BMC Geriatrics

RESEARCH

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Association between edaravone use and activities of daily living in older patients with atherothrombotic stroke: an observational study using Japanese real-world data

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Abstract

Background Edaravone is marketed in nine countries, although only Japan has approved edaravone for improvement of neurological symptom, disability of activities of daily living (ADL), and functional disability associated with acute stroke. This study aimed to elucidate the association of edaravone use with ADL using real-world data of older patients with atherothrombotic stroke.

Methods This retrospective observational research using the Medical Data Vision database in Japan included patients aged 65 years and older who had acute ischemic stroke of the atherothrombotic subtype. Primary outcome was ADL improvement defined as change in Barthel Index from admission to discharge of greater than zero points. The major secondary outcome was good functional outcome (Barthel Index ≥ 90 or modified Rankin Scale 0–2 at discharge). Multivariate logistic regression analyses were conducted to calculate odds ratios with 95% confidence intervals for the outcomes. We further compared the change in Barthel Index from admission to discharge and in-hospital death rate between the edaravone- and non-edaravone- treated patients.

Results A total of 5,576 patients were included in this study, and were divided into edaravone group ($n = 3,825$) and non-edaravone group ($n = 1,751$). The median age of this cohort was 79 years, and median Barthel Index at admission was 30 points. Edaravone use was associated with improved ADL with an adjusted odds ratio of 1.18 (95% confidence interval: 1.01−1.37). However, no significant association was observed between edaravone use and good functional outcome. The edaravone group had significantly greater change in Barthel Index from admission to discharge than the non-edaravone group, with a difference of 5 points. The in-hospital death rate was comparable between the two groups.

Conclusions Edaravone use may contribute to improve ADL at discharge in patients aged 65 years and older with atherothrombotic stroke.

Keywords Activities of daily living, Aged, Edaravone, Ischemic stroke, Recovery of function

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Introduction

Stroke is a major cause of disability in activities of daily living (ADL), impacting functional independence and quality of life. Atherothrombotic stroke is a subtype of acute ischemic stroke [1] that develops from atherosclerosis involving specific sites in the extracranial and major intracranial arteries. Previous study in European population reported that atherothrombotic stroke accounted for 13.3% of ischemic stroke cases, 67% of which were over 65 years of age [2]. In Japan, 31.5% of ischemic stroke cases were atherothrombotic stroke [3]. Atherothrombotic stroke is the most common ischemic stroke subtype among patients in the age group of 70 years, and the number of patients with severe disability has been shown to increase with age in Japan [3]. Therefore, aherothrombotic stroke is a significant healthcare concern, particularly among older population. Additionally, previous study has reported worse functional outcome with increasing age [4].

Edaravone is a cerebroprotectant that scavenges and detoxifies radicals that cause damages to cerebral blood vessels and nerve cells [5]. In a phase III trial on acute ischemic stroke patients, edaravone initiated within 72 h of stroke onset significantly improved functional outcomes as measured by the modified Rankin Scale (mRS) compared to placebo [6]. Currently, edaravone is marketed in nine countries including Japan, China and the United States of America. However, only Japan has approved edaravone for the improvement of neurological symptoms, disability of ADL, and functional impairment associated with acute stroke. The Japanese Guidelines for the Management of Stroke 2021 recommend edaravone for the treatment of acute ischemic stroke (grade B recommendation) [7]. Therefore, this drug is widely used in acute stroke patients in Japan.

This study focused on the association between edaravone use and functional outcome in atherothrombotic stroke. The mRS is a scale that grades the degree of disability and evaluates the overall impact on the individual's walking performance and functions in ADL [8, 9]. However, there is a concern that evaluation using mRS is based on the subjective judgment of the assessor, which may lead to bias in the evaluation result [10, 11]. On the other hand, Barthel Index (BI) is a numerical scale and focuses on basic ADL such as bathing and grooming [12]. BI is most commonly used to measure ADL disability and dependence in stroke patients.

To the best of our knowledge, there are no studies on the association of edaravone use with ADL improvement measured by BI in older patients with acute stroke based on big data of medical care. Previous study using real-world data has shown the effect of edaravone on neurological symptoms, although the difference from non-edaravone group was small and the clinical significance was limited [13]. The present study aimed to elucidate the association of edaravone use with ADL improvement measured by BI using real-world data of older patients.

Methods

Study design and population

The study design was a retrospective, observational research utilizing anonymized patient data managed by the Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). The MDV database supports the Japanese Diagnosis Procedure Combination (DPC) hospitals in the collection and reporting of administrative data, and provides anonymized pharmacy claims as well as hospital-based and insurance-related data. In this study, the administrative claims data provided by the MDV database were used to conduct a retrospective evaluation. For disease data, diagnosis codes according to the International Classification of Diseases, 10th Revision (ICD-10), Japanese disease codes, and dates of diagnosis were registered in the database. For medication data, Japanese treatment codes, health insurance claims codes, drug prescription dates, routes of administration, and prescribed doses were registered. All patient data were coded prior to entry. From the MDV database, we selected the older population comprising 1,830,338 patients aged 65 years and above. Data were retrieved from hospitalization records at DPC hospitals in Japan between April 2008 and December 2021.

The inclusion criteria of this study were (1) newly diagnosed with atherothrombotic stroke (ICD-10 code: I633); (2) brain imaging (CT or MRI) findings at diagnosis; and (3) hospitalized within 3 days of stroke onset. Exclusion criteria were (1) under 65 years of age at the start of observation; (2) missing mRS data prior to stroke onset; (3) missing BI data at admission; (4) atherothrombotic stroke diagnosed after admission; (5) unknown date of stroke onset. According to the Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labour and Welfare, informed consent and ethics approval were not required for this study that used anonymized patient data from the MDV database [14].

Data collection

Patient demographics and clinical data of newly diagnosed atherothrombotic stroke patients were collected, including age, sex, height, body weight, BI at admission and discharge, mRS prior to stroke onset and at discharge, Japan Coma Scale (JCS) score at admission, and laboratory data including serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate (eGFR). Intravenous treatments after atherothrombotic stroke,

such as edaravone and alteplase, were also collected. Additionally, we retrieved the information about the medications used at stroke onset, such as antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

Primary and secondary outcome measures

Primary outcome was improvement in ADL at discharge, defined as change in BI from admission to discharge (Δ BI = BI at discharge minus BI at admission) of greater than zero points (Δ BI > 0). BI is a 10-item scale that focuses on ADL (bathing, grooming, ascending and descending stairs, bladder management, bowel management, dressing, feeding, toilet use, transfers, and walking). Bathing and grooming are scored 0 or 5 points; ascending and descending stairs, bladder management, bowel management, dressing, feeding, and toilet use are scored 0, 5 or 10 points; and transfers and walking are scored 0, 5, 10 or 15 points. The scores of the ten items are summed to give a maximum possible score of 100 points (independent) and a minimum possible score of 0 points (totally dependent) [12].

The major secondary outcome was the association between good functional outcome and edaravone use. Good functional outcome was defined as BI score 90–100 points or mRS grade 0–2 at discharge [15]. The mRS grades range from 0 to 6: 0 indicates no symptoms; 1, no disability; 2, slight disability; 3 to 4, needing some help with daily activities; 5, dependent or bedridden; and 6, death [8]. Other secondary outcomes consisted of Δ BI, length of hospital stay, and in-hospital death rate.

Statistical analysis

Numerical data are expressed as median and interquartile range (IQR) and categorical data as number and percentage. We divided the study population into two groups: edaravone group and non-edaravone group. Demographic and clinical variables were compared between the two groups. Mann–Whitney U test and chi-squared test were used to compare numerical and categorical data, respectively. Univariate and multivariate logistic regression analyses were conducted to identify clinical factors associated with the improvement of ADL. Results are presented as crude and adjusted odds ratios (OR) and 95% confidence intervals (CI). An OR less than 1 indicates a negative association with outcome, while an OR greater than 1 indicates a positive association. Covariates incorporated in multivariate logistic regression analysis included at least patient background factors such as age and body mass index (BMI) less than 20 kg/m^2, and edaravone use. The cut off value of BMI was based on the criterion of sarcopenia [16]. In addition to the variables specified above, other variables with P values less than 0.10 in the univariate analyses were also included as covariates in the multivariate analysis. We examined the existence of multicollinearity between factors using Spearman's rank-correlation coefficient, Mann–Whitney U test, and chi-square test. When there was significant multicollinearity between variables, we selected one of them based on clinical relevance. In particular, factors that showed significant differences in patient backgrounds between the two groups were included as covariates, taking their correlations into account. For outcomes that showed significant association with edaravone use, we performed subgroup analyses with stratification by mRS grade prior to stroke onset (mRS 0–2 and 3–5 subgroups) and by BI score at admission (BI ≥ 90, 70–85, and < 70 subgroups) to evaluate the interactions of these factors with the outcomes. ADL dependence was defined as BI < 70 points, according to previous studies [17, 18]. Statistical significance was defined by a two-sided alpha level of 0.05. All statistical analyses were performed using Stata® 15 (College Station, TX).

Results

Patient characteristics

The flow of patient selection is shown in Fig. 1. A total of 5,576 patients were included in this analysis. Patient characteristics of the present cohort are presented in Table 1. Of all patients included, 3,825 patients (68.6%) were edaravone users, and 1,751 (31.4%) were non-users. Among the edaravone users, 1,554 (27.9%) patients were aged above 85 years. In the edaravon users, 3340 patients (88.9%) of patients started edaravone on the first day of hospital admission.

In the total cohort, 4,163 patients (74.7%) had mRS grades 0–2 prior to atherothrombotic stroke onset. The proportion of patients with smoking habit before onset was not difference between edaravone and non-edaravone groups [1,584 patients (41.4%) and 709 patients (40.5%), respectively; $p = 0.517$]. A total of 87 (2.3%) patients in edaravone group were in a semi-coma or coma state, as defined by JCS scores 100–30, at admission. The edaravone and non-edaravone groups differed significantly in baseline clinical data including age, proportion of BMI < 20 kg/m^2, JCS score at admission, proportion of mRS 0–2 before stroke onset, BI score at admission, renal function, diabetes mellitus and hypertension medications, and use of intravenous drugs after onset (Table 1).

Primary and secondary outcomes

The primary outcome was ADL improvement at discharge (Δ BI > 0). Excluding 551 patients with missing data at discharge, a total of 5025 patients were evaluated. Among them, 3,018 patients (60.1%) achieved ADL improvement, while 2,007 patients (40.0%) showed no

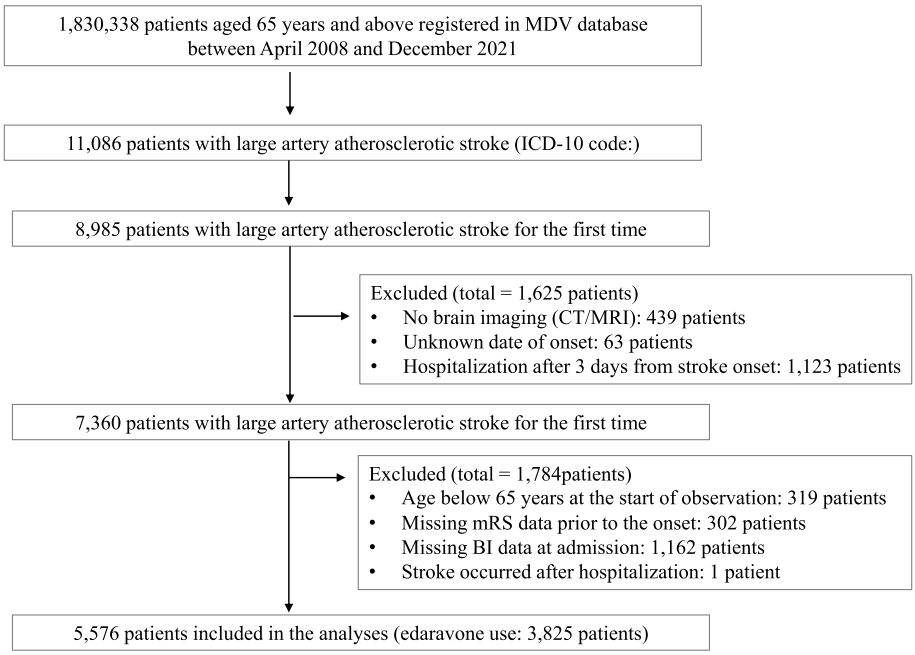

Fig. 1 Flow chart for selection of the study cohort

improvement. Table 2 shows the results of logistic regression analyses for the association between ADL improvement and patient clinical factors including age, sex, BMI < 20 kg/m^2, and JCS at admission. Edaravone use was significantly associated with ADL improvement [adjusted OR (95% CI): 1.18 (1.01—1.37), $p = 0.032$]. Male sex showed a positive association with ADL improvement. In addition, age and JCS score at admission showed a negative association with ADL improvement.

To further examine the association of edaravone use with ADL improvement, we performed subgroup analyses with stratification by mRS grade before stroke and by BI score at admission. The association tended to be similar regardless of the ADL level before stroke onset [adjusted OR (95% CI): 1.10 (0.92—1.31) in pre-stroke mRS 0–2 subgroup, 1.20 (0.88—1.66) in pre-stroke mRS 3–5 subgroup]. Likewise, similar association was observed regardless of the ADL level at admission due to atherothrombotic stroke [adjusted OR (95% CI): 1.01 (0.63—1.60) in admission BI ≥ 90 subgroup, 1.18 (0.54 – 2.57) in BI 70–85 subgroup, and 1.14 (0.94—1.38) in BI < 70 subgroup].

Regarding the major secondary outcome, logistic regression analyses showed no association between edaravone use and good functional outcomes defined as BI at discharge ≥ 90 or mRS at discharge 0–2 (Table 3).

Among the edaravone user group, there were 425 patients who started edaravone administration after the second day of hospital admission. A subgroup analyses were performed excluding these patients, and the results are shown in Table 4. There was a significant association with edaravone use for the primary and secondary outcomes, mRS grade 0–2 at discharge. Hence, there was a significant improvement in ADL in the group that received edaravone on the first day of hospital admission.

Table 5 compares the outcomes between edaravone and non-edaravone groups. Edaravone group had significantly higher Δ BI than non-edaravone group, with a difference in median score of 5 points. The length of hospital stay was significantly longer by a median of 3 days in the edaravone group. The total number of in-hospital deaths among all patients was 228 (4.1%), with no difference in in-hospital death rate between edaravone and non-edaravone groups.

Discussion

This study investigated the association between edaravone use and ADL improvement after stroke in older population aged 65 and above with atherothrombotic stroke. Our results showed that edaravone use was one of the independent factors predicting ADL improvement at discharge, measured by BI. The association between edaravone use and ADL improvement was not affected by the ADL level at admission, as shown in a subgroup analysis involving stratification by BI at admission. Additionally, Δ BI in edaravone group was significantly higher by 5 points compared to non-edaravone group. The 5-point difference indicates a trend toward greater

Table 1 Patient characteristics in the present cohort

	All patients ($n=5576$)	Edaravone group ($n=3825$)	Non-edaravone group ($n=1751$)	*P* value[a]
Age, years	79 [73, 85]	78 [72, 84]	80 [74, 87]	< 0.001
Male, n (%)	3,154(56.6)	2,149(56.2)	1,005 (57.4)	0.396
BMI, kg/m^2	22.5 [20.2, 24.9]	22.6 [20.4, 25.0]	22.5 [20.0, 24.8]	0.095
BMI < 20, n (%)	1,133/5,200 (21.8)	734/3,553 (20.7)	399/1,647 (24.2)	0.004
JCS at admission, n (%)				0.001
0	2,737 (49.1)	1,812 (47.4)	925 (52.8)	
1–3	2,264 (40.6)	1,602 (41.9)	662 (37.8)	
10–30	445 (8.0)	324 (8.5)	121 (6.9)	
100–300	130 (2.3)	87 (2.3)	43 (2.5)	
mRS 0–2 before stroke, n (%)	4,163 (74.7)	2,945 (78.0)	1,218 (69.6)	< 0.001
BI at admission, points	30 [0, 70]	25 [0, 65]	35 [0, 75]	< 0.001
BI at admission ≥ 90, n (%)	1,070 (19.2)	713(18.6)	357 (20.4)	0.124
eGFR, mL/min /1.73m^2	63.2 [50.2, 77.3]	66.5[55.4, 79.8]	54.0 [37.4, 70.0]	< 0.001
eGFR < 60, n (%)	1,813/4,208 (43.1)	1,000/2,831 (35.3)	813/1,377 (59.0)	< 0.001
BUN/Cr ratio	20.8 [16.6, 26.0]	21.3 [17.0, 26.3]	19.6 [15.8, 25.1]	< 0.001
Mediation at onset, n (%)				
DM medication	657 (11.8)	399 (10.4)	258 (14.7)	< 0.001
HTN medication	1,560 (28.0)	1,020 (26.7)	540 (30.8)	0.001
HL medication	1,266 (22.7)	864 (22.6)	402 (23.0)	0.759
Oral antiplatelet	1,812 (32.5)	1,251 (32.7)	561 (32.0)	0.622
Intravenous drug use after onset, n (%)				
Alteplase	56 (1.0)	48 (1.3)	8 (0.5)	0.006
Argatroban	670 (12.0)	514 (13.4)	156 (8.9)	< 0.001
Ozagrel	4 (0.1)	0 (0)	4 (0.2)	0.003

Data are expressed as median [interquartile range], or number (%)

BI Barthel Index, *BMI* Body mass index, *BUN* Blood urea nitrogen, *Cr* Creatinine, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HL* Hyperlipidemia, *HTN* Hypertension, *JCS* Japan coma scale, *mRS* modified Rankin Scale

[a] Mann–Whitney U test and chi-squared test were used to compare numerical and categorical data, respectively

Table 2 Logistic regression analysis for the primary outcome. Dependent variable: improvement of ADL

	Crude			Adjusted		
Independent variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Edaravone use	1.21	1.07–1.36	0.002	1.18	1.01–1.37	0.032
Age, per 10 years	0.68	0.63–0.73	< 0.001	0.72	0.65–0.79	< 0.001
Male	1.33	1.18–1.49	< 0.001	1.18	1.02–1.36	0.025
BMI < 20 kg/m^2	0.80	0.69–0.92	0.002	0.93	0.79–1.11	0.439
JCS at admission						
0	reference			reference		
1–3	0.99	0.88–1.11	0.847	1.04	0.89–1.20	0.623
10–30	0.55	0.44–0.69	< 0.001	0.63	0.48–0.83	0.001
100–300	0.32	0.20–0.51	< 0.001	0.38	0.21–0.67	0.001
eGFR < 60 mL/min /1.73m^2	0.92	0.81–1.06	0.243	1.08	0.93–1.25	0.304
HTN medication at onset	0.86	0.76–0.98	0.019	0.86	0.74–1.01	0.058
Intravenous drug use[a]	1.08	0.92–1.28	0.338	0.94	0.77–1.15	0.527

BMI Body mass index, *CI* Confidence interval, *eGFR* estimated glomerular filtration rate, *HTN* Hypertension, *JCS* Japan Coma Scale, *OR* odds ratio

[a] Alteplase, argatroban or ozagrel

Table 3 Logistic regression analyses for secondary outcomes

	Crude			Adjusted		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Dependent variable: BI at discharge ≥ 90						
Edaravone use	1.00	0.89–1.13	0.962	0.91	0.77–1.08	0.274
Age, per 10 years	0.37	0.34–0.40	<0.001	0.43	0.38–0.47	<0.001
Male	1.97	1.75–2.20	<0.001	1.56	1.34–1.83	<0.001
BMI < 20kg/m^2	0.49	0.42–0.57	<0.001	0.59	0.49–0.72	<0.001
JCS at admission						
0	reference			reference		
1–3	0.30	0.27–0.34	<0.001	0.35	0.30–0.41	<0.001
10–30	0.10	0.07–0.13	<0.001	0.13	0.09–0.19	<0.001
100–300	0.04	0.02–0.11	<0.001	0.07	0.02–0.22	<0.001
eGFR < 60 mL/min /1.73m^2	0.71	0.62–0.81	<0.001	0.90	0.77–1.06	0.210
HTN medication at onset	0.83	0.74–0.94	0.004	0.86	0.73–1.02	0.084
Intravenous drug use[a]	0.70	0.60–0.83	<0.001	0.72	0.57–0.89	0.003
Dependent variable: mRS at discharge 0–2						
Edaravone use	1.00	0.90–1.13	0.948	0.91	0.78–1.06	0.215
Age, per 10 years	0.46	0.42–0.49	<0.001	0.56	0.51–0.61	<0.001
Male	1.69	1.52–1.89	<0.001	1.30	1.12–1.50	<0.001
BMI < 20 kg/m^2	0.55	0.48–0.64	<0.001	0.69	0.58–0.83	<0.001
JCS at admission						
0	reference			reference		
1–3	0.32	0.28–0.35	<0.001	0.39	0.33–0.45	<0.001
10–30	0.10	0.08–0.14	<0.001	0.16	0.11–0.22	<0.001
100–300	0.04	0.02–0.09	<0.001	0.06	0.02–0.15	<0.001
eGFR < 60 mL/min /1.73m^2	0.72	0.64–0.82	<0.001	0.89	0.77–1.03	0.119
HTN medication at onset	0.82	0.73–0.92	0.001	0.83	0.71–0.97	0.016

BI Barthel Index, *BMI* Body mass index, *CI* Confidence interval, *eGFR* Estimated glomerular filtration rate, *HTN* Hypertension, *JCS* Japan coma scale, *mRS* Modified Rankin Scale, *OR* Odds ratio

[a] Alteplase, argartoban or ozagrel

Table 4 Sub-analyses for primary and secondary outcomes for edaravone use

Dependent variable	**aOR**	**95%CI**
Primary outcome		
improvement of ADL	1.19	1.02–1.39
Secondary outcome		
BI at discharge ≥ 90	0.94	0.79–1.11
mRS at discharge 0–2	1.51	1.27–1.81

Sub-analyses were performed on patients who received edaravone on the first day of hospital admission. Full covariates adjustment included age, male, BMI < 20 kg/m^2, JCS at admission, eGFR < 60 mL/min/1.73m^2, HTN medication at onset and intravenous drug use (alteplase, argartoban or ozagrel)

ADL Daily activities of living, *BI* Barthel Index, *CI* Confidence interval, *mRS* modified Rankin Scale, *aOR* adjusted odds ratio

independence in any one of the 10 ADL items (bathing, grooming, ascending and descending stairs, bladder management, bowel management, dressing, feeding, toilet use, transfers, and walking). Analysis of the major secondary outcome defined as BI at discharge ≥ 90 or mRS at discharge 0–2 showed no association between edaravone use and good functional outcome. A previous subset analysis of a phase III trial reported clearer ADL improvement in patients treated with edaravone within 24 h of stroke onset [6]. The data in the present study contained not only patients admitted within 24 h of stroke onset, but also those admitted after 24 h, whose response to edaravone is expected to be weaker. Thus, the results of this study may be underestimated. Previous studies have also suggested differences in the efficacy of edaravone according to stroke subtype [13, 19]. Edaravone scavenges free radicals produced by activation of the arachidonic acid cascade during cerebral ischemic reperfusion. Cardioembolic stroke is severe at admission and edaravone treatment may be more effective than atherothrombotic stroke, because large quantities of free radicals are produced. On the contrary, atherothrombotic stroke is less severe and the efficacy of edaravone treatment for atherothrombotic stroke patients may be

Table 5 Comparisons of outcomes between edaravone and non-edaravone groups

	Edaravone group ($n=3825$)	Non-edaravone group ($n=1751$)	*P* value[a]
Length of stay, days	21 [13, 33]	18 [11, 32]	< 0.001
Δ BI[b]	15 [0, 50]	10 [0, 45]	< 0.001
BI at discharge	85 [25, 100]	75 [20, 100]	0.602
ADL improvement[§], n (%)	2,122/3,452 (61.5)	896/1,573 (57.0)	0.002
BI at discharge ≥ 90, n (%)	1,565/3,452 (45.3)	712/1,573 (45.3)	0.962
mRS at discharge 0–2, n (%)	1,692/3,777 (44.8)	7698/1,718 (44.7)	0.948
in-hospital death, n (%)	150 (3.9)	78 (4.5)	0.351

ADL, activities of daily living; BI, Barthel Index; mRS, modified Rankin Scale

Data are expressed as median [interquartile range], or number (%)

[a] Mann–Whitney U test and chi-squared test were used to compare numerical and categorical data, respectively

[b] BI at discharge – BI at admission

[§] (BI at discharge – BI at admission) > 0

limited. In this study, it was difficult to determine the exact date of stroke onset. However, patients who started edaravone on the first day of admission significantly had a favorable functional outcome, defined as an mRS of 0–2 at discharge. In other words, the results suggest that edaravone significantly improves ADL in older patients who started edaravone administration at least within 3 days of stroke onset. Since this study was conducted as a subgroup analysis, further investigation is needed in the future.

In a phase III randomized controlled trial [6], the effects of edaravone on functional outcomes in patients with consciousness levels between JCS score 0 (alert) and 30 at admission were significantly superior compared to placebo, but patients in a semi-coma or coma state (JCS scores 100–300) were excluded from that trial. In the present study of real-world clinical practice, edaravone was used in 87 (2.3%) older patients who were in a semi-coma or coma state at admission.

A previous report showed that sarcopenia at admission and aging affected ADL improvement in older patients with stroke [20]. Our results similarly showed that aging and low BMI (a criterion of sarcopenia [16, 21]) were negatively associated with ADL improvement and good functional outcome. Additionally, men had significantly better ADL improvement than women, consistent with previous reports [3, 22]. These results suggest that the real-world data used in the present study reflect the general population.

In this study, use of intravenous drugs (i.e., alteplase, argatroban, or ozagrel) was negatively associated with good functional outcome. A possible explanation of this finding is that patients receiving intravenous treatment were more severe (median BI at admission: 10 in patients receiving intravenous treatment, 35 in patients not receiving intravenous treatment).

This study had some limitations. First, edaravone and non-edaravone groups differed in several patient background factors such as age, proportion of BMI less than 20 kg/m^2, and eGFR. The proportion of patients with reduced renal function (eGFR lower than 60 mL/min /1.73m^2) was higher in edaravone group than in non-edaravone group (Table 1). One of the adverse effects of edaravone is acute kidney injury (AKI). A Yellow Letter (Dear Healthcare Professional Letter of Emergent Safety Communications) cautioning about AKI during or after edaravone administration was issued by the Pharmaceuticals and Medical Devices Agency in Japan one year after the drug was launched, and healthcare professionals were advised to monitor patients' renal function closely when using edaravone [23]. The differences between edaravone and non-edaravone groups potentially influence the results in this study. Accordingly, we performed multivariate logistic regression analyses including those variables as covariates. Second, this study has a limitation due to potential selection bias associated with the MDV database. Since it covers approximately 27% of DPC hospitals in Japan, primarily acute care hospitals, the findings may not be generalizable to smaller hospitals. Additionally, regional variations and differences in hospital practices may affect the representativeness of the data. Furthermore, the database relies on insurance claims and laboratory data, which may lack detailed clinical information or data on non-billed medical practices. These factors should be considered when interpreting the results. In this study, we were unable to accurately obtain precise information regarding the timing, the dose and duration of edaravone administration. Moreover, it was difficult to collect accurate data on the date of stroke onset, undergoing mechanical thrombectomy, degree of stenosis, site of infarction, and hematoma

volume. The possibility that these factors influenced the results cannot be ruled out. This is a limitation of the study utilizing the claims database. Therefore, further studies, such as prospective cohort studies, are necessary in the future.

Third, we were unable to obtain blood pressure data before and during hospitalization. In this study, use of antihypertensive medications at admission was negatively associated with good functional outcome (mRS at discharge 0–2). Blood pressure at admission could be one of the independent predictive factors of ADL improvement, but this data were not available for analysis. Finally, since this study focused on the efficacy of edaravone, we did not investigate adverse effects such as AKI. However, there were no significant differences in in-hospital death rate and length of hospital stay between edaravone and non-edaravone groups (Table 5). We therefore consider that at least there were no critical adverse effects associated with edaravone use.

Conclusion

In older patients aged 65 years and above with atherothrombotic stroke who were admitted within 3 days of onset, edaravone use was found to contribute to ADL improvement at discharge compared to admission, as measured by BI. Edaravone is a treatment strategy that aims not only to improve the quality of life of older atherothrombotic stroke patients, but also to reduce the burden on caregivers.

Abbreviations

ADL	Activities of daily living
AKI	Acute kidney injury
BI	Barthel Index
BMI	Body mass index
CI	Confidence interval
DPC	Diagnosis Procedure Combination
eGFR	Estimated glomerular filtration rate
ICD-10	International Classification of Diseases, 10th Revision
IQR	Interquartile range
JCS	Japan Coma Scale
MDV	Medical Data Vision
mRS	Modified Rankin Scale
OR	Odds ratio

Acknowledgements

Not applicable.

Authors' contributions

The authors contributed to the manuscript as follows: All authors designed the study, YO, HA and TH collected and analyzed the data, YO and TH interpreted the results, YO and HA drafted the manuscript. All authors contributed to the article and approved the submitted version.

Funding

No funding.

Data availability

The dataset used to support the findings of this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted following the ethical principles of the Declaration of Helsinki. According to the Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labour and Welfare, informed consent and ethics approval were not required for this study that used anonymized patient data from the MDV database.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

Received: 26 April 2024 Accepted: 30 December 2024
Published online: 15 January 2025

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