between October 11, 2005, and August 30, 2012).
Group B: Patients who received IVT after the extension of the therapeutic time window of IVT (patients registered between August 31, 2012, and April 30, 2015).
Group C: Patients who received IVT after the establishment of clinical evidence of mechanical thrombectomy for AIS (patients registered between May 1, 2015, and December 31, 2020).

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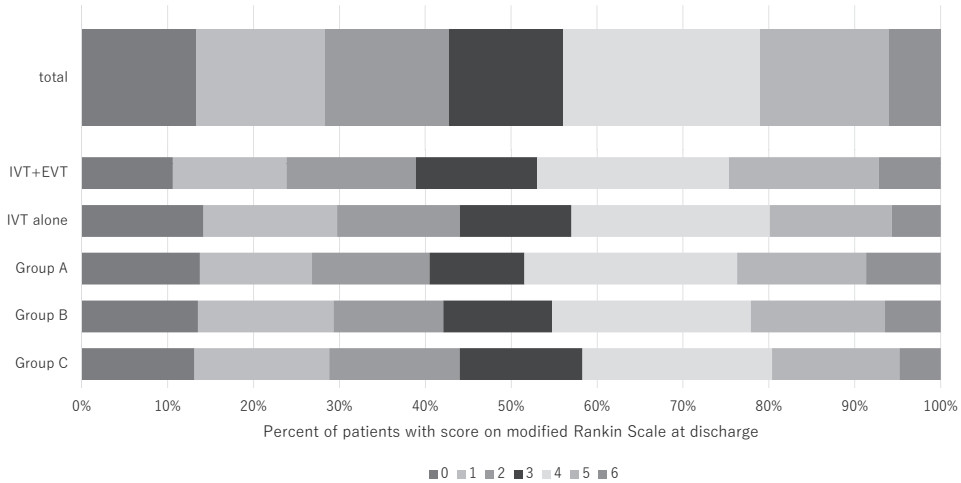

Fig. 3. Distribution of modified Rankin Scale at discharge

Group A: Patients who received intravenous thrombolysis (IVT) before the extension of the therapeutic time window of IVT (patients registered between October 11, 2005, and August 30, 2012).
Group B: Patients who received IVT after the extension of the therapeutic time window of IVT (patients registered between August 31, 2012, and April 30, 2015).
Group C: Patients who received IVT after the establishment of clinical evidence of mechanical thrombectomy for acute ischemic stroke (patients registered between May 1, 2015, and December 31, 2020).

Table 2. Secular changes in outcome at discharge

	Total		Patients with IVT + EVT		Patients with IVT alone	
	cOR (95% CI)	aOR (95% CI)*	cOR (95% CI)	aOR (95% CI)*	cOR (95% CI)	aOR (95% CI)*
mRS 0-1**	1.03 (1.02, 1.05)	1.01 (0.99, 1.03)	1.07 (1.02, 1.12)	1.11 (1.04, 1.18)	1.04 (1.03, 1.06)	0.99 (0.97, 1.01)
mRS 0-2***	1.03 (1.02, 1.05)	1.02 (1.01, 1.04)	1.05 (1.01, 1.10)	1.10 (1.04, 1.16)	1.04 (1.03, 1.06)	1.01 (0.99, 1.03)
mRS 5-6	0.98 (0.97, 0.99)	0.96 (0.94, 0.98)	0.94 (0.90, 0.97)	0.88 (0.84, 0.92)	0.97 (0.96, 0.99)	0.98 (0.95, 1.00)
In-hospital death	0.94 (0.92, 0.96)	0.90 (0.88, 0.93)	0.89 (0.84, 0.95)	0.86 (0.80, 0.91)	0.93 (0.91, 0.96)	0.92 (0.89, 0.95)

IVT, intravenous thrombolysis; EVT, endovascular therapy; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence intervals; mRS, modified Rankin Scale
*models adjusted for sex, age, baseline NIHSS, atrial fibrillation, premorbid independency, premorbid anticoagulation, stroke history, and EVT.
**Patients with a pre-stroke mRS score ≥ 2 were excluded.
***Patients with a pre-stroke mRS score ≥ 3 were excluded.

increased by multivariable adjustment when the patients receiving both IVT and EVT were analyzed. Conversely, the proportion of unfavorable outcomes (mRS score of 5–6) and in-hospital mortality decreased over time, even after adjustments were made. As shown in **Table 3**, changes in the outcomes of the three groups were also confirmed, and the results were similar to those of the annual changes. Additionally, the results were similar when patients who received IVT with EVT were analyzed separately.

In contrast, there was no significant difference in the proportion of favorable outcomes and the proportion of mRS scores of 5–6 after multivariate adjustments in patients who received IVT only. However, the proportions of mortality in the hospital decreased, even after adjusting for regulators.

Supplementary Table 1 presents the changes in outcome at discharge among three groups by comparing Groups B and C with Group A. There was no significant difference in the analysis for an mRS score of 0–1 when Group B or C was compared with Group A as the reference. In the analysis for mRS scores of 0–2 and 5–6 and in-hospital death, significant differences were observed in Group C compared with Group A as the reference. It was clear that the longer the time after the introduction of IVT, the greater the influence on outcomes.

Discussion

Two notable findings were observed in this study. First, the IVT implementation rate increased until

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Table 3. Changes in outcome at discharge among the three groups

	Total				
	Group A	Group B	Group C	cOR (95%CI)	aOR* (95%CI)
mRS 0-1**	640 (30.1%)	337 (36.1%)	1641 (37.1%)	1.17 (1.09, 1.24)	1.07 (0.97, 1.18)
mRS 0-2***	957 (42.8%)	481 (48.0%)	2520 (51.7%)	1.18 (1.12, 1.26)	1.14 (1.04, 1.24)
mRS 5-6	587 (23.4%)	273 (22.0%)	1139 (19.6%)	0.91 (0.85, 0.97)	0.82 (0.74, 0.91)
In-hospital death	215 (8.6%)	80 (6.4%)	279 (4.8%)	0.74 (0.67, 0.83)	0.63 (0.54, 0.73)
	Patients with IVT + EVT				
	Group A	Group B	Group C	cOR (95%CI)	aOR* (95%CI)
mRS 0-1**	22 (19.1%)	38 (33.0%)	464 (29.9%)	1.31 (1.04, 1.65)	1.69 (1.21, 2.34)
mRS 0-2***	37 (30.6%)	59 (48.0%)	761 (44.8%)	1.29 (1.06, 1.57)	1.61 (1.23, 2.10)
mRS 5-6	47 (36.2%)	40 (29.4%)	461 (23.5%)	0.75 (0.62, 0.91)	0.52 (0.41, 0.67)
In-hospital death	21 (16.2%)	12 (8.8%)	127 (6.5%)	0.59 (0.45, 0.78)	0.47 (0.34, 0.65)
	Patients with IVT alone				
	Group A	Group B	Group C	cOR (95%CI)	aOR* (95%CI)
mRS 0-1**	618 (30.8%)	299 (36.6%)	1177 (41.0%)	1.22 (1.13, 1.31)	0.99 (0.89, 1.10)
mRS 0-2***	920 (43.5%)	422 (48.0%)	1759 (55.4%)	1.24 (1.16, 1.32)	1.06 (0.96, 1.17)
mRS 5-6	540 (22.7%)	233 (21.1%)	678 (17.6%)	0.88 (0.82, 0.95)	0.90 (0.80, 1.01)
In-hospital death	194 (8.1%)	68 (6.1%)	152 (3.9%)	0.71 (0.62, 0.80)	0.69 (0.58, 0.81)

IVT, intravenous thrombolysis; EVT, endovascular therapy; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence intervals; mRS, modified Rankin Scale

*models adjusted for sex, age, baseline NIHSS, atrial fibrillation, premorbid independency, premorbid anticoagulation, stroke history, and EVT.

**Patients with a pre-stroke mRS score ≥ 2 were excluded.

***Patients with pre-stroke mRS score ≥ 3 were excluded.

Group A: Patients who received IVT before the extension of the therapeutic time window of IVT (patients registered between October 11, 2005, and August 30, 2012).

Group B: Patients who received IVT after the extension of the therapeutic time window of IVT (patients registered between August 31, 2012, and April 30, 2015).

Group C: Patients who received IVT after the establishment of clinical evidence of mechanical thrombectomy for acute ischemic stroke (patients registered between May 1, 2015, and December 31, 2020).

2017 but plateaued at approximately 11% in recent years. Second, the proportion of favorable outcomes at discharge increased, whereas the proportion of unfavorable outcomes and in-hospital deaths decreased over time.

There are several possible reasons for this increase in the IVT implementation rate. For the first time, the TTW for IVT with alteplase was extended from within 3–4.5 h of symptom onset in 2012, and the number of eligible patients for alteplase increased. Additionally, at the time of approval of this treatment in 2005, the Ministry of Health, Labor, and Welfare of Japan attached some conditions, such as preparing proper treatment guidelines and implementing proper use training. The Japan Stroke Society published domestic guidelines[4] and organized training sessions for the proper use of alteplase for all physicians who had the opportunity to provide IVT to patients with stroke; these conditions were maintained even after the TTW of IVT was extended in 2012 [5]. These guidelines and training sessions have enabled stroke centers to provide IVT appropriately to eligible patients who had been properly transported to the hospital within the TTW. Another reason might be that efforts to raise awareness about stroke symptoms and what to do at stroke onset have made patients visit the hospital earlier[17]. Furthermore, the possible reasons for the plateaued implementation rate after 2017 are IVT was no longer the only treatment for the acute phase of stroke and EVT instead of IVT was provided more frequently to patients expected to be at high risk of hemorrhage. In a study on IVT implementation rates in 44 European countries in 2015 and 2016, 7.3% of patients with incident ischemic stroke received IVT overall, and the highest practice rate was 20.6%[18]. The rates in our study were not extremely low; however, there was room for improvement. On the basis of the results of the

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Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial[19], the Japanese guideline[6] recommended IVT to be considered if the time of onset was estimated to be within 4.5 h based on advanced magnetic resonance imaging findings, even if it was unknown. Additionally, a meta-analysis of the WAKE-UP[19], THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0.6 mg/kg trial (THAWS)[20], Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND)[21], and ECASS-4 [22] trials revealed that IVT was eligible even in patients with AIS with an unknown time of onset when properly extracted; therefore, the proportion of IVT might increase further in the future[23].

The proportion of patients with favorable outcomes at discharge also increased over time. Because this result was not observed in the group that received IVT only, the increase in favorable outcomes was considered partially due to the combination of IVT and EVT. However, because a positive result was also observed in all patients after adjustment for EVT, other factors might play a role. For example, it has become possible to treat patients more appropriately because of the accumulation of physicians' treatment experiences over time. Another reason might be that the treatment environment had improved, such as the emergency transportation support system and the establishment of the Stroke Care Unit. Furthermore, the proportion of mRS scores of 5–6 and in-hospital death decreased over time because of reasons similar to those for the increase in favorable outcomes.

Notably, the median age of onset increased with time. This might be because the age range for administering IVT with caution in the Japanese guideline was increased from ≥ 75 to ≥ 81 years in 2012 [5]. Additionally, although the elderly living alone was reported to be the reason for the long onset-to-needle time[24], the extension of TTW might have made it possible for elderly patients living alone or in elderly households to visit the hospital within the TTW of IVT. Furthermore, because the national average life expectancy of the Japanese population has continued to increase, the average age at ischemic stroke onset has increased[13].

Another finding of this study was that the rate of patients with concomitant atrial fibrillation decreased with time. Because of the extension of the TTW, patients with AIS with more mild symptoms, whose AIS type was not a cardioembolic stroke, might be able to visit the hospital within the TTW. Moreover, European retrospective studies have observed a decline in atrial fibrillation-related stroke rates associated with high prescriptions of direct oral anticoagulants[25, 26]. Interestingly, pre-stroke warfarin use was rare (0.6%) in Group A. Because the initial IVT guidelines in Japan published in 2005 stated that patients with anticoagulant therapy should be treated very carefully even if PT-INR is not high, IVT would not be selected often for anticoagulated patients within several years after approval of IVT in Japan.

This study had some limitations. First, there were decent data defects because this was a retrospective analysis. For example, a large difference in the number of patients between those developing cardioembolic stroke and those with atrial fibrillation in this study might be due to the lack of input data on emboligenic heart diseases including atrial fibrillation. Second, because the reason why IVT could not be performed was not registered, it was impossible to determine the adequacy of the implementation rate and consider how to intervene to improve alteplase administration. Third, because high-volume stroke centers tended to join JSDB, the results of this study would not be generalizable to low-volume hospitals in Japan.

Conclusions

In conclusion, we verified real-world data on IVT in Japan in this study. IVT implementation rates in patients with AIS have increased over 15 years, and the functional outcome in these patients has improved. Therefore, the Japanese IVT dissemination strategy was considered effective; however, further study is needed to consider the ideal state of IVT after the evidence of MT was established.

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Conflict of Interest

The following conflicts exist outside the submitted work: Dr. Toyoda reports personal fees from Daiichi-Sankyo, Bayer Yakuhin, Bristol-Myers Squibb, Otsuka, and Novartis. Dr. Nakahara received honoraria from Alexion, Takeda, Mitsubishi-Tanabe, Chugai, Novartis, Biogen, research funding from Biogen, and scholarship grants from Daiichi-Sankyo, Eisai, Otsuka, Shionogi, Sumitomo, Mitsubishi-Tanabe and Chugai. Dr. Suzuki received honoraria

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Supplementary Table 1. Changes in outcome at discharge among three groups by comparing Group B and Group C in reference to Group A

		Total		Patients with IVT+EVT		Patients with IVT alone	
		Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR (95%CI)
mRS0-1*	Group A	reference	reference	reference	reference	reference	reference
	Group B	1.23 (1.04, 1.47)	0.96 (0.74, 1.25)	2.03 (1.09, 3.79)	2.01 (0.79, 5.10)	1.22 (1.01, 1.46)	0.90 (0.67, 1.19)
	Group C	1.37 (1.20, 1.56)	1.14 (0.94 , 1.38)	1.99 (1.19, 3.31)	2.99 (1.47, 6.11)	1.48 (1.29, 1.71)	0.98 (0.80, 1.20)
mRS0-2**	Group A	reference	reference	reference	reference	reference	reference
	Group B	1.14 (0.98, 1.34)	0.97 (0.76, 1.23)	2.03 (1.19, 3.47)	2.87 (1.33, 6.18)	1.12 (0.95, 1.33)	0.85 (0.66, 1.11)
	Group C	1.40 (1.24, 1.57)	1.28 (1.08, 1.53)	1.92 (1.25, 2.94)	3.04 (1.69, 5.45)	1.53 (1.34, 1.75)	1.12 (0.93, 1.35)
mRS5-6	Group A	reference	reference	reference	reference	reference	reference
	Group B	1.01 (0.85, 1.20)	0.98 (0.75, 1.27)	0.79 (0.46, 1.33)	0.59 (0.30, 1.19)	0.98 (0.81, 1.18)	1.00 (0.74, 1.34)
	Group C	0.84 (0.74, 0.96)	0.68 (0.55, 0.84)	0.57 (0.38, 0.86)	0.28 (0.17, 0.48)	0.78 (0.67, 0.91)	0.81 (0.64, 1.02)
In-hospital death	Group A	reference	reference	reference	reference	reference	reference
	Group B	0.83 (0.63, 1.10)	0.72 (0.49, 1.06)	0.54 (0.25, 1.16)	0.63 (0.26, 1.53)	0.81 (0.59, 1.09)	0.68 (0.44, 1.04)
	Group C	0.56 (0.45, 0.69)	0.39 (0.29, 0.54)	0.34 (0.19, 0.60)	0.23 (0.12, 0.46)	0.50 (0.39, 0.64)	0.47 (0.33, 0.66)

IVT, intravenous thrombolysis; EVT, endovascular therapy; mRS, modified Rankin Scale; OR, odds ratio
*Patients with a pre-stroke mRS score ≥ 2 were excluded.
**Patients with a pre-stroke mRS score ≥ 3 were excluded.

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