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

Kimihiko Tanizawa,1,2 Yuki Nishimura,3 Shoji Sera,2 Daichi Yaguchi,2 Akira Okada,2 Masakatsu Nishikawa,3 Satoshi Tamari,3 Naomi Nagai2

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).


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 NAVF 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. The rates of bleeding events 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 non-valvular atrial fibrillation (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 2060.1 The incidence of non-valvular atrial fibrillation (NVAF) increases with age.2 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.3 Oral anticoagulation is recommended as the standard therapy for patients with NVAF with a CHADS2 score of ≥1.4 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...
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(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-NVAF) 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.

Figure 1  Distribution of treatment for patients with NVAF by each CHADS2 score. CHADS2, 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; DOAC, direct oral anticoagulant; HD, high dose; LD, low dose; NVAF, non-valvular atrial fibrillation; UD, under dose (patients who did not meet the criteria for a low dose, but were treated with a low dose).

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 Mie-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, intraocular 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, intraocular haemorrhage,
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

<table>
<thead>
<tr>
<th>Men</th>
<th>Age, years</th>
<th>&lt;65</th>
<th>65 to&lt;75</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>1474 (57.8)</td>
<td>75.4±12.7</td>
<td>202 (43.9)</td>
<td>202 (28.4)</td>
<td>117 (16.9)</td>
</tr>
<tr>
<td>712 (27.9)</td>
<td>363 (53.9)</td>
<td>363 (52.5)</td>
<td>281 (39.5)</td>
<td>154 (22.3)</td>
</tr>
<tr>
<td>58 (8.4)</td>
<td>117 (16.9)</td>
<td>76 (11.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>&lt;60</th>
<th>≤60</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.0±15.3</td>
<td>60.8±15.0</td>
<td>60.8±15.6</td>
<td>58.9±15.6</td>
</tr>
<tr>
<td>62.3±13.1</td>
<td>62.3±13.1</td>
<td>62.3±13.1</td>
<td>62.3±13.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>1275 (50.0)</th>
<th>111 (15.6)</th>
<th>203 (29.3)</th>
<th>511 (73.8)</th>
<th>566 (82.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>720 (28.2)</td>
<td>653 (27.0)</td>
<td>414 (24.6)</td>
<td>178 (32.2)</td>
<td>213 (37.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>357 (14.0)</td>
<td>1007 (48.2)</td>
<td>316 (53.9)</td>
<td>254 (45.9)</td>
<td>214 (37.2)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>325 (12.7)</td>
<td>1007 (48.2)</td>
<td>316 (53.9)</td>
<td>254 (45.9)</td>
<td>214 (37.2)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>366 (14.4)</td>
<td>1007 (48.2)</td>
<td>316 (53.9)</td>
<td>254 (45.9)</td>
<td>214 (37.2)</td>
</tr>
<tr>
<td>GI bleiding</td>
<td>25 (1.0)</td>
<td>25 (1.0)</td>
<td>7 (1.0)</td>
<td>5 (0.7)</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>194 (7.6)</td>
<td>194 (7.6)</td>
<td>43 (6.0)</td>
<td>57 (8.2)</td>
<td>84 (12.2)</td>
</tr>
<tr>
<td>ADPR inhibitor use</td>
<td>145 (5.7)</td>
<td>145 (5.7)</td>
<td>39 (5.5)</td>
<td>34 (4.9)</td>
<td>63 (9.2)</td>
</tr>
</tbody>
</table>

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.

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

**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.
The characteristics of the 7001 patients with NVAF are shown in table 1. The mean CHADS2 score was 2.00±1.30, and the mean age was 74±12.0 years. Hypertension (57.3%) was the most common comorbidity, 32.6% of the patients had diabetes mellitus, 29.3% 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±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.

### Patients’ characteristics

The characteristics of the 7001 patients with NVAF are shown in table 1. The mean CHADS2 score was 2.00±1.30, and the mean age was 74±12.0 years. Hypertension (57.3%) was the most common comorbidity, 32.6% of the patients had diabetes mellitus, 29.3% 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±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.

### EVENT OCCURRENCE

The 1-year incidence rate of SSEs by the CHADS2 score (0, 1, 2 and 3–6) in the no treatment group was 1.4% (95% CI 0.6 to 3.0), 1.4% (95% CI 0.7 to 3.1), 3.2% (95% CI 1.9 to 5.0) and 8.0% (95% CI 6.1 to 10.5), respectively (figure 2A). The 1-year incidence rate of bleeding events by the CHADS2 score (0, 1, 2, 3–6) in the no treatment group was 0.7% (95% CI 0.2 to 2.2), 1.0% (95% CI 0.4 to 2.3), 1.2% (95% CI 0.6 to 2.6) and 2.9% (95% CI 1.8 to 4.6), respectively (figure 2B).

### MULTIVARIATE COX REGRESSION ANALYSIS

A multivariate analysis of SSEs in the no treatment group was performed with components of the CHADS2 score (table 3). The adjusted HR for heart failure was 2.32 (95% CI 1.44 to 3.75), that for an age ≥75 years was 1.66 (95% CI 1.11 to 2.47), that for diabetes mellitus was 1.81 (95% CI 1.20 to 2.72) and that for prior stroke or TIA was 5.84 (95% CI 3.89 to 8.75). However, the adjusted HR for hypertension was 1.32 (95% CI 0.86 to 2.03), which was not significant.

### 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 (AF) 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 Ila-B) and warfarin (class Ila-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 in Japanese patients who had not received anticoagulation 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 ≥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 ≥2. 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 scores 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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Contributors KT, YN, AO, MN, ST and NN designed and conducted the study; KT is acting as guarantor and corresponding author; YN, MN and ST interpreted the data; KT, SS, DY and AO carried out statistical analyses; KT, YN, AO, MN, ST and
Patient and public involvement Patients and/or the public were not involved in the design, 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@dalichi sankyo.co.jp and may be reviewed by a committee chaired by Daiichi Sankyo, Musashino University and Mie University Hospital.

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