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RESEARCH ARTICLE

# Hospitalization period and direct medical cost in patients using warfarin or novel oral anti-coagulants after a cerebral embolism

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## Abstract

*Background* Warfarin has been used in Japan for a long time in patients after cerebral embolism to prevent recurrence. Recently, several novel oral anti-coagulants (NOACs) have been approved for use and are gradually replacing warfarin. However, it remains unclear whether warfarin and other NOACs differ from each other with respect to drug costs and length of stay (LOS) during treatment in Japan. *Objective* To assess differences in LOS and direct medical cost between patients after cerebral embolism treated with warfarin and those treated with NOACs. *Setting* Thirteen acute care hospitals in Japan. *Method* For hospitalized patients with cerebral embolisms who were treated with NOACs and/or warfarin between April 2012 and March 2014, we assessed LOS for patients with warfarin and NOAC using log-rank test, and stratified proportional hazard regression. Also, we assess direct medical cost using paired-t test. *Main Outcome measure* LOS and medical cost after first treatment with warfarin and NOAC. *Results* The median LOS for NOACs-treated patients was 12.5 days and that for warfarin treated patients was 19.0 days while the corresponding mean medical costs were USD 7151 ± 6228 [JPY 736,546 ± 641,437] and USD 8950 ± 5891 [JPY 921,830 ± 606,765]. The drug cost for NOACs-treated patients was higher but costs for laboratory-test and hospitalization were lower than those for warfarin-treated patients. *Conclusions* For NOAC-treated patients, LOS was shorter, and medical cost during hospitalization tended to be lower than those for warfarin-treated patients, whereas NOACs prices were higher than warfarin price.

**Keywords** DOAC · Hospitalization period · Japan · Medical cost · NOAC · Novel oral anti-coagulants · Warfarin

## Impacts on practice

- Although the prices of NOACs in Japan are higher than those of warfarin, NOACs seem to be more beneficial for patients post cerebral embolism.
- The use of NOACs instead of warfarin in cerebral embolism patients in Japan leed to shorter length of stay and reduced medical cost during hospitalization.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s11096-019-00792-9) contains supplementary material, which is available to authorized users.

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## Introduction

The Diagnosis Procedure Combination (DPC) system was proposed for use in 2003 as a novel medical reimbursement system for inpatients; this system is based on a daily fixed payment system per diagnosis [1]. In this system, detailed data not only for medical treatment and procedures but also for patient summary [such as diagnosed disease, modified Rankin scale, Japan coma scale (JCS), outcomes at discharge, and re-hospitalization] are uniformly formatted. Therefore, these data are widely used for developing clinical paths, treatment assessments, and hospital management based on the length of stay (LOS) and variance for long-term hospitalization, and are similar to real- world settings [2–5].

Several new drugs have been approved over a period of time for preventing recurrence in patients after cerebral embolism. In particular, in Japan, 26–44 new chemical entities have been newly used for various medical conditions in the past decade [6, 7]. However, new drugs with novelty are generally expensive, which ultimately increases the cost of medical treatment. On the other hand, In Japan, national medical expenditure in 2015 was about JPY 42 trillion which was an increase of JPY 1.5 trillion from 2014, and the national medical expenditure is increasing year by year. And sometimes, higher price for new drugs are discussed as one of the reasons for medical expenditure increasing without consideration of total medical cost for target disease [8].

For a long time, warfarin potassium (warfarin), oral anticoagulant, has been widely used for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), In addition to this, Recently, novel oral anti-coagulants (NOACs), such as dabigatran etexilate (dabigatran), rivaroxaban, and apixaban, have received approval in Japan. Diverse clinical studies have confirmed the efficacy of these NOACs and recommended their use in common medical conditions [9–13]. On the other hand, the average daily cost of these NOACs is JPY 530.4, which is higher than that of warfarin (JPY 10.1). However, in this situation, it is still unclear whether the drug cost between and LOS of patients treated with warfarin or NOACs are different in Japan.

## Aim of the study

In the present study, we analyzed DPC data from the point of view of LOS, and total hospitalization cost to assess whether there are any differences between NOAC-treated patients and warfarin-treated patients based on real-world data in Japan.

## Ethics approval

This research was approved by the Ethics Review Committee of Pharmacy Management Institute in Japan University of Economics (Reference Number: 2017-0831-01).

## Methods

### Data sources

We used Japanese DPC data obtained from 13 hospitals, which included 141,196 cases between April 1, 2012 and March 31, 2014. The median number of hospital beds was 199. From this dataset, we extracted patient data meeting the following inclusion criteria for further analysis:

(1) Patients with cerebral embolism: ICD10 code with I631 and I634.
(2) Patients with no history of surgical operation.
(3) Patients receiving treatment with warfarin and/or NOACs.
(4) Patients not transferred to the sub-acute ward and/or sub-acute rehabilitation ward.

For determining LOS, we calculated the duration between the first NOACs/warfarin treatment date and the discharge date. We counted the number of medical treatments and procedures, including drug treatment, injection, laboratory tests, and imaging diagnosis, the first NOAC/warfarin treatment. To clarify the characteristics of patients in the NOAC-treated and warfarin-treated groups, we considered whether patients received pre-treatment, such as tissue plasminogen activator (t-PA) for hyper-acute phase stroke, edaravone for acute phase, heparins, and anti-platelet drugs. For the assessment of patient complication and age, we calculated the CHADS2 score by using extracted data that met the following ICD-10 code and age category:

(1) TIA and stroke (ICD-10): G45, I63.
(2) Heart failure (ICD-10): I50.
(3) Diabetes (ICD-10): E11, E12, E13, E14.
(4) Hypertension (ICD-10): I10.
(5) Age: $\geq 75$ years.

### Cost calculation

We conducted cost analysis for NOAC/warfarin treatment from the perspective of the healthcare payer. We focused on costs from the first NOAC/warfarin treatment date to the discharge date from the hospital, which included the fees for hospitalization, examinations, drugs, imaging, testing, injections, operations, non-drug treatments, and food. We calculated cumulative costs for the year 2013 according to the Japanese drug tariff [14] and medical treatment fee per treatment/procedure [15] and converted costs from USD to JPY (1 USD = JPY 103) based on the purchasing power of the involved parties in 2013. [16].

### Statistical analysis

We used the free statistical software R (ver.3.0) and its plugin packages EZR (ver.1.27) for statistical analysis [17]. For LOS determination after the first NOAC/warfarin treatment and cost analysis, results were expressed as medians with 95% confidence intervals. For LOS and medical costs from day one of hospitalization to the day of the first NOAC/warfarin treatment, results were expressed as medians with 95% confidence intervals and as means with standard deviations.

As this was a retrospective study, we used propensity score matching [18, 19]. We computed propensity scores (PSs) using logistic regression analysis based on age (≥ 75 years); gender; site; modified Rankin scale at baseline; JCS at baseline; hospitalization time from cerebral embolism onset; treatment with t-PA, heparin, or edaravone; diabetes; heart failure; hypertension; TIA/cerebral infarction; year (2012 or 2013); and duration from day one of hospitalization to the day of the first NOAC/warfarin treatment. We used Fisher's test for the assessment of differences between patients with NOAC treatment and those with warfarin treatment for pre-/post-PS matching. Finally, for LOS assessment for patients after PS matching, we conducted stratified proportional hazard regression analysis. In addition, we used the Kaplan–Meier method to compare LOS after the first NOAC or warfarin treatment; we also used the log-rank test to compare differences in LOS between both groups and applied stratified proportional hazard regression to clarify factors related to LOS, with the treatment drug, site, gender, age, year, Rankin scale, JCO, re-hospitalization, complication (diabetes, TIA/cerebral infarction, hypertension, heart failure), ambulance use, pre-treatment (edaravone, heparin, t-PA), and time to hospitalization as explanatory variables.

For the assessment of cost for patients after PS matching, we performed the paired *t* test, and considered $p < 0.05$ to be statistically significant.

## Results

### Extract data for analysis

The total number of patients in the dataset was 141,196. The number of patients with cerebral embolism and having ICD-10 codes I631 and I634 was 690. We excluded patients without either NOAC or warfarin treatment. We extracted 340 patients (warfarin, $n = 242$, NOACs, $n = 98$) and finally used 196 patients (warfarin, $n = 98$, NOAC, $n = 98$) after PS matching (Fig. 1). Patient profiles before/after PS matching are shown in Table 1. Differences in patients before PS matching between the warfarin and NOAC groups were in relation to age (≥ 75 years), modified Rankin scale, CHADS2 score, diabetes, and heart failure score. In the present study, more severe patients were treated with warfarin than with NOACs. After PS matching, no significant difference was noted between NOAC and warfarin treatment.

### LOS after the first NOAC/Warfarin treatment

Some patients had cerebral embolism during hospitalization for other diseases, while others were hospitalized after cerebral embolism out of the hospital. Therefore, we calculated LOS after the first NOAC/warfarin treatment and carefully assessed them for any drug effects. For PS-matched data, median LOSs for patients treated with NOACs and warfarin were 12.5 (95% CI: 10–15 days) and 19.0 days (95% CI: 16–24 days), respectively. The former was significantly shorter in NOAC-treated patients than in warfarin-treated patients by the log-rank test ($p < 0.01$; Fig. 2).

To clarify factors related to LOS, we performed stratified proportional hazard regression analysis (Table 2). NOAC treatment [hazard ratio (HR): 3.924 (95% CI: 1.034–14.9), $p = 0.0446$], elderly patients (≥ 75 years) [HR: 0.2381 (95% CI: 0.06593–0.8596), $p = 0.02845$], severe Rankin scale (4 or 5) [HR: 0.06933 (95% CI: 0.004855–0.9899), $p = 0.04913$], pre-treatment duration for cerebral embolism [HR: 1.097 (95% CI: 1.003–1.199), $p = 0.04337$], and site C [HR: 1887 (95% CI: 2.284–1559000), $p = 0.02774$] were significantly correlated to LOS.

### Medical cost for NOAC/Warfarin treatment

The results of cost assessment for prescription, injection, procedure, test, and imaging are shown in Table 3. The total cost for patients in the NOAC-treated group (USD 7151 ± 6228 or JPY 736,546 ± 641,437) tended to be lower than that for those in the warfarin-treated group (USD 8950 ± 5891 or JPY 921,830 ± 606,765) ($p = 0.054$). More than half of the total costs in both the groups were attributable to the cost for hospitalization and rehabilitation. In addition, because of the high cost of NOACs, the mean prescription cost for patients treated with NOACs was USD 102 (JPY 10,487), which was significantly higher than that incurred in warfarin treatment (USD 16 or JPY 1599) ($p < 0.001$). On the other hand, the mean laboratory test cost for NOAC-treated patients was significantly lower and the procedure cost for NOAC-treated patients tended to decrease compared with those for warfarin-treated patients ($p = 0.022$ and $p = 0.073$, respectively). The hospitalization cost for patients treated with NOACs (USD 3966 ± 3366 or JPY 408,526 ± 346,681) was lower than that for patients treated with warfarin (USD 119 ± 3339 or JPY 527,278 ± 343,907) ($p = 0.026$), but it could be due to the nearly 1-week longer LOS for warfarin-treated patients.

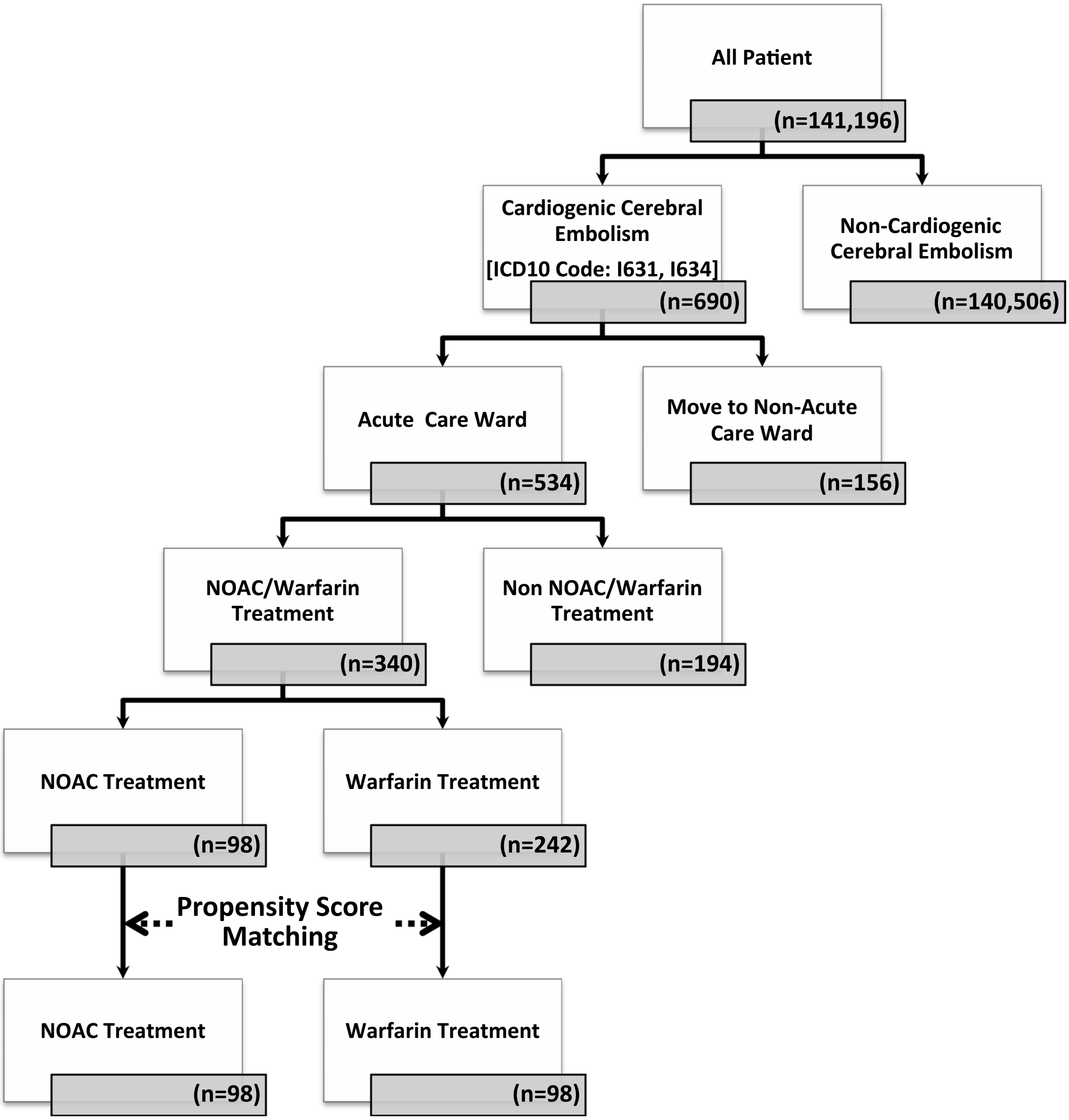


**Fig. 1** Patient disposition in this study

## Discussion

Warfarin has been widely used for treating patients with cerebral embolism and for preventing recurrence [9–11]. However, after the approval of the use of NOACs and its easy availability, the number of patients opting for NOAC treatment has been steadily increasing in Japan. In the present study, we noted the same trend (Supplemental Figure 1), and this may be one of the reasons for the publishing of new treatment guidelines for NVAF in 2013 [20].

In the present study, we demonstrated two main merits regarding the use of NOACs: comparatively shorter LOS and lower medical expenditure. In addition, our stratified proportional hazard analysis revealed that NOAC treatment contributes to shortening of LOS. Farr et al. [21] and Laliberte et al. [22] reported that LOS for patient receiving apixaban and rivaroxaban treatment were shorter than that for patients receiving warfarin treatment, which agrees with the results of our study. However, the LOS difference between NOAC and warfarin treatments in our study (of approximately 6.5 days) was greater than that between apixaban/rivaroxaban and warfarin treatments (1 day/0.8 days) in the study by Farr et al. and Laliberte et al. Generally, LOS in patients in Japan is longer than that of patients in other countries as both treatment at the acute phase and patient rehabilitation are conducted in the same hospital. Owing to

**Table 1** Patient background for the non-matched group (before matching) and propensity score matched group (after matching)

| Factor | Group *n* | Non-matching | | | Propensity score matching (1:1) | | |
|---|---|---|---|---|---|---|---|
| | | Warfarin | NOAC | *p* value | Warfarin | NOAC | *p* value |
| | | 242 | 98 | | 98 | 98 | |
| *Demography* | | | | | | | |
| Gender (%) | Female | 118 (48.8) | 41 (41.8) | 0.281 | 42 (42.9) | 41 (41.8) | 1 |
| | Male | 124 (51.2) | 57 (58.2) | | 56 (57.1) | 57 (58.2) | |
| Age (%) | ≥ 75 yr. | 162 (66.9) | 51 (52.0) | 0.013 | 55 (56.1) | 51 (52.0) | 0.667 |
| *Complications* | | | | | | | |
| Diabetes (%) | | 40 (16.5) | 7 (7.1) | 0.024 | 12 (12.2) | 7 (7.1) | 0.334 |
| Heart Failure (%) | | 41 (16.9) | 8 (8.2) | 0.041 | 11 (11.2) | 8 (8.2) | 0.63 |
| Hypertension (%) | | 121 (50.0) | 42 (42.9) | 0.281 | 48 (49.0) | 42 (42.9) | 0.474 |
| TIA_Cerebral Infarction (%) | | 7 (2.9) | 3 (3.1) | 1 | 5 (5.1) | 3 (3.1) | 0.721 |
| *Baseline scores* | | | | | | | |
| CHADS2_Score (%) | 0 | 36 (14.9) | 28 (28.6) | 0.027 | 22 (22.4) | 28 (28.6) | 0.63 |
| | 1 | 81 (33.5) | 34 (34.7) | | 29 (29.6) | 34 (34.7) | |
| | 2 | 85 (35.1) | 29 (29.6) | | 38 (38.8) | 29 (29.6) | |
| | 3 | 34 (14.0) | 6 (6.1) | | 6 (6.1) | 6 (6.1) | |
| | 4 | 5 (2.1) | 1 (1.0) | | 2 (2.0) | 1 (1.0) | |
| | 5 | 1 (0.4) | 0 (0.0) | | 1 (1.0) | 0 (0.0) | |
| JCS (%) | ≥ 30 | 27 (11.2) | 5 (5.1) | 0.101 | 2 (2.0) | 5 (5.1) | 0.445 |
| Modified Ranckin Scale (%) | Mild (0, 1) | 87 (36.0) | 62 (63.3) | < 0.001 | 57 (58.2) | 62 (63.3) | 0.708 |
| | Moderate (2, 3) | 47 (19.4) | 11 (11.2) | | 13 (13.3) | 11 (11.2) | |
| | Severe (4, 5) | 100 (41.3) | 20 (20.4) | | 25 (25.5) | 20 (20.4) | |
| | Unknown | 8 (3.3) | 5 (5.1) | | 3 (3.1) | 5 (5.1) | |
| *Pre-treatment* | | | | | | | |
| t.PA (tissue plasminogen activator) (%) | | 27 (11.2) | 14 (14.3) | 0.463 | 11 (11.2) | 14 (14.3) | 0.669 |
| Edaravone (%) | | 145 (59.9) | 66 (67.3) | 0.219 | 66 (67.3) | 66 (67.3) | 1 |
| Heparin (%) | | 160 (66.1) | 71 (72.4) | 0.305 | 69 (70.4) | 71 (72.4) | 0.874 |
| Oral antiplatelet drug (%) | | 13 (5.4) | 7 (7.1) | 0.611 | 4 (4.1) | 7 (7.1) | 0.537 |
| *Pre-treatment information* | | | | | | | |
| Ambulance (%) | | 159 (65.7) | 54 (55.1) | 0.083 | 60 (61.2) | 54 (55.1) | 0.469 |
| Time since | ≤ 3 Days | 234 (96.7) | 95 (96.9) | | 96 (98.0) | 95 (96.9) | |
| Cerebral embolism attack (%) | 4–7 Days | 6 (2.5) | 0 (0.0) | 0.092 | 0 (0.0) | 0 (0.0) | 1 |
| | ≥ 8 Days | 2 (0.8) | 2 (2.0) | | 2 (2.0) | 2 (2.0) | |
| | Asymptomatic | 0 (0.0) | 1 (1.0) | | 0 (0.0) | 1 (1.0) | |
| Re-hospitalization (%) | | 13 (5.4) | 2 (2.0) | 0.247 | 1 (1.0) | 2 (2.0) | 1 |
| *Site* | | | | | | | |
| Site (%) | A | 40 (16.5) | 2 (2.0) | NA | 0 (0.0) | 2 (2.0) | 0.805 |
| | B | 17 (7.0) | 16 (16.3) | | 11 (11.2) | 16 (16.3) | |
| | C | 4 (1.7) | 2 (2.0) | | 2 (2.0) | 2 (2.0) | |
| | D | 12 (5.0) | 8 (8.2) | | 8 (8.2) | 8 (8.2) | |
| | E | 49 (20.2) | 25 (25.5) | | 28 (28.6) | 25 (25.5) | |
| | F | 13 (5.4) | 14 (14.3) | | 11 (11.2) | 14 (14.3) | |
| | G | 62 (25.6) | 8 (8.2) | | 7 (7.1) | 8 (8.2) | |
| | H | 1 (0.4) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| | I | 30 (12.4) | 16 (16.3) | | 23 (23.5) | 16 (16.3) | |
| | J | 8 (3.3) | 6 (6.1) | | 5 (5.1) | 6 (6.1) | |
| | K | 1 (0.4) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| | L | 3 (1.2) | 1 (1.0) | | 3 (3.1) | 1 (1.0) | |
| | M | 2 (0.8) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |

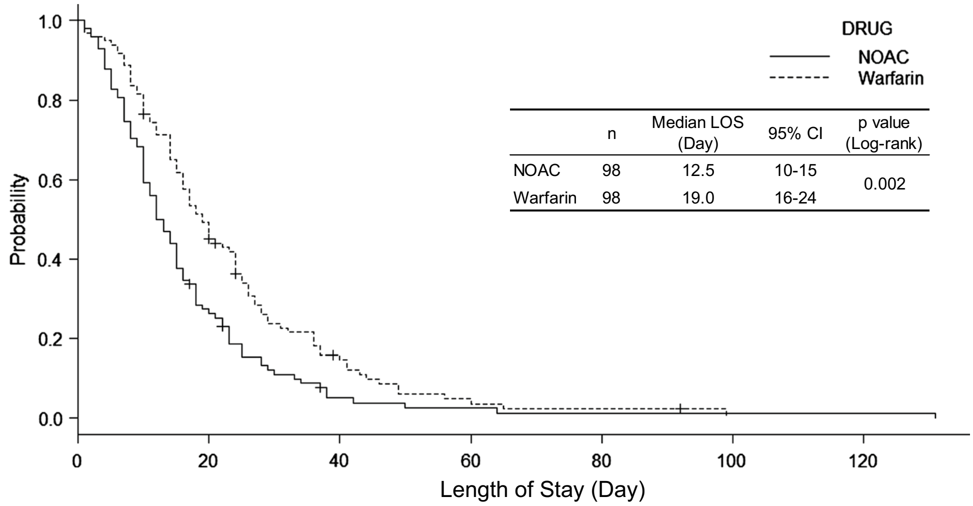


**Fig. 2** Kaplan-Meier curve for length of stay of NOAC/warfarin treatment patient with cardiogenic cerebral embolism matched by propensity score

**Table 2** Results of stratified proportional hazard regression analysis for patients matched by propensity socre

| Factor | | Hazard ratio | 95% CI (Lower–Upper) | *p* value |
|---|---|---|---|---|
| Treatment | NOAC | 3.924 | (1.034–14.9) | 0.04460 |
| Gender | Female | 0.5494 | (0.1859–1.623) | 0.2786 |
| Age | ≥ 75 years | 0.2381 | (0.06593–0.8596) | 0.02845 |
| JCS (Japan Coma Scale) | ≥ 30 | 0.1515 | (0.01569–1.464) | 0.1030 |
| FY_2012 | | 3.672 | (0.1616–83.46) | 0.4144 |
| RankinScale | Mild (0, 1) | 0.1523 | (0.00788–2.945) | 0.2130 |
| | Moderate (2, 3) | 1.034 | (0.05963–17.94) | 0.9815 |
| | Severe (4, 5) | 0.06933 | (0.00486–0.9899) | 0.04913 |
| Complication | TIA_Cerebral Infarction | 8.530 | (0.2273–320.1) | 0.2465 |
| | Hypertension | 3.820 | (0.962–15.17) | 0.05679 |
| | Heart Failure | 0.9122 | (0.09903–8.403) | 0.9354 |
| | Diabates | 1.884 | (0.3413–10.39) | 0.4675 |
| Time since | 0–3 Days | 0.0000294 | (0–Inf) | 0.9994 |
| Cerebral embolism attack | 4–7 Days | NA | (NA–NA) | NA |
| | 8–Days | 0.00004149 | (0–Inf) | 0.9995 |
| | Ambulance Use | 0.5152 | (0.08918–2.977) | 0.4586 |
| | Re-Hospitalization | 25.45 | (0.506–1280) | 0.1054 |
| Pretreatment | t-PA | 0.2139 | (0.02591–1.766) | 0.1521 |
| | Heparin | 0.2913 | (0.08471–1.002) | 0.05028 |
| | Edaravone | 0.6371 | (0.1291–3.143) | 0.5798 |
| | Treatment Duration | 1.097 | (1.003–1.199) | 0.04337 |
| Site | A | 291,600,000 | (0–Inf) | 0.9989 |
| | B | 12.13 | (0.2241–656.7) | 0.2204 |
| | C | 1887 | (2.284–1,559,000) | 0.02774 |
| | D | 0.5102 | (0.00562–46.34) | 0.7699 |
| | E | 4.245 | (0.06912–260.6) | 0.4914 |
| | F | 46.14 | (0.6755–3152) | 0.07541 |
| | G | 11.46 | (0.1153–1138) | 0.2986 |
| | H | NA | (NA–NA) | NA |
| | I | 23.17 | (0.5444–986.5) | 0.1005 |
| | J | 6.441 | (0.1049–395.6) | 0.3753 |
| | K | NA | (NA–NA) | NA |
| | L | NA | (NA–NA) | NA |

This analysis was conducted by stratified proportional hazard regression model

**Table 3** Results of medical cost (USD) for patients treated with NOACs or warfarin matched by the propensity score

| | Warfarin ($n=98$) | NOAC ($n=98$) | $p$ value |
|---|---|---|---|
| Total | 8950 ± 5891 | 7151 ± 6228 | 0.054 |
| Examination | 123 ± 97 | 103 ± 62 | 0.077 |
| Prescription | 142 ± 144 | 218 ± 123 | < 0.001 |
| Warfarin/NOAC | 16 ± 41 | 102 ± 74 | <0.001 |
| Others | 127 ± 127 | 116 ± 103 | 0.531 |
| Injection | 462 ± 582 | 412 ± 781 | 0.623 |
| Procedure | 126 ± 212 | 66 ± 250 | 0.073 |
| Operation | Not applicable | Not applicable | – |
| Test | 297 ± 301 | 203 ± 243 | 0.022 |
| Imaging | 265 ± 279 | 228 ± 306 | 0.405 |
| Other | 2008 ± 1902 | 1676 ± 1693 | 0.235 |
| Hospitalization | 5119 ± 3339 | 3966 ± 3366 | 0.026 |
| Food | 406 ± 331 | 278 ± 215 | 0.003 |

Data are expressed as mean ± SD (Standard Deviation)

Other: Including Rehabilitation Cost

this situation, LOSs for patients treated with NOACs and warfarin in our study were 12.5 days and 19.0 days, respectively, whereas they were shorter by almost 10 days in other studies. In our study, age (≥ 75 years), Rankin scale score (4 or 5), pre-treatment duration, and site C were also significantly correlated to LOS; these were the result of stratified proportional hazard analysis. However, we found that LOS was less probably as a result of NOAC treatment because no significant differences were obtained between NOAC-treated patients and warfarin-treated patients for other tested factors.

Some reports regarding difficulties in dose setting and adjustment as well as in the control of anti-coagulant activity indicate that adequate treatment for patients needing anti-coagulants may not be always provided [23, 24]. In the present study, although we did not discuss detailed data, after NOAC/warfarin treatment, the prothrombin time (PT) test results for patients treated with warfarin was significantly different from that for patients treated with NOACs, whereas the PT test results conducted before NOAC/warfarin treatment was similar. Finding an appropriate dose for warfarin is difficult, which may explain the difference in LOS between NOAC and warfarin treatments.

We employed PS matching method [25, 26] to obtain well-balanced patient backgrounds between patients in the NOAC- and warfarin-treated groups. As shown in Table 1, more patients with a CHADS2 score of > 2 and/or with modified Rankin score of 4 or 5 were treated with warfarin. The median LOS for patients treated with warfarin on non-matching data was 20 days, which is longer than that after PS matching (median LOS: 19 days). Therefore, although data from several patients were unavailable, the PS matching method was found to be useful for assessing and comparing LOS between warfarin and NOAC treatments.

In recent years, several pharmacoeconomic studies have compared NOAC with warfarin, and more recently, a comprehensive review was published on the same topic [27]. Most of these reports found NOACs to be more cost effective than warfarin for clinical use. In Japan, available results of clinical studies are still limited [28–31], but their results of cost-effectiveness have been shown to be similar to that in other countries. According to Kansal et al. [32] treatment costs with dabigatran was less than that with warfarin. Generally, these past studies were conducted using 2–3 year data and/or simulating patient clinical scenarios based on past results. In contrast, we focused on inpatient data only, so that we could assess outcomes such as hospitalization period and resources with the use of NOACs or warfarin. From the perspective of hospital management, shorter LOS can enable the treatment of more patients.

From the point of view of medical cost, the prescription cost for NOAC-treated patients was higher than that for warfarin-treated patients in the present study. On the other hand, the costs for laboratory tests and hospitalization with NOAC treatment was significantly lower than those with warfarin treatment. For other costs including the gross cost of prescription (i.e., cost of NOAC/warfarin plus other prescription drugs), injection, and imaging examination conducted per hospitalization, no significant difference were noted between the two groups. However, the laboratory test cost for warfarin-treated patients was greater than that for NOAC-treated patients. Hospitalization cost for patients treated with warfarin could be greater because of the longer hospitalization period required due to the frequent testing of blood coagulation activity. Thus, the total cost for NOAC treatment tended to be lower than that for warfarin treatment.

There are some limitations in our study. First, our examination and analysis were conducted in only 13, middle-sized, acute care hospitals with less than 200 beds. Therefore, it is difficult to generalize our results to a larger population. Detailed analysis using data from other hospitals would be needed in the future. Second, we calculated the PS using background data of several patients. However, it was calculated based on the reported values only, and we did not consider other potentially confounding factors.

## Conclusion

Although some limitations were identified, we demonstrated a meaningful comparison of oral anti-coagulants for cerebral embolism in adult patients using real world data in Japan. Generally, the cost of NOACs is higher than that of warfarin, but the NOACs are beneficial for patients from the perspective of lower LOS and medical cost during hospitalization.

In the future, we plan to undertake cost-effectiveness analysis with reference to the results of the present study.

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**Conflicts of interest** Tomohide Akase has no conflicts of interest to declare. Masami Morita (M.M) was an employee at Shionogi & Co., Ltd at the time of performing this research. Takanori Tsuchiya (T.T) is an employee for Pfizer Japan Inc. However, the roles of M.M and T.T in these companies were not related to this research at the time of conducting the research.

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