Incidence of stroke, systemic embolism and bleeding events in patients without anticoagulation based on real-world data in Japan: a retrospective cohort study

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ABSTRACT

Objectives To examine the incidence of stroke or systemic embolic events (SSEs) and bleeding events in untreated patients with non-valvular atrial fibrillation (NVAF) after widespread use of direct oral anticoagulant agents (DOACs).

Design Multicentre, non-interventional, observational, retrospective cohort study using real-world data in Japan (2016-2018).

Setting The Mie, Musashino University study of NVAF, which used the Mie-Life Innovation Promotion Center Database. This is a regional clinical database involving one university hospital and eight general hospitals in Mie Prefecture in Japan.

Participants Japanese patients with NVAF (n=7001).

Primary and secondary outcome The incidence of SSEs and bleeding events.

Results A total of 7001 patients with NVAF were registered, and 53.0% were treated with DOACs, 10.6% were treated with warfarin and 36.4% had no treatment. Additionally, 29.5% of patients with a CHADS2 (congestive heart failure, hypertension, age≥75 years, diabetes, previous stroke or transient ischemic attack) score of 3–6 were untreated. In the no treatment group, the SSE rates by the CHADS2 score (0, 1, 2 and 3–6) in the no treatment group were 0.7%, 1.0%, 1.2% and 2.9%, respectively. A multivariate analysis of SSEs in components of the CHADS2 showed that the adjusted HRs were 2.32 for heart failure, 1.66 for an age ≥75 years, 1.81 for diabetes mellitus and 5.84 for prior stroke or transient ischaemic attack.

Conclusions Approximately one-third of the patients do not receive any anticoagulation in the modern DOAC era in Japan. The SSE rate increases by the CHADS2 score. The SSE rate is low in patients with a CHADS2 score <1, supporting no indication of anticoagulation in current guidelines. In patients with a CHADS2 score ≥1, the use of anticoagulant drug therapy is recommended because of a higher risk of stroke.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This large-scale analysis of the Mie-Life Innovation Promotion Center Database (Mie-LIP DB) provides important information on the real-world population in 2550 patients with NVAF with no anticoagulant therapy.

⇒ This study examined the incidence of SSEs and bleeding events after widespread use of direct oral anticoagulant agents using real-world data in Japan.

⇒ This study was restricted to Japanese patients, which may limit the generalisability of the data to patient populations of other races.

⇒ This study has non-randomised data.

⇒ We could not obtain important confounders of the specific types of NVAF (paroxysmal/persistent/permanent) or the duration of NVAF and lifestyle habits, such as smoking and drinking, were not available from the Mie-LIP DB.

INTRODUCTION

In recent years, Japan’s population has been ageing rapidly, and the number of people aged 75 years or older will reach 18% of the total population by 2025 and 27% by 2060. The incidence of non-valvular atrial fibrillation (NVAF) increases with age.

The CHADS2 score (CHADS2 scoring system assigning 1 point each for congestive heart failure, hypertension, age ≥75 years and diabetes mellitus, and 2 points for prior stroke or transient ischaemic attack) is the most popular tool to estimate the individual stroke risk. Oral anticoagulation is recommended as the standard therapy for patients with NVAF with a CHADS2 score ≥2.

The antithrombotic agents used for preventing stroke in NVAF are oral anticoagulants, especially vitamin K antagonists and direct oral anticoagulant agents (DOACs). In Japan, dabigatran etexilate methanesulfonate
(dabigatran) was introduced for preventing stroke in 2011,6 followed by rivaroxaban in 2012,7 apixaban in 2013 8 and edoxaban tosilate hydrate (edoxaban) in 2014.9 Generically, data of these clinical trials were limited. Therefore, many pharmacoepidemiological studies based on real-world data surveys and case registries using medical information derived from receipt information, Diagnosis Procedure Combination information, the National Database and electronic medical records have been conducted to supplement them.10 The use of DOACs is expanding rapidly, but observational data on the background and clinical outcomes of patients are limited, and there are still some patients who are not receiving anticoagulation therapy. Therefore, we started the Mie, Musashino University study of non-valvular atrial fibrillation (MIE-MU-NV AF) in collaboration with Musashino University to analyse the actual use, and the rate of SSEs and bleeding events of anticoagulation therapy using the Mie-Life Innovation Promotion Center Database (Mie-LIP DB) was managed by Mie University. This study aimed to examine the background, rate of SSEs and bleeding events in patients with NVAF who are not being treated.

**METHODS**

**Study design**

Using the Mie-LIP DB managed by Mie University, we conducted a multicentre, non-interventional, observational, retrospective cohort study. We extracted medical records of patients with newly diagnosed NVAF from a cohort of patients who had inpatient and outpatient prescription records over a 3-year period from January 2016 to December 2018. We also investigated medical records to collect data of the patients’ background, treatment status, and comorbidities.

**Data source**

The Mie-LIP DB is a database of medical information derived from electronic medical records managed by Mie University, Mie Prefecture, Mie University Hospital and core hospitals in the region are collaborating and cooperating with this project (online supplemental figure 1). With the agreement of the patients, some medical information from the electronic medical records and Diagnosis Procedure Combination information of the participating medical institutions are shared using Standardized Structured Medical Information eXchange V.2, which is a standardised standard of the Ministry of Health, Labour and Welfare. This is performed to collect the names of diseases, prescriptions and injections, laboratory data and other medical information. As of the end of December 2018, nine hospitals are participating in this project. The project was originally launched to support emergency medical treatment when medical institutions lose their medical records due to disaster. Under normal conditions, the collected medical information is anonymised (personal information is removed) to create a database that can be aggregated and analysed and is used to improve the quality of medical care and to develop future medical care. The Mie-LIP DB is an electronic medical record database that can obtain information tailored to the situation of each patient because it is real-world data that uses part of the medical record data in daily practice.

**Study population**

Eligible patients had a confirmed new diagnosis of NVAF in the Mie-LIP DB during the study period (1 January 2016 to 31 December 2018) and had medical information for at least 180 days after the start date of follow-up (the date when the first inpatient or outpatient record exists). Patients whose evaluable event occurred within 180 days were included in the study. The exclusion criteria were stroke, systemic embolism or haemorrhagic events within 30 days before the start date of follow-up (including the
day of follow-up) or the start and end dates of follow-up were the same day.

**Study variables**

Clinical data of eligible patients were obtained from the Mic-LIP DB. Baseline data included sex, age, weight, serum creatinine concentrations and the presence of a prior medical history (hypertension, diabetes mellitus, congestive heart failure, prior stroke or transient ischaemic attack (TIA, vascular disease and prior gastrointestinal bleeding). The CHADS2 score is defined in the 10th Revision International Classification of Diseases codes as follows: C, congestive heart failure (I50, I11.0, I13.0, I13.2); H, hypertension (I10–I15, O14.0, O14.1); A, age, ≥75 years; D, diabetes mellitus (E10–E14) and S, prior stroke or TIA (I63, G45).

To understand the treatment status of patients with NVAF, the following data were collected: NVAF drug treatment, warfarin medication, DOAC medication, DOAC treatment group (high dose, low dose and under dose (an inappropriate low dose was provided to patients who did not meet the criteria for a low dose, but were treated with a low dose)), aspirin medication and ADP inhibitor medication.

The primary endpoint was the incidence of SSEs during the observation period. The secondary endpoint was the incidence of bleeding events (bleeding requiring blood transfusion, intracranial haemorrhage, intracranial haemorrhage, upper gastrointestinal bleeding and lower gastrointestinal bleeding) during the observation period. We obtained data on SSEs, the presence of bleeding events, the time from the start to the final record and the time from observation to onset/censoring. SSEs and bleeding events (haemorrhage requiring transfusion, intracranial haemorrhage, intracranial haemorrhage,

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**Table 1** Total patients' characteristics

| Total (n=7001) | CHADS2 score (n=1785) | 1 (n=2005) | 2 (n=1005) | 3–6 (n=2328) |
|----------------|----------------------|-------------|-------------|--------------|
| Men            | 4142 (59.2)          | 593 (67.2)  | 1120 (62.7) | 1122 (56.0)  | 1307 (56.1)   |
| Age, years     | 74.9±12.0            | 62.2±11.6   | 72.8±11.6   | 77.1±10.5    | 79.3±9.5      |
| <65            | 1160 (16.6)          | 397 (45.0)  | 371 (20.8)  | 225 (11.2)   | 167 (7.2)     |
| 65 to<75       | 1861 (26.6)          | 486 (55.0)  | 620 (34.7)  | 422 (21.0)   | 333 (14.3)    |
| ≥75 to<80      | 1263 (18.0)          | 0 (0.0)     | 254 (14.2)  | 452 (22.5)   | 557 (23.9)    |
| ≥80            | 2717 (38.8)          | 0 (0.0)     | 540 (30.3)  | 906 (45.2)   | 1271 (54.8)   |
| Weight, kg     | 60.4±15.6            | 62.3±12.8   | 61.5±15.1   | 59.8±15.8    | 59.3±16.6     |
| ≤60            | 3772 (55.5)          | 394 (45.9)  | 883 (51.1)  | 1129 (58.2)  | 1366 (60.2)   |
| >60            | 3027 (44.5)          | 465 (54.1)  | 846 (48.9)  | 812 (41.8)   | 904 (39.8)    |
| CrCL (mL/min)  | 59.6±26.0            | 74.7±39.0   | 63.4±23.9   | 57.1±22.2    | 53.3±21.45    |
| <30            | 538 (8.7)            | 14 (1.8)    | 92 (5.8)    | 160 (9.1)    | 272 (12.9)    |
| 30 to<50       | 1636 (26.3)          | 67 (8.8)    | 339 (21.3)  | 513 (29.2)   | 717 (34.0)    |
| 50 to<80       | 3062 (49.3)          | 458 (59.9)  | 865 (54.9)  | 852 (48.5)   | 887 (42.1)    |
| ≥80            | 979 (15.8)           | 226 (29.5)  | 292 (18.4)  | 230 (13.1)   | 231 (11.0)    |
| Hypertension   | 4011 (57.3)          | 0 (0.0)     | 637 (35.7)  | 1429 (71.3)  | 1945 (83.5)   |
| Diabetes mellitus | 2281 (32.6)      | 0 (0.0)     | 284 (15.9)  | 663 (33.1)   | 1334 (57.3)   |
| Heart failure | 1422 (20.3)          | 0 (0.0)     | 70 (3.9)    | 322 (16.1)   | 1030 (44.2)   |
| Stroke/TIA    | 1137 (16.2)          | 0 (0.0)     | 0 (0.0)     | 119 (5.9)    | 1018 (43.7)   |
| Vascular disease | 1213 (17.3)      | 56 (3.6)    | 220 (12.3)  | 348 (17.4)   | 589 (25.3)    |
| GI bleeding   | 75 (1.1)             | 7 (0.8)     | 21 (1.2)    | 18 (0.9)     | 29 (1.2)      |
| Aspirin use   | 759 (10.8)           | 32 (3.6)    | 126 (7.1)   | 212 (10.6)   | 389 (16.7)    |
| ADPR inhibitor use | 544 (7.8)   | 26 (2.9)    | 98 (5.5)    | 144 (7.2)    | 276 (11.9)    |

Values are mean±SD or n (%).

CHADS2 score, scoring system assigning one point each for congestive heart failure, hypertension, age≥75 years, and diabetes mellitus, and two points for prior stroke or transient ischaemic attack;

ADPR, adenosine diphosphate receptor; CrCL, creatinine clearance; DOAC, direct oral anticoagulant; GI, gastrointestinal; HD, high dose; LD, low dose; TIA, transient ischaemic attack; UD, under dose (patients who did not meet the criteria for a low dose, but were treated with a low dose).
upper gastrointestinal haemorrhage and lower gastrointestinal haemorrhage) were defined according to previously reported methods for validation11 12 (online supplemental table 1).

### Statistical analysis

Descriptive statistics were used to summarise the data. Categorical variables are expressed as the frequency (percentage) and quantitative variables as the mean and SD. Descriptive statistics were calculated for each group using the full analysis set (FAS). The FAS included patients who did not violate the inclusion/exclusion criteria and for whom laboratory results and information necessary for the primary endpoint were available. Analyses of primary and secondary endpoints were performed in the FAS. The incidence rates of SSEs and bleeding events were calculated for each group, and their 95% CIs were calculated for the FAS. A multivariate Cox regression analysis was performed to determine the independent risk factors for SSEs. All analyses were performed using EZR (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).13

### Table 2  Characteristics of patients in the no treatment group by the CHADS2 score

| CHADS2 score | Total (n=2550) | 0 (n=460) | 1 (n=712) | 2 (n=692) | 3–6 (n=686) |
|--------------|----------------|-----------|-----------|-----------|-------------|
| **Men**      |                |           |           |           |             |
| Age, years   | 1474 (57.8)    | 292 (63.5) | 434 (61.0) | 378 (54.6) | 370 (53.9)  |
| <65          | 75.4±12.7      | 61.7±12.39 | 74.9±11.7 | 79.1±10.2 | 81.4±8.8    |
| 65 to<75     | 413 (16.2)     | 202 (43.9) | 122 (17.1) | 58 (8.4)  | 31 (4.5)    |
| 75 to<80     | 653 (25.6)     | 258 (56.1) | 202 (28.4) | 117 (16.9) | 76 (11.1)   |
| ≥80          | 412 (16.2)     | 0 (0.0)    | 107 (15.0) | 154 (22.3) | 151 (22.0)  |
| Weight, kg   | 60.0±15.3      | 62.3±13.1  | 60.8±15.0 | 58.9±15.6 | 58.8±16.5   |
| ≤60          | 1415 (57.1)    | 208 (46.6) | 369 (53.9) | 408 (60.7) | 430 (63.8)  |
| >60          | 1062 (42.9)    | 238 (53.4) | 316 (46.1) | 264 (39.3) | 244 (36.2)  |
| CrCL (mL/min)| 59.0±30.3      | 76.4±49.6  | 60.7±23.0 | 54.2±21.3 | 50.7±21.7   |
| <30          | 203 (9.7)      | 10 (2.7)   | 41 (7.0)  | 63 (11.4) | 89 (15.5)   |
| 30 to<50     | 563 (27.0)     | 28 (7.5)   | 144 (24.6) | 178 (32.2) | 213 (37.0)  |
| 50 to<80     | 1007 (48.2)    | 223 (59.6) | 316 (53.9) | 254 (45.9) | 214 (37.2)  |
| ≥80          | 315 (15.1)     | 113 (30.2) | 85 (14.5)  | 58 (10.5)  | 59 (10.3)   |
| Hypertension | 1275 (50.0)    | 0 (0.0)    | 198 (27.8) | 511 (73.8) | 566 (82.5)  |
| Diabetes mellitus | 720 (28.2) | 0 (0.0)    | 111 (15.6) | 203 (29.3) | 406 (59.2)  |
| Heart failure | 357 (14.0)    | 0 (0.0)    | 15 (2.1)  | 89 (12.9) | 253 (36.9)  |
| Stroke/TIA   | 325 (12.7)     | 0 (0.0)    | 0 (0.0)   | 32 (4.6)  | 293 (42.7)  |
| Vascular disease | 366 (14.4) | 27 (5.9)   | 78 (11.0) | 104 (15.0) | 157 (22.9)  |
| GI bleeding  | 25 (1.0)       | 4 (0.9)    | 7 (1.0)   | 5 (0.7)   | 9 (1.3)     |
| Aspirin use  | 194 (7.6)      | 10 (2.2)   | 43 (6.0)  | 57 (8.2)  | 84 (12.2)   |
| ADPR inhibitor use | 145 (5.7) | 9 (2.0)    | 39 (5.5)  | 34 (4.9)  | 63 (9.2)    |

Values are mean±SD or n (%).

CHADS2 score, scoring system assigning one point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and two points for prior stroke or transient ischaemic attack.

ADPR, adenosine diphosphate receptor; CrCL, creatinine clearance; GI, gastrointestinal; TIA, transient ischaemic attack.

Figure 2  (A). Kaplan-Meier curves for the cumulative incidence of SSEs. (B) Kaplan-Meier curves for the cumulative incidence of bleeding events. SSEs, stroke or systemic embolic events.
Patients’ characteristics

The characteristics of the 7001 patients with NAVF are shown in Table 1. The mean CHADS2 score was 2.00±1.30, and the mean age was 74.9±12.0 years. Hypertension (57.3%) was the most common comorbidity, 32.6% of the patients had diabetes mellitus, 20.3% had heart failure and 16.2% had a history of stroke or TIA. We examined the patients’ background (Table 2) in the 2550 patients in the no treatment group, which accounted for 36.4% of the total patient population. The mean CHADS2 score was 1.76±1.29, and the mean age was 75.4±12.7 years. Hypertension (50.0%) was the most common comorbidity, 28.2% of the patients had diabetes mellitus, 14.0% had heart failure and 13.7% had a history of stroke or TIA. The percentages of patients with CHADS2 scores of 0, 1, 2 and 3–6 were 18.0%, 27.9%, 27.1% and 26.9%, respectively.

Table 3

Multivariate Cox regression analysis with components of the CHADS2 score for SSEs

| Variable                      | HR   | 95% CI  |
|-------------------------------|------|---------|
| Heart failure                 | 2.32 | 1.44 to 3.75 |
| Hypertension                  | 1.32 | 0.86 to 2.03 |
| Age ≥75 years                 | 1.66 | 1.11 to 2.47 |
| Diabetes mellitus             | 1.81 | 1.20 to 2.72 |
| Prior stroke or TIA           | 5.84 | 3.89 to 8.75 |

CHADS2 (congestive heart failure, hypertension, age≥75 years, diabetes, previous stroke or transient ischemic attack) score

SSEs, stroke or systemic embolic events; TIA, transient ischaemic attack.

Ethics

This study was an observational study that did not use human biological specimens. Therefore, written informed consent was not obtained from each patient for their clinical records to be used in this study, in accordance with the ethical guidelines by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan. We have published all relevant details regarding this study to be carried out and have provided each patient the opportunity to refuse inclusion in this study by posting the details at the homepages of institutions. Because consent was not obtained, patient records and information were anonymised and deidentified before the analysis.

Patient and public involvement statement

Patients and the public were not involved in the development of this study cohort.

Registration

This study was non-interventional, observational, retrospective cohort study.

RESULTS

There were 7001 patients who were diagnosed with NAVF in the patient cohort who had inpatient and outpatient prescription records from January 2016 to December 2018. The mean and median follow-up times were 396.7 days and 350 days, respectively. Treatment for NVAF in these patients consisted of DOAC treatment in 53.0% (3712), warfarin treatment in 10.6% (739) and no treatment in 36.4% (2550). DOAC treatment consisted of the following: high dose, 36.1% (1339); low dose, 34.1% (1266) and under dose, 29.8% (1266). The percentage of each treatment by the CHADS2 score is shown in Figure 1. As the CHADS2 score increased, the percentage of having no treatment decreased, and low-dose DOACs, under-dose DOACs and warfarin treatment increased.

DISCUSSION

In Japan, the J-RHYTHM registry, the Shinken database, the FUSHIMI AF registry and the SAKURA AF registry were reported from 2011 to 2014. With regards to the patients’ background in the MIE-MU-NVAF study and the FUSHIMI AF registry, their mean age was 74.9 years versus 74.2 years, the rate of hypertension was 57.3% versus 60.6%, the rate of diabetes mellitus was 32.6% versus 23.2% and the rate of stroke/TIA was 16.2% versus 21.9%. As a result, the mean CHADS2 score was 2.09 versus 2.00. Although the MIE-MU-NVAF study and the FUSHIMI AF registry differed in terms of the region, number of hospitals and size, the patients’ background was similar between the MIE-MU-NVAF study and the FUSHIMI AF registry.
The Japanese Circulation Society 2013 guidelines for the Treatment of Atrial Fibrillation (drugs) recommend anticoagulation with dabigatran, rivaroxaban, apixaban, edoxaban and warfarin for a CHADS2 score of ≥2 (class 1A). These guidelines recommend dabigatran (class 1B), apixaban (class 1A), edoxaban (class IIa-B) and warfarin (class IIa-B) for a CHADS2 score of 1. The European Society of Cardiology 2010 guidelines for the management of AF emphasise the use of the CHA2DS2-VASc-score (age (65–74 years), vascular disease and female sex). An integrated analysis of atrial fibrillation registry studies in Japan showed that additional factors in the CHA2DS2-VASc score were not significant risk factors for stroke or systemic embolism events in Japanese patients who had not received antiagulation therapy. The Japanese Circulation Society 2013 guidelines were revised in 2020. These guidelines were judged appropriate to base the risk assessment of Japanese patients on the CHADS2 score. ≥1.20

In the FUSHIMI AF registry, 2% of patients took DOACs in 2011 and 26% took them in 2015. CHADS2 scores of 1, 2 and 3–6 in untreated patients in the FUSHIMI AF registry were 55%, 46% and 37%, respectively, in 2011, and decreased to 38%, 34% and 30% in 2015. In the MIE-MU-NVAF study, these rates were 39.9%, 34.5% and 29.5%, respectively. These findings suggest that although DOACs have been introduced and their use is expanding, a certain percentage of patients remain untreated.

In an integrated analysis of atrial fibrillation registry studies in Japan, the annual incidence of cerebral infarction in anticoagulation-naive patients according to each CHADS2 score (0–6) was 0.5%, 0.9%, 1.5%, 2.7%, 6.1%, 3.9% and 7.2%, respectively. In the MIE-MU-NVAF study, incidence of SSEs was 1.4%, 1.4%, 3.2% and 8.0% for CHADS2 scores of 3–6 points, respectively. The primary event incidence tended to be higher in this study than that in the integrated analysis. One reason for this difference between studies could be the difference in the patients’ background, especially age. The mean age of patients in the present study was 74.9 years, while that in the integrated analysis was 68.1 years. The previous integrated analysis also compared the event incidence rate by age and showed the following: 0.69% for those aged <65 years, 0.98% for those aged 65–74 years and 2.45% for those aged ≥75 years, with events 3.37 times higher in those aged ≥75 years than in those aged <65 years. A recent study showed the efficacy of DOACs in older patients who were not eligible for standard dosage and administration owing to concerns about the risk of bleeding. The incidence of SSEs was 6.7% in the placebo group. A Korean cohort study extracted data on 10,846 patients with newly diagnosed NVAF who were naive to oral anticoagulants. This previous study reported that the annual incidence rates of ischaemic stroke according to CHADS2 scores of 2, 3 and ≥4 were 2.77%, 4.64% and 15.2%, respectively. The ChiOTEAF registry, which extracted data on 6416 patients, reported that 1215 (18.9%) patients were aged >85 years, and only 320 (26.4%) of them were treated with an oral anticoagulant. They also reported that the use of an oral anticoagulant was an independent predictor of a lower risk of the composite outcome (OR: 0.46; 95% CI 0.32 to 0.66) among these very old patients with atrial fibrillation. Therefore, the incidence of events is high in older people without treatment, especially in patients with a CHADS2 score of ≥1. Additionally, treatment in accordance with guidelines is considered necessary, taking into account the annual incidence of bleeding events of 1.2% for a CHADS2 score of 2 and 2.9% for a CHADS2 score of 3–6.

An integrated analysis of atrial fibrillation registry studies in Japan showed that an age ≥75 years, hypertension and a prior stroke or TIA were independent risk factors for ischaemic stroke in multivariate Cox regression analysis. Recently, a new stroke risk prediction score called the HELT-E2S2 score was reported. Significant risk factors were as follows: an older age (75–84 years; E), extreme old age (≥85 years; EE), hypertension (H), prior stroke (SS), type of AF (persistent/permanent) (T) and a low body mass index <18.5 kg/m2 (L) after adjusting for oral anticoagulant treatment. In the MIE-MU-NVAF analysis, heart failure, an age ≥75 years, diabetes mellitus and a history of stroke or TIA were significant risk factors for SSEs. Among them, heart failure and a prior stroke or TIA showed particularly high s of 2.32 and 5.84, respectively.

This study has several limitations. First, this study collected non-randomised data. Second, we could not obtain important confounders on the specific types of NVAF (paroxysmal/persistent/permanent) or the duration of NVAF and lifestyle habits, such as smoking and drinking, were not available from the Mie-LIP DB. In the HELT-E2S2 score, the type of AF (persistent/permanent) was a significant risk factor (HR=1.59) associated with ischaemic stroke after adjusting for oral anticoagulant agent administration. There may be unbalanced and unadjusted confounders, which may have affected the validity of results. Third, the study was restricted to Japanese patients, and this may limit the generalisability of the data to patient populations of other races.

CONCLUSIONS

In this study, we conducted a stratified analysis of the CHADS2 score according to SSEs. This study showed that 36.4% of patients were in the no treatment group from 2016 to 2018 after widespread use of DOACs. The SSE rate was low in patients with a CHADS2 score <1, supporting no indication of anticoagulation in current guidelines. In patients with a CHADS2 score >1, the use of anticoagulant drug therapy is recommended with caution for bleeding events because of the higher risk of stroke.

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Competing interests

KT is an employee of Daiichi Sankyo.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This study was conducted under the approval of the Research Ethics Committee of the Faculty of Pharmaceutical Sciences and Institute of Pharmaceutical Research, Musashino University, 2019/3 (approval number: H30-3) and the Clinical Research Ethics Review Committee of Mie University Hospital, 2019/6 (approval number: H2019-112). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request.

De-identified participants’ data underlying the results reported in this article will be made available to researchers for 36 months following article publication, upon submission of a methodologically sound proposal and a signed data access agreement. Proposals should be submitted to tanizawa.kimihiko.me@daiichisankyo.co.jp and may be reviewed by a committee chaired by Daiichi Sankyo, Musashino University and Mie University Hospital.

Supplemental material

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REFERENCES

1 Change in the population pyramid. Available: http://www.mhlw.go.jp/ english/social_security/kaikaku_1.html [Accessed 01 Nov 2022].

2 Incue H, Fujiy A, Origasa H, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 2009;137:102–7.

3 Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of atrial fibrillation. JAMA 2001;285:2864–70.

4 JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ J 2014;78:1997–2021.

5 January CT, Wann LS, Alpert JS. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation 2014:e199–267.

6 Available: http://www.pmda.go.jp/drugs/2011/P201100019/530353000_22300AMX00433000_A100_1.pdf [Accessed 01 Nov 2022].

7 Available: http://www.pmda.go.jp/drugs/2012/P201200011/630004000_22400AMX00041_A100_2.pdf [Accessed 01 Nov 2022].

8 Available: http://www.pmda.go.jp/drugs/2012/P201200166/670605000_22400AMX01496_A100_1.pdf [Accessed 01 Nov 2022].

9 Available: http://www.pmda.go.jp/drugs/2014/P201400133/430574000_22300AMX00547_A100_1.pdf [Accessed 01 Nov 2022].

10 Kawakami K. Application of the Real World Data for Pharmacoepidemiology Research &gt; Japanese Journal of Pharmacoepidemiology/Yakuzai eikaku 2017;22:37–43.

11 Koresutse Y, Yamashita T, Yasaka M, et al. Usefulness of a healthcare database for epidemiological research in atrial fibrillation. J Cardiol 2017;70:169–79.

12 Yamauchi T, Fuji T, Akagi M. The epidemiological study of venous thromboembolism and bleeding events using a Japanese healthcare database - validation study. Jpn J Drug Inform 2015;17:87–93.

13 Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013;48:452–8.

14 Arataami H, Inoue H, Okumura K, et al. The present status of anticoagulant treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM registry. Circ J 2011;75:1528–33.

15 Suzuki S, Yamashita T, Otsuka T, et al. Recent mortality of Japanese patients with atrial fibrillation in an urban city of Tokyo. J Cardiol 2011;58:116–23.

16 Akao M, Chun Y-H, Wiada H, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF registry. J Cardiol 2013:61:260–6.

17 Murata N, Okumura Y, Yokoyama K, et al. Clinical outcomes of off-label dosing of direct oral anticoagulant therapy among Japanese patients with atrial fibrillation identified from the SAKURA AF registry. Circ J 2019;85:277–35.

18 Camm AJ, Kirchho P, GHY L, European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31:2369–29.

19 Suzuki S, Yamashita T, Okumura K, et al. Incidence of ischemic stroke in Japanese patients with atrial fibrillation not receiving anticoagulation therapy--pooled analysis of the Shinken Database, J-RHYTHM Registry, and Fushimi AF Registry. Circ J 2015;79:432–8.

20 JCS/JHRS. Guideline on pharmacotherapy of cardiac arrhythmias, 2020. Available: https://www.j-circ.or.jp/cms/wp-content/uploads/2020/01/JCS2020_00pdf [Accessed 01 Nov 2022].

21 Okumura K, Akaa M, Yoshida T. ELDERCARE-AF committees and Investigators. low-dose edoxaban in very elderly patients with atrial fibrillation. N Engl J Med 2020;383:1735–45.

22 Kang S-H, Choi E-K, Han K-D, et al. Risk of Ischemic Stroke in Patients With Non-Valvular Atrial Fibrillation Not Receiving Oral Anticoagulants - Korean Nationwide Population-Based Study. Circ J 2017;81:1158–64.

23 Guo Y, Kotalczyk A, Ibertiri JF, et al. Oral anticoagulation improves survival in very elderly Chinese patients with atrial fibrillation: a report from the optimal thromboprophylaxis in elderly Chinese patients with atrial fibrillation (ChiTOEAF) registry. Int J Stroke 2022;17:661–8.

24 Okumura K, Tomita H, Nakai M, et al. A novel risk stratification system for ischemic stroke in Japanese patients with non-valvular atrial fibrillation. Circ J 2021;85:1254–62.