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Phased changes in strategies can reduce delay of intravenous thrombolysis administration to 15 min

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ABSTRACT

Objectives: The present study aimed to determine whether phased changes in strategies including the Helsinki model affect the delay of intravenous thrombolysis (IVT) using tissue plasminogen activator (tPA) to treat acute ischemic stroke.

Method: We retrospectively studied 516 consecutive patients treated with IVT in our department between October 2005 and December 2018. We implemented a system of hospital pre-notification in 2005, when IVT was initially implemented at our center. We then improved the IVT strategy by simplifying brain imaging (July 2011), premixing tPA (April 2014), locating a blood cell counter in the emergency room (June 2015), manually administering a tPA bolus before preparing a continuous infusion (January 2016), awarding a prize to members of the acute stroke team (November 2016), and completing registration before arrival and sending patients directly to computed tomography (February 2017). We analyzed the effects of these strategic changes on annual median door-to-needle times (DTN).

Results: The DTN was annually reduced, from a median of 90 [interquartile range, 55–98] minutes in 2006 to 15 [12–24.25] minutes in 2017. By 2017, 94% of patients were treated within 60 min of arrival. Multivariate logistic regression analysis revealed that initial NIHSS score ≤ 4 (OR 2.67, 95% CI 1.3–5.7) and anticoagulation before onset (OR 6.00, 95% CI 2.47–14.58) were independently associated with 20 min or more of DTN in 186 patients treated from 2016 to 2018.

Conclusions: Phased strategic change to reduce the delay in delivering IVT reduced median DTN to 15 min at a single Japanese stroke center.

1. Introduction

The effects of intravenous thrombolysis (IVT) using tissue plasminogen activator (tPA) on acute ischemic stroke are time-dependent. Earlier treatment is associated with more benefits [1]. The median door-to-needle time (DTN) has been shortened to 20 min by twelve separate interventions at Helsinki University (Helsinki thrombolysis model) [2]. Although the validity of this model for other countries with different health care systems should be verified, the key components of this model have been implemented at an Australian stroke center to reduce the delay in DTN [3]. The ability of interventions to reduce time metrics in acute stroke therapy would vary among institutions, countries, and regions with different health-care infrastructures and medical systems. A literature search produced no publications on reducing the delay in delivering IVT by applying the Helsinki model at a Japanese stroke center. The present study aimed to determine the effects of phased strategic changes on IVT including the Helsinki model to reduce DTN at a single Japanese stroke center.

2. Methods

2.1. Study population

We retrospectively studied 516 consecutive patients treated using IVT at the Department of Stroke Neurology at Kohnan Hospital (Sendai, Miyagi, Japan) from October 2005 through December 2018. Kohnan Hospital is a stroke center that specializes in neurocritical care and covers the southern half of the Sendai metropolitan area (total population, 600,000). Approximately 500 patients are annually admitted with acute ischemic stroke. In Japan, IVT was approved in October

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2005 to treat acute ischemic stroke and the therapeutic time window of IVT was extended from 3 to 4.5 h in September 2012. Clinical and investigative data that were prospectively collected in a standardized fashion and entered into the Kohnan Hospital Stroke Registry included age, sex, time of onset, neurological status, door time, vital status, brain imaging, needle time, and oral anticoagulation before stroke onset. Neurological deficits were evaluated using scores on the National Institutes of Health stroke scale (NIHSS) upon admission [4]. Time of onset was defined as the last known time and date when the patient appeared well and free of index stroke symptoms. Door time was defined as the time when the patient arrived at the emergency room (ER). Needle time was defined as the time when the patient received a bolus injection of tPA. Because we did not use electronic chart system, we obtained all the timepoints manually. Symptomatic intracranial hemorrhage (sICH) was defined as a new intracranial hemorrhage within 36 h after IVT concurrent with neurological deterioration (increment in NIHSS score ≥ 4). Stroke mimic was defined as clinical symptoms or neurologic deficits attributed to a non-cerebrovascular etiology diagnosed by at least two board-certified neurologists who were specialized in the care of stroke patients. The Kohnan Hospital Ethics Committee approved the study protocol. Due to the retrospective nature of the study, the need for written informed consent was waived.

2.2. Setting for acute stroke treatment

The stroke team comprised board-certified neurologists who specialized in the care of stroke patients, a laboratory analyst, general neurologists or neurosurgeons, neuro-critical care nurses, and a radiology technician available 24/7. All patients who presented at the ER were initially examined by neurologists, neurosurgeons, or both. Moreover, patients with symptoms of acute stroke were immediately evaluated by computed tomography (CT) and magnetic resonance imaging (MRI) that are both available 24/7/365 at our institute. The CT equipment is located on the same floor close to the ER, but the MRI equipment is on another floor. We obtained the written informed consent for IVT from all included participants. In some case such as comatose patients not accompanied by family, however, we obtained oral informed consent from families or relatives by telephone followed by written informed consent after administration of tPA.

2.3. Change of strategies

Immediate CT interpretation, alarm signaling an incoming candidate, rapid neurological evaluation, and pre-notification were already started when IVT was implemented at our center in October 2005. The emergency medical service (EMS) pre-notified on-site hospital physicians in the ER about patients who were potentially eligible for IVT. Thereafter, the notified on-site stroke neurologist, or if unavailable, an on-site physician, activated other members of the stroke team including on-call stroke neurologists and the CT suite was emptied before patient arrival at the time of pre-notification (phase 1).

We increased efforts to reduce DTN in thrombolysis from July 2011 and improved the strategies step by step according to the Helsinki model after the publication at 2012.

We simplified the brain imaging protocol from both CT and MRI before IVT, to CT before IVT and MRI during continuous IVT (from July 2011, phase 2).

We mixed tPA before receiving platelet counts except when patients had a history of hematological disorders or liver cirrhosis (from April 2014, phase 3). Before April 2014, we prepared and mixed tPA after laboratory data including blood cell counts were available.

We placed a blood cell counter in the ER for rapid platelet counts by physicians or nurses before receiving the core laboratory results from technicians (from June 2015, phase 4). Our 10-year experience with IVT revealed that the platelet count was the rate-determining step of IVT at our institute. Both platelet counts and blood glucose must be measured before treatment according to the Japanese guidelines, while only patients with coagulopathy or who were on anticoagulation before stroke onset require prothrombin time-international normalized ratio (PT-INR) and activated partial thromboplastin time (APTT) [5]. Blood glucose was measured immediately on arrival by finger stick.

We manually administer a tPA bolus before preparing continuous tPA infusions (from January 2016, phase 5). An infusion or syringe pump system is widely applied in Japan according to the recommendations of the Japanese Guidelines for IVT [5], we had conducted bolus injection by rapid infusion with syringe pump after preparation of continuous infusion of t-PA until 2016. We have changed to administer manually a bolus infusion of tPA in the CT suite, the ER, or anywhere else before preparing continuous tPA infusions with a pump.

We began awarding prizes to members of the acute stroke team (from November 2016, phase 6). When time parameters were particularly tight, such as a DTN of 10 min, members participated in treatment of the patient would confirm time parameters and were awarded a prize for rapid treatment.

EMS provide registration information during patient transportation for rapid registration, and directly transfer IVT candidates to the CT suite (from February 2017, phase 7).

Regional electronic patient records such as those implemented in the Helsinki protocol are not available in Japan; thus acquiring patient histories depended on information derived from only eyewitnesses or families.

The CT suite was not relocated to the ER because it takes only one minute to transport a patient there from the ER. We also did not implement point-of-care (POC) international normalized ratio (INR) which was implemented in the Helsinki protocol [2,6].

2.4. Analysis

We analyzed the effects of these strategic changes on the rate of patients without MRI before IVT, annual median DTN and onset-to-needle time (OTN), and clinical safety during hospital stay. We selected 20 min as the cut off value as the goal for reduction of DTN from Helsinki's results [2]. Clinical or logistic factors associated with 20 min or more of DTN in the 2016, 2017 and 2018 (most recent three years of the study period) subpopulations were evaluated using binary logistic regression analysis. Moreover, linear regression analyses were performed. Because the distribution of DTN time was skewed to the right, it was converted to square root for linear regression. We selected low initial NIHSS, high blood pressure, sooner arrival, out-off-hours arrival, and wait for laboratory results as independent factors for multivariate regression models according to the previous studies [12,13,19]. Data were statistically analyzed using JMP (SAS Institute Inc., Cary, NC, USA) software. P values $< .05$ (two-sided) were considered significant.

3. Results

Table 1 shows the clinical characteristics of the patients. The median NIHSS score at baseline was 11 (interquartile range [IQR], 5–19). The numbers of patients with sICH and stroke mimics were 16 (3.1%) and 4 (0.8%), respectively.

Fig. 1 shows annual changes in the number of patients treated with IVT. After the brain imaging protocol was simplified in July 2011, the rate of patients without MRI data before IVT increased to approximately 80%.

The median DTN was annually reduced from 90 (55–98) to 22 min (17–38) between 2006 and 2015, then to 15 (12–24.25) minutes in 2017 and 17 (14–23) minutes in 2018 (Fig. 2). By 2017, 94% of patients were treated within 60 min of arrival. The median OTN did not significantly change until it decreased from 129 (83.5–167.5) minutes in 2016 to 94 (68.5–166.25) minutes in 2017 (Fig. 3). The median DTN and OTN corresponding to each strategy were also changed. The change of time between each phase were as follows: 23 min (phase1–2), 4 min

Table 1
Characteristics of patients.

Factors	n = 516
Age (years), median [IQR]	76 [68–82]
Male, No. (%)	310 (60.1)
Initial NIHSS, median [IQR]	11 [5–19]
DTN (minute), median [IQR]	28 [17–49.75]
OTN (minute), median [IQR]	129 [91.25–167]
Arrival at out-of-hours, No. (%)	340 (65.9)
Systolic blood pressure at arrival (mmHg), means ± SD	154.6 ± 27.3
Diastolic blood pressure at arrival (mmHg), means ± SD	84.9 ± 19.2
MRI prior to IVT, No. (%)	178 (34.5)
Anticoagulation before onset, No. (%)	67 (13.0)
sICH, No. (%)	16 (3.1)
Modified RS at discharge, median [IQR]	3 [1–4]
Modified RS 0–1 at discharge, No. (%)	147 (28.5)
Stroke mimics, No. (%)	4 (0.8)

Abbreviations: DTN, door-to-needle time; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; OTN, onset-to-needle time; RS, Rankin scale.

(phase 2–3), 6 min (phase 3–4), 4 min (phase 4–5), 1 min (phase 5–6), 0 min (phase 6–7) (Table 2). Linear regression analysis for delay of DTN revealed that initial NIHSS score ≤ 4 (β coefficient 0.26, 95% CI 0.037–0.49) and anticoagulation before onset (β coefficient 0.51, 95% CI 0.25–0.77) were independently associated with delay of DTN in 186 patients treated from 2016 to 2018 (Table 3). In addition, multivariable logistic regression analysis also revealed that initial NIHSS score ≤ 4 (OR 2.67, 95% CI 1.3–5.7) and anticoagulation before onset (OR 6.00, 95% CI 2.47–14.58) were independently associated with 20 min or more of DTN (Table 4).

4. Discussion

We showed that phased changes in strategies according to the Helsinki thrombolysis model reduced DTN to 15 min, which cut the delay in administering IVT at a single Japanese stroke center. The prevalence of sICH and stroke mimics was comparable with that found by others [7–10]. The high volume of patients was reported to be associated with shorter DTN [11], however, we have implemented the Helsinki model and reached the enough short DTN which would be the shortest in the previous reports despite the small to moderate number of patients.

Several studies of steps to improve DTN at single centers have been reported since the seminal report from Helsinki was published. Although the degree of improvement would be affected by local policies, volumes, layout, or context of facilities, most of them adopted components of the Helsinki model and achieved substantial improvements on time metrics [12]. Efforts to improve IVT efficiency have also been implemented in multi-center studies. The Target: Stroke campaign to improve tPA administration, which was launched in 1030 hospitals in the USA, resulted in the median DTN falling from 77 to 59 min in the second phase of initiatives [13]. The European-based ANGELS initiative was established to improve acute stroke care including thrombolysis rate and efficiency [14]. In addition to these large registries, national and regional registries for reducing IVT treatment delays have been established in Sweden [15], Korea [16], and Canada [17]. However, such initiatives have not yet been implemented in Japan.

A narrative review of improving DTN suggests that hospital pre-notification of incoming stroke, stroke team activation by a single call, rapid registration process, patient transfer to imaging suite by EMS stretcher, simplification of laboratory or POC tests, and tPA administration in imaging suites are key strategies to reduce DTN [12]. We implemented almost all these strategies in the Helsinki model [2] but were unable to move the CT equipment to the ER and conduct POC tests to evaluate PT-INR. Our study revealed that anticoagulation before stroke onset, which requires knowing PT-INR and APTT results, was closely associated with delayed treatment during the latest three years (Tables 3, 4). The implementation of POC would reduce the amount of time spent waiting for PT-INR results of patients on oral vitamin K antagonists, but the spread of direct oral anticoagulants requires knowing not only PT-INR but also APTT [18], which is not evaluated at POC. We should consider the cost of introducing POC and the frequency of requiring PT-INR tests before IVT.

In the Japanese guidelines for intravenous thrombolysis, it is recommended that eligibility for severe cases with NIHSS ≥29 or mild cases with NIHSS ≤4 should be determined carefully [5]. So, we treated with IVT for patients with NIHSS ≤4 whose deficit would be disabling for daily-life (e.g. hemianopsia, severe monoparesis, or aphasia). In the present study, both linear regression and multivariable logistic regression analyses revealed that initial NIHSS scores ≤4 was also independently associated with delayed treatment during the latest three years (Tables 3, 4). The association of delays in DTN with stroke severity was noted previously [19]. Poor recognition of minor symptoms by patients and uncertainty about use of IVT by physician may affect the delay in DTN [19].

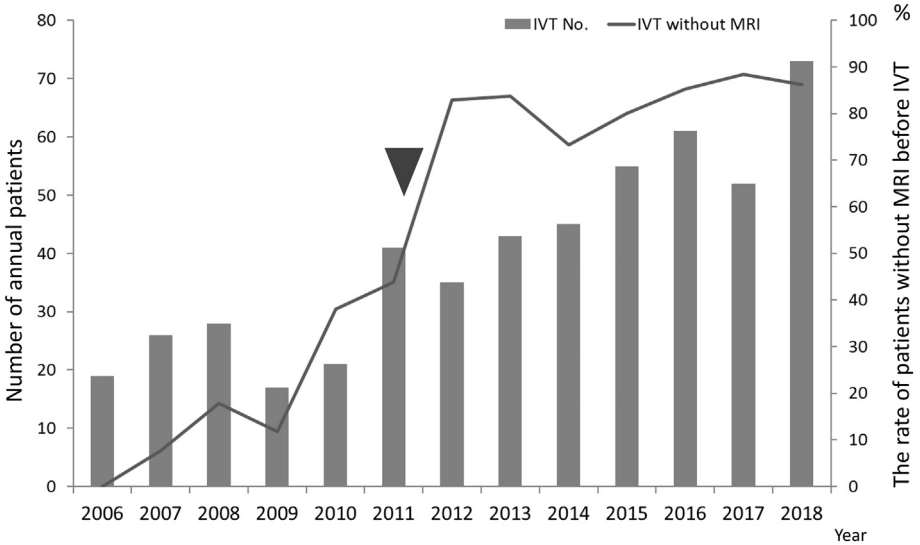

Fig. 1. Annual changes in numbers of patients treated by IVT and the rate of patients without MRI before IVT. Black arrowhead indicates the simplification of brain imaging. Abbreviations: IVT, intravenous thrombolysis; MRI, magnetic resonance imaging.

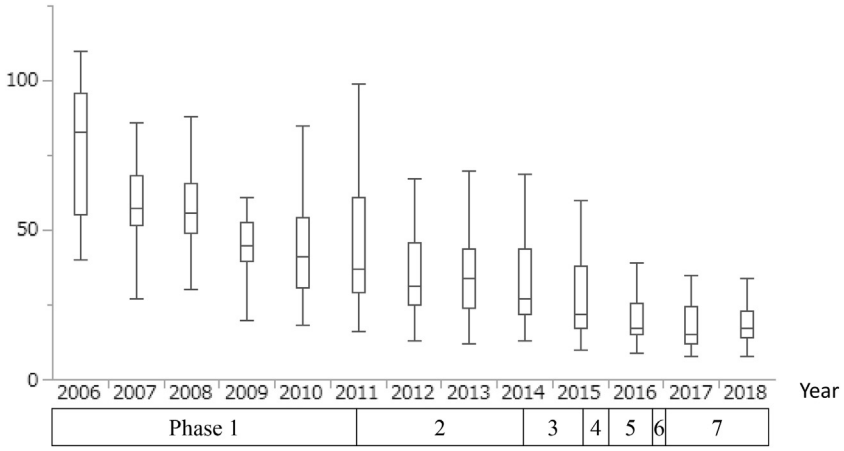

Fig. 2. Annual changes in median DTN with interquartile ranges. Horizontal line within the box-and-whisker plot represents the median; the top and bottom edges of each box indicate interquartile ranges. Whiskers indicate that they are within 1.5 times the interquartile range of lower and upper quartiles. The labels of each phase corresponding to each strategy are shown at the bottom of the figure. Abbreviations: DTN, door-to-needle time.

Simplification of brain imaging, from both CT and MRI to only CT, before starting IVT seemed to be a key strategy on shorting DTN (Table 2). The proportion of patients without MRI before IVT has markedly increased after implementation of simplification of brain imaging (Fig. 1). Although there is no published literature, performing both MRI and CT to achieve both rapid exclusion of intracranial hemorrhage and reliable assessment of early ischemic change was not considered as a special procedure in Japan according to the discussion at a Japanese conference several years ago. Since the Japanese guidelines contraindicate a large extent of early ischemic changes on CT or MRI for IVT [5], most physicians in Japan would prefer to evaluate ischemic changes by MRI including diffusion-weighted imaging before IVT because of its higher detection sensitivity for early ischemic change. On the other hand, CT is useful for immediately excluding intracerebral hemorrhage, which accounts for 20–30% of acute strokes in Japan [20]. Emergency MRI acquisition is widely available in Japan [21,22] and thus can easily proceed before IVT. One Japanese stroke center reported the feasibility of using MRI before IVT [7]. The advantage of MRI instead of CT-based selection for IVT was that it might reduce risk of intracranial hemorrhage [8,9] or IVT for stroke mimics [10]. However, the value of MRI-based selection for IVT has not yet been proven. On balance, CT might be more useful in the meantime in terms of shortening the time metrics of IVT.

This study has some limitations. The single-center design is one of them. However, our institute specializes in acute neurological disorders. We could construct a simple hospital pre-notification and alarm system partly because we do not have a general emergency department or emergency physicians. In addition, we could not compare our results with the usual practice in Japan because we could not obtain the usual time parameters for IVT from nationwide Japanese registries or previous multi-center studies. Regardless, the present study is the first to evaluate the ability of strategies including the Helsinki model to reduce the delay in administering IVT to acute stroke patients at a Japanese stroke center despite low to moderate volume of cases. We believe that our results would promote the reduction in delay of IVT not only at Japanese centers but also at other centers. To improve DTN among stroke centers nationwide, registries should be implemented, or multi-hospital improvement initiatives should focus on acute stroke care including IVT in Japan.

5. Conclusions

We found that gradual strategic changes reduced DTN to 15 min and thus reduced the delay before receiving IVT at a single Japanese stroke center. These findings showed that strategic changes based on the Helsinki model to reduce the delay before IVT administration to stroke patients were applicable at a Japanese stroke center.

Statement of ethics

The Kohnan Hospital Ethics Committee approved the study protocol. Due to the retrospective nature of the study, the need for written informed consent was waived.

Disclosure statement

Ryo Itabashi received honoraria for oral presentations from Tanabe-Mitsubishi Parma and Kyowa Hakko Kirin. Yuya Shigehatake, Yukako

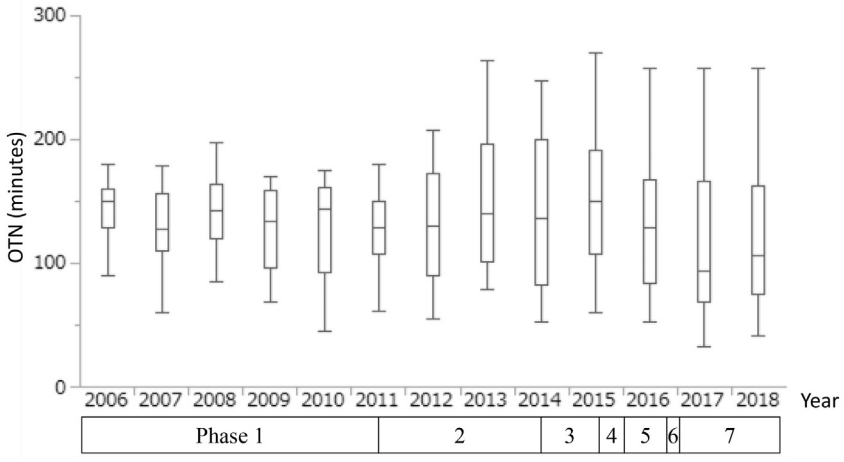

Fig. 3. Annual changes in median OTN with interquartile ranges. The horizontal line within the box-and-whisker plot represents the median; the top and bottom edges of each box indicate interquartile ranges. Whiskers indicate that they are within 1.5 times the interquartile range of lower and upper quartiles. Abbreviations: OTN, onset-to-needle time.

Table 2
The median DTN and OTN at phases corresponding to each strategy.

	Phase 1	2	3	4	5	6	7
DTN (minute), median [IQR]	54 [42–71]	31 [24–44]	27 [21–39]	21 [15.75–25]	17 [15–26]	16 [14–26]	16 [13 − 23]
OTN (minute), median [IQR]	137.5 [111.5–158.5]	134 [97–173]	129 [88–188]	154.5 [97.5–218.5]	129.5 [84–173.25]	100 [76–167]	102 [70.5–161]

Abbreviations: DTN, door-to-needle time; OTN, onset-to-needle time; IQR, interquartile range.

Table 3
Linear regression analysis for delay of DTN among patients treated in 2016, 2017, and 2018 respectively.

	2016		2017		2018		2016–2018	
Variable	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value
Over 75 years old	0.19(−0.20–0.58)	0.33	−0.14(−0.59–0.30)	0.52	0.28(−0.031–0.59)	0.077	0.13(0.063–0.32)	0.19
Male	0.31(−0.062–0.68)	0.10	−0.14(−0.59–0.31)	0.53	−0.011(−0.31–0.28)	0.94	0.083(0.11–0.27)	0.39
Initial NIHSS ≤4	0.23(−0.18–0.63)	0.27	0.36(−0.12–0.85)	0.14	0.22(−0.14–0.57)	0.22	0.26(0.037–0.49)	0.023
Out-of-hours arrival	0.23(−0.14–0.59)	0.22	0.36(−0.11–0.84)	0.13	0.15(−0.19–0.49)	0.39	0.20(0.0065–0.41)	0.058
SBP ≥ 185 mmHg or DBP ≥ 110	−0.24(−0.18–0.63)	0.33	0.061(−0.53–0.65)	0.83	−0.16(−0.51–0.20)	0.38	−0.14(−0.38–0.099)	0.25
Onset to door time ≤ 60 min	0.23(−0.14–0.68)	0.19	−0.015(−0.46–0.43)	0.68	0.032(−0.29–0.35)	0.84	0.087(−0.12–0.29)	0.40
Oral anticoagulation before onset	0.71(0.25–1.17)	0.0029	0.36(−0.26–0.98)	0.25	0.43 (−0.0012–0.86)	0.051	0.51(0.25–0.77)	0.0002

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; NIHSS, National Institute of Health stroke scale; OR, odds ratio; SBP, systolic blood pressure.

Table 4
Binary logistic regression analysis for DTN > 20 among patients treated in 2016, 2017, and 2018 respectively.

	2016		2017		2018		2016–2018	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Over 75 years old	1.39 (0.30–6.33)	0.67	0.13 (0.019–0.94)	0.043	1.56 (0.51–4.82)	0.44	0.95(0.48–1.89)	0.88
Male	2.76 (0.57–13.27)	0.21	0.50 (0.10–2.48)	0.39	0.66 (0.23–1.90)	0.44	1.01(0.51–1.97)	0.99
Initial NIHSS ≤4	3.07 (0.63–14.89)	0.16	5.74 (1.04–31.80)	0.046	2.33 (0.70–7.75)	0.17	2.67(1.3–5.7)	0.0011
Out-of-hours arrival	0.96 (0.23–3.99)	0.95	1.58 (0.27–9.23)	0.61	1.59 (0.45–5.60)	0.47	1.14(0.54–2.41)	0.74
SBP ≥ 185 mmHg or DBP ≥ 110	0.32 (0.029–3.61)	0.36	1.61 (0.23–11.30)	0.63	0.36 (0.086–1.49)	0.16	0.61(0.25–1.52)	0.29
Onset to door time ≤ 60 min	2.41 (0.49–11.87)	0.17	0.27 (0.047–1.52)	0.14	0.83 (0.26–2.61)	0.75	0.91(0.44–1.87)	0.79
Oral anticoagulation before onset	12.38 (1.93–79.53)	0.008	13.53 (1.40–130.88)	0.025	4.17 (0.91–19.08)	0.066	6.00(2.47–14.58)	< 0.0001

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; NIHSS, National Institute of Health stroke scale; OR, odds ratio; SBP, systolic blood pressure.

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Author contributions

Ryo Itabashi: data acquisition, data analysis, and writing of the manuscript. Yuya Shigehatake, Yukako Yazawa, Kaoru Endo, Takuya Saito, Kazuki Fukuma, and Eisuke Furui: data acquisition. Etsuro Mori: critical revision of the manuscript.

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