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ORIGINAL ARTICLE

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Safety and effectiveness of apixaban in Japanese patients with nonvalvular atrial fibrillation in clinical practice: A regulatory postmarketing surveillance, the STANDARD study

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Abstract

Background: Apixaban, a non-vitamin K oral anticoagulant (NOAC), was approved in Japan in 2012 for the prevention of thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF). However, the safety and effectiveness of apixaban in clinical practice have not yet been elucidated thoroughly among Japanese NVAF patients.

Methods: A postmarketing surveillance study was conducted to determine the safety and effectiveness of apixaban. Patients were followed-up for 104 weeks. Outcome events included adverse drug reactions (ADRs), hemorrhages, and thromboembolic events (ischemic stroke, systemic embolism [SE], and transient ischemic attack [TIA]).

Results: Among 6306 NVAF patients in the safety analysis set (age, 74.5 ± 10.1 years; women, 41.1%; and $CHADS_2$ score, 2.0 ± 1.4), 3600 patients (57.1%) received the standard dose (5 mg twice daily) and 2694 (42.7%) received a reduced dose (2.5 mg twice daily) of apixaban. ADRs occurred in 604 patients (9.58%), with the most common being epistaxis (0.86%), subcutaneous hemorrhage (0.67%), and hematuria (0.57%). Incidence rate of any hemorrhages and major hemorrhage was 5.52% per year and 2.36% per year, respectively. Incidence rate of ischemic stroke/SE/TIA was 1.00% per year among 6286 patients in the effectiveness analysis set. Among three subgroups (3106 apixaban initiators, 2038 patients switched from warfarin, and 1118 patients switched from other NOACs), incidence rates of major hemorrhage ($P = 0.221$ for trend) and ischemic stroke/SE/TIA ($P = 0.686$ for trend) were comparable.

Conclusions: No new safety signals of apixaban were identified in Japanese NVAF patients. Safety and effectiveness of apixaban were consistent with those in the ARISTOTLE study.

KEYWORDS

apixaban, atrial fibrillation, postmarketing surveillance, safety

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence of 0.56%-1.6% in Asian countries (China, Japan, Korea, and Singapore).[1,2] AF is an independent risk factor for stroke (a nearly five-fold increase[3]) and is associated with stroke death (a nearly three-fold increase[4]), making the growing prevalence of AF a major healthcare concern. For decades, warfarin has been used for prevention of ischemic stroke in patients with AF. However, several new non-vitamin K oral anticoagulants (NOACs) are now available in many countries to alleviate the unmet need left by traditional anticoagulants, and are recommended for use in the latest guidelines in the United States,[5] Europe,[6] and Japan.[7]

The randomized controlled trial ARISTOTLE showed that apixaban, an oral direct factor Xa inhibitor, was effective in preventing stroke and systemic embolism (SE) in patients with nonvalvular AF (NVAF).[8,9] Apixaban received regulatory approval in Japan in 2012 for the prevention of ischemic stroke and SE in patients with NVAF. To date, the real-world safety and effectiveness of apixaban in patients with NVAF have been assessed in retrospective claims database studies both outside of Japan[10–13] and in Japan.[14] However, data are still limited in Japanese NVAF patients.

After introduction of NOACs into clinical practice, the proportion of NVAF patients now given NOACs has been increasing worldwide.[15,16] In a certain proportion of these patients, warfarin was switched to NOACs and NOACs were switched to other NOACs.[16] However, reasons for the switch, as well as safety and effectiveness of the switch have not been elucidated thoroughly yet in clinical practice.

As required for a new medicine approved by the Ministry of Health, Labour and Welfare, safety and effectiveness information for the medicine should be provided in the setting of routine practice. Consequently, we conducted a postmarketing surveillance (PMS) study, STroke prevention ANticoagulant Drug Apixaban Real-world Data (STANDARD, ClinicalTrials.gov ID: NCT02007655), to assess the safety and effectiveness of apixaban in Japanese NVAF patients in routine clinical practice. Herein, we report baseline clinical characteristics and incidences of outcome events among all the study patients, as well as among the patient groups based on prior status of anticoagulation therapy.

2 | METHODS

2.1 | Study design, study period, and sample size setting

This PMS study was conducted at 811 sites across Japan from September 2013 (start of registration) until August 2016 (end of follow-up). On the basis of the incidence rate of major bleeding observed in the ARISTOTLE study,[8] a target sample size of 1000 and 1600 was set for patients receiving apixaban 2.5 and 5 mg twice daily (BID), respectively. These sample size settings aimed to extract background risk factors having a risk ratio of ≥2.5 by using the chi-squared test. Taking into account the proportion of patients meeting the dose reduction criteria in daily clinical settings, it was anticipated that by the time 1000 patients receiving apixaban 2.5 mg BID were registered, 4495 patients receiving 5 mg BID would have been registered. Accordingly, the final sample size was set to 5500 including at least 1000 patients receiving apixaban 2.5 mg BID.

Registration was possible before the start of treatment with apixaban or within 14 days after the start of treatment. Apixaban doses were selected at the discretion of each treating physician. The follow-up period was 104 weeks for each patient. Data collection was performed at baseline and at 12, 52, and 104 weeks of treatment or at discontinuation of apixaban using case report forms (CRFs) from the participating sites.

This PMS study was conducted as a condition of approval for the use of apixaban in Japanese NVAF patients, and in accordance with the Declaration of Helsinki and the Good Post-marketing Study Practice (GPSP) ordinance of Japan. Approval of the institutional review board of each participating institution and written informed consent were not required because this study was conducted as a regulatory and legal requirement in accordance with the GPSP guidelines.

2.2 | Assessments and outcomes

Assessment included baseline characteristics, ie, age, gender, body weight, serum creatinine value, past history, comorbidities, past anticoagulant treatment, $CHADS_2$ scores,[17] CHA_2DS_2-VASc scores,[18] HAS-BLED scores,[19] and apixaban dosing conditions (dosing period and dosage). Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation.[20]

Outcome events for safety analysis included adverse drug reactions (ADRs) and hemorrhages. All patients were evaluated for safety during apixaban use and for 28 days after the last study drug dose to confirm the safety profile of apixaban under routine, daily practice or to obtain information on any previously unsuspected ADRs. ADRs were events with a possible causal relationship with apixaban. Hemorrhage included all the major and nonmajor hemorrhagic events. Major hemorrhages were defined as per the criteria of the International Society of Thrombosis and Haemostasis[21] with modification in the number of blood transfusion units and included (a) fatal hemorrhage; (b) hemorrhage with a decrease in hemoglobin levels of 2 g/dL or more; (c) hemorrhage requiring blood transfusion of four units or more; and (d) hemorrhage in a critical region or organ, including intracranial, intraspinal, intraocular, pericardial, intra-articular, and retroperitoneal hemorrhages, and intramuscular hemorrhage with compartment syndrome. Outcome events for effectiveness analysis included thromboembolic events, such as ischemic stroke, SE, and transient ischemic attack (TIA).

2.3 | Statistical analysis

Data are expressed as mean ± standard deviation (SD), median, or percentage. The incidence (%) of ADRs was tabulated. The incidence rates (% per year) of major hemorrhage, any hemorrhage,

and effectiveness outcomes were also calculated, and cumulative incidence was analyzed using a Kaplan-Meier curve. In the three subgroups categorized by prior anticoagulation status, differences in continuous variables were analyzed using analysis of variance, differences in categorical variables were analyzed using the chi-squared test, and incidence rates were tested by the log-rank test. $P < 0.05$ were considered statistically significant. Statistical analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Of 6455 patients enrolled from September 2013 to August 2014, four patients were excluded from the registration owing to duplicate registration (n = 1), absence of study drug initiation (n = 2), and registration from an institution not participating in this registry (n = 1); CRFs were not obtained from 79 patients (Figure 1). Additionally, 66 patients were not included in the analysis; therefore, 6306 patients constituted the study group for safety analysis. Of these, 20 patients who were given apixaban for treatment of diseases other than AF were excluded, and the remaining 6286 patients thus constituted the study group for the effectiveness analysis (Figure 1). Four patients had a CrCl value of <15 mL/min, a contraindication of apixaban treatment, but were included in the present analyses.

3.1 | Baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of the 6306 patients in the safety analysis set. Of these, 34.6% of patients were ≥80 years of age, 52.0% weighed ≤60 kg, and 3.5% had serum creatinine values of ≥1.5 mg/dL. Moderate-to-severe renal dysfunction (CrCl ≤ 50 mL/min) was observed in 31.4% of patients. Standard dose apixaban, ie, 5 mg BID, was given to 57.1% of patients, and reduced dose, ie, 2.5 mg BID, was given to 42.7% of patients. The

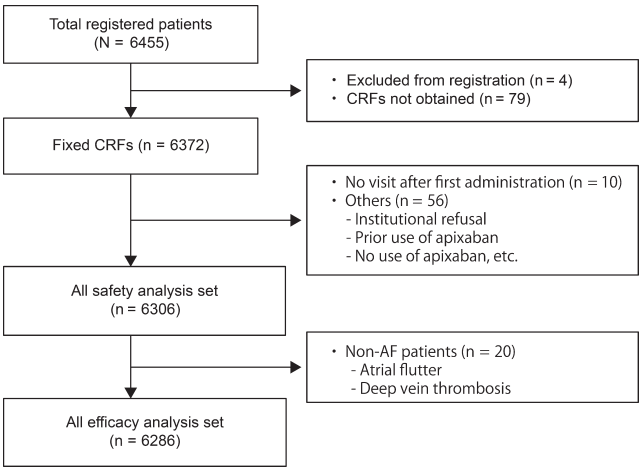

FIGURE 1 Patient disposition. AF, atrial fibrillation; CRF, case report form

TABLE 1 Baseline demographics and characteristics of 6306 patients in the safety analysis set

Characteristics	Overall n = 6306
Women	2592 (41.1)
Age (y)	74.5 ± 10.1 (median 76.0)
<70	1715 (27.2)
≥70 to <75	1189 (18.9)
≥75 to <80	1220 (19.3)
≥80 to <85	1231 (19.5)
≥85 to <90	729 (11.6)
≥90	222 (3.5)
Weight (kg) (n = 5896)	59.6 ± 12.6 (median 59.0)
≤60	3282 (52.0)
>60	2614 (41.5)
Unknown	410 (6.5)
Serum creatinine (mg/dL) (n = 5820)	0.90 ± 0.37
<1.5	5597 (88.8)
≥1.5	223 (3.5)
Unknown	486 (7.7)
Creatinine clearance (mL/min) (n = 5552)	62.2 ± 26.8
<15	4 (0.1)
≥15 to <30	382 (6.1)
≥30 to ≤50	1590 (25.2)
>50 to ≤80	2426 (38.5)
>80	1150 (18.2)
Unknown	754 (12.0)
Past history	
Clinically important hemorrhage	221 (3.5)
Congenital or acquired hemorrhagic disease	102 (1.6)
Gastrointestinal ulcer	147 (2.3)
Ischemic stroke and transient ischemic attack	1101 (17.5)
Comorbidity	
Hypertension	3855 (61.1)
Heart failure	1921 (30.5)
Diabetes mellitus	1121 (17.8)
Renal disorder	930 (14.7)
Liver disorder	771 (12.2)
Apixaban dosage	
5 mg twice daily	3600 (57.1)
2.5 mg twice daily	2694 (42.7)
Others[a]	12 (0.2)
Antiplatelet drug use[b]	1184 (18.8)

Note: Values are mean ± standard deviation or number (%) of patients.
[a]See text for details.
[b]Antiplatelet drugs that were used during the apixaban dosing period.

remaining patients (0.2%) received other doses: 5 mg once daily in five patients, 2.5 mg once daily in six patients, and 1.25 mg BID in one patient. Of 2694 patients receiving 2.5 mg BID apixaban, 1682 patients (62.4%) met ≥2 dose reduction criteria (age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL),[22] but 941 patients (34.9%) met <2 dose reduction criteria. Information of the dose reduction criteria was not obtained in 71 patients (2.6%). Mean risk scores were 2.0 for $CHADS_2$, 3.4 for CHA_2DS_2-VASc, and 1.7 for HAS-BLED (Figure S1).

Of 6306 patients included in the safety analysis set, 3106 patients (49.3%) started apixaban as their initial anticoagulation treatment for NVAF. In 2038 patients (32.3%), warfarin was switched to apixaban, and in 1118 patients (17.7%), other NOACs (dabigatran in 613 and rivaroxaban in 508 patients; three patients had received both dabigatran and rivaroxaban) were switched to apixaban. Among those patients who switched, nine patients had received both warfarin and NOAC. Other anticoagulants including heparin were switched to apixaban in 53 patients.

TABLE 2 Reasons for switching from other anticoagulants to apixaban

Reasons for switching from warfarin to apixaban (n = 2038)	
Poor INR control	36.4%
INR control and adverse events	0.9%
Physician's decision	25.0%
Patient's preference	10.3%
Dietary restrictions	7.3%
Others	10.6%
Unknown	9.4%
INR values at the time of switching from warfarin (n = 760)	
<1.6	61.2%
1.6 to <2.0	8.3%
2.0 to <2.6	2.9%
2.6 to <3.0	2.4%
≥3.0	7.1%
Unknown	18.1%
Reasons for switching from other NOACs (n = 776)	
Physician's decision	33.1%
Efficacy	15.3%
Safety concerns	5.9%
Blood test results	5.3%
Adverse events	23.3%
Gastrointestinal symptoms	10.0%
Bleeding	6.1%
Patient characteristics	19.8%
Renal function	12.9%
Age	4.9%
Patient's preference	15.7%
Others	8.1%

Abbreviations: INR, international normalized ratio; NOACs, non-vitamin K oral anticoagulants.

Of 2038 patients in whom warfarin was switched to apixaban, the most common reason (37.3%) for switching was poor control of INR values (poor INR control, 36.4%; INR control and adverse events, 0.9%; Table 2). Of 760 patients with poor INR control, 69.5% had INR values of <2.0 at the time of switching as recommended in the Japanese package insert.[22] However, 12.4% of patients had INR values of ≥2.0. Reasons for switching from other NOACs are also shown in Table 2.

Baseline clinical characteristics of the three subgroups are shown in Table 3. Patients in whom warfarin had been switched to apixaban were older, had lower body weight and CrCl values, and had higher thromboembolic and bleeding risk scores compared with the remaining two subgroups.

3.2 | Outcome events

Of 6306 patients included in the safety analysis set, follow-up was discontinued in 2381 patients (37.8%) before completion of the 104-week follow-up; before 52 weeks in 1807 patients and between 52 and 104 weeks in 574 patients. Reasons for discontinuation of follow-up were adverse events in 585 patients, transfer to other hospitals/clinics in 837, and discontinuation of visit in 381, death in 119, poor adherence in 108, surgery/invasive procedures in 82, discontinuation of apixaban owing to medication cost in 58, and others.

Major hemorrhage occurred in 210 patients (2.36% per year) during a mean follow-up period of 17.4 months (Table 4, Figure 2). Intracranial hemorrhage occurred in 67 patients (0.75% per year). Incidence rates of major hemorrhage by baseline HAS-BLED scores are shown in Figure 3. Common (≥0.5%) ADRs were epistaxis, subcutaneous hemorrhage, and hematuria (Table S1). Of 6286 patients included in the effectiveness analysis set, ischemic stroke, SE, and TIA occurred in 89 patients (1.00% per year; Table 5, Figure 2). Of 79 episodes of ischemic stroke, 57% were of cardioembolic origin. Incidence rates of ischemic stroke/SE/TIA by baseline risk scores are shown in Figure 3. No outcome events were observed in four patients (79-89 years old; three women; and apixaban 2.5 mg BID in three and 5 mg BID in one) who had baseline CrCl values of <15 mL/min.

As shown in Tables 4 and 5, incidence rates of outcome events did not differ significantly among the three subgroups divided by prior status of anticoagulation therapy.

4 | DISCUSSION

This PMS study included more than 6000 patients with NVAF and identified the following major findings. First, 42.7% of the patients received 2.5 mg BID apixaban. Second, incidence rates of major hemorrhage and thromboembolic events were 2.36% per year and 1.00% per year, respectively. No new safety signals were identified. Third, some clinical characteristics differed among the three subgroups based on the status of anticoagulation therapy prior to apixaban treatment, but incidence rates of hemorrhagic and thromboembolic events did not differ among the three subgroups.

TABLE 3 Baseline demographics and characteristics by subgroup (safety analysis set)

Characteristics	Apixaban initiators (n = 3106)	From warfarin (n = 2038)	From other NOACs (n = 1118)	*P* value for trend
Women	1278 (41.1)	844 (41.4)	450 (40.3)	0.811
Age (y)	73.6 ± 10.8	76.0 ± 9.0	74.3 ± 9.6	<0.001
Weight (kg)	60.0 ± 12.6 (n = 2923)	58.8 ± 12.6 (n = 1898)	59.8 ± 12.9 (n = 1032)	0.004
Serum creatinine (mg/dL)	0.87 ± 0.43 (n = 2914)	0.93 ± 0.29 (n = 1855)	0.93 ± 0.30 (n = 1007)	<0.001
Creatinine clearance (mL/min)	65.4 ± 27.0 (n = 2796)	58.0 ± 26.0 (n = 1760)	60.4 ± 26.0 (n = 953)	<0.001
$CHADS_2$ score	1.9 ± 1.3	2.3 ± 1.4	2.1 ± 1.4	<0.001
CHA_2DS_2-VASc score	3.2 ± 1.7	3.7 ± 1.7	3.5 ± 1.7	<0.001
HAS-BLED score	1.4 ± 1.0	2.1 ± 1.1	1.7 ± 1.0	<0.001
Antiplatelet use	534 (17.2)	442 (21.7)	200 (17.9)	<0.001

Note: Values are mean ± standard deviation or number of patients (%).
Abbreviation: NOACs, non-vitamin K oral anticoagulants.

TABLE 4 Incidence rate of hemorrhagic events

	Overall (n = 6306)	Apixaban initiators (n = 3106)	From warfarin (n = 2038)	From other NOACs (n = 1118)	*P* value for trend[a]
Any hemorrhage	480 (5.52)	204 (5.03)	179 (5.88)	94 (5.98)	0.127
Major hemorrhage	210 (2.36)	86 (2.07)	82 (2.63)	40 (2.49)	0.221
Intracranial	67 (0.75)	31 (0.74)	22 (0.70)	13 (0.80)	0.939
Cerebral	44 (0.49)	21 (0.50)	18 (0.57)	5 (0.31)	0.446
Subarachnoid	7 (0.08)	2 (0.05)	1 (0.03)	4 (0.25)	NA
Chronic subdural	9 (0.10)	7 (0.17)	1 (0.03)	1 (0.06)	NA
Others	8 (0.09)	1 (0.02)	2 (0.06)	4 (0.25)	NA
Gastrointestinal	90 (1.01)	34 (0.82)	37 (1.18)	17 (1.05)	0.232

Note: Number of patients (% per year).
Abbreviations: NA, not assessed due to lower event rates; NOACs, non-vitamin K oral anticoagulants.
[a]Comparison among three subgroups.

4.1 | Comparison with the ARISTOTLE study

A comparison with the apixaban group of the ARISTOTLE study[8] showed that patients in the present study were at a higher hemorrhagic risk associated with their higher age (76.0 years [median] vs 70 years [median]), lower body weight (59.0 kg [median] vs 82 kg [median]), and reduced renal function (CrCl >80 mL/min, 18.2% vs 41.2%). Nevertheless, the incidence rates of major hemorrhage (present study, 2.36% per year vs ARISTOTLE, 2.13% per year), ischemic stroke (0.88% per year vs 0.97% per year), and SE (0.03% per year vs 0.09% per year) were comparable between the two studies. Similarly, a comparison with the ARISTOTLE subgroup analysis in an East Asian population (median age, 69 years; median body weight, 66 kg; CrCl >80 mL/min, 25.7%)[23] also revealed that the incidence rates of major hemorrhage (present study, 2.36% per year vs ARISTOTLE subgroup analysis, 2.02% per year), any hemorrhages (5.52% per year vs 20.47% per year), and ischemic stroke (0.88% per year vs 2.22% per year) were comparable or lower in the present study. Consequently, the safety and effectiveness profiles of apixaban observed in our study were consistent with those reported in the ARISTOTLE study.[8,23]

4.2 | Patient characteristics

Age (mean, 74.5 years) and thromboembolic risk (mean $CHADS_2$ score, 2.0 and CHA_2DS_2-VASc score, 3.4) of the present study population were similar to those in the Fushimi AF Registry (74.2 years, 2.09, and 3.43, respectively),[24] and a Japanese claims database study (77.0 years, 2.2 and 3.4, respectively).[25] This finding indicates that the patients included in the present study were at a similar risk of

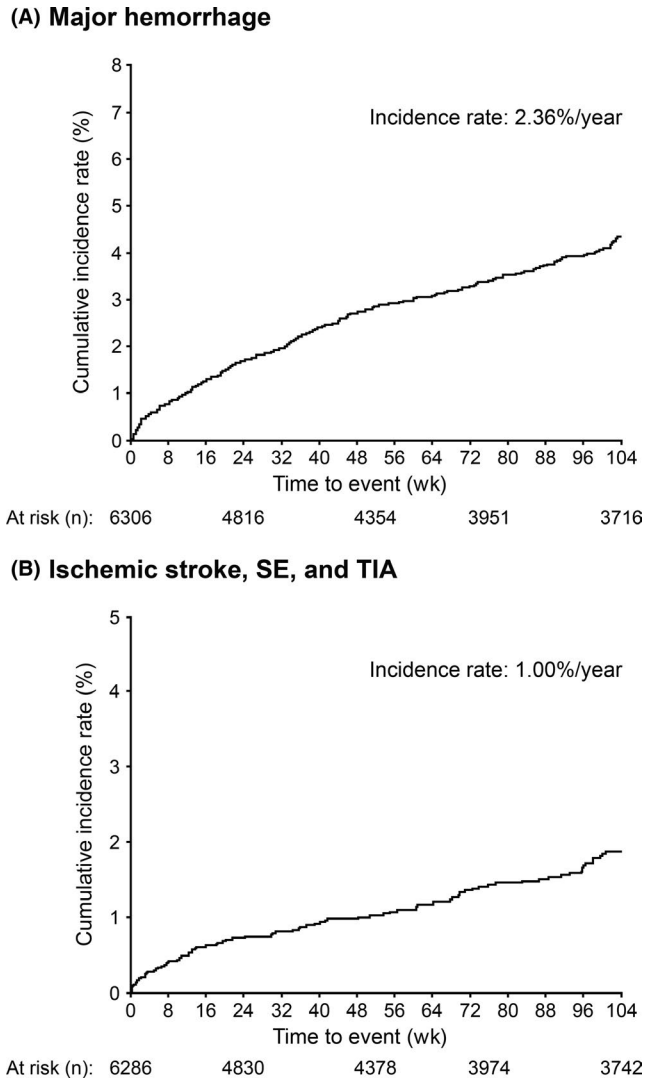

FIGURE 2 Cumulative incidence rate of (A) major hemorrhage and (B) ischemic stroke, SE, and TIA. SE, systemic embolism; TIA, transient ischemic attack

thromboembolism compared with the general Japanese population with NVAF.

The hemorrhagic risk of apixaban, dabigatran, and rivaroxaban, compared with warfarin, was assessed in a retrospective claims database study in Japanese NVAF patients using a propensity-matched analysis.[14] Before the propensity matching, patients receiving apixaban were older (mean age, 76.7 vs 72.3-74.4 years) and had reduced renal function (comorbid renal dysfunction, 4.9% vs 2.4%-3.3%) compared with those receiving dabigatran or rivaroxaban.[14] These findings were consistent with the present study in comparison with the PMS studies of rivaroxaban[26] and dabigatran[27] in terms of higher mean age (74.5 vs 73.1[26] and 70.8 years[27]) and reduced CrCl (62.2 vs 67.7[26] and 72.8 mL/min[27]) in patients receiving apixaban.

In the present study, 42.7% of the patients received 2.5 mg BID apixaban. This frequency was similar to that in Japanese registration studies (40.4%[28] and 44%[16]), but lower than that in a Japanese claims database study (60.6%[25]).

4.3 | Switch from other anticoagulants

Patients who switched from warfarin to apixaban were older, and had lower body weight and CrCl values compared with the other two subgroups. Moreover, thromboembolic and bleeding risk scores were higher in this subgroup. Nevertheless, incidence rates of outcome events did not differ significantly among all the subgroups.

In our study, poor INR control was the most common reason for switching from warfarin to apixaban, with the risk score of stroke or hemorrhage being higher in patients who switched from warfarin compared with apixaban initiators (Tables 2 and 3). Indeed, results from a nationwide database study indicated that Japanese NVAF patients who continued to receive warfarin had both poor or inadequate INR control and higher stroke risk compared with those who switched from warfarin to NOACs.[29]

Approximately 70% of patients who switched from warfarin to apixaban due to uncontrolled INR started apixaban at an INR value of <2.0 as recommended in the Japanese package insert of apixaban.[22] Importantly, the incidence rate of hemorrhagic events did not increase in patients switching from warfarin to apixaban (Table 4). Thus, it remains crucial for physicians to follow this INR prerequisite in patients who are to switch from warfarin to apixaban. With regard to switching from other NOACs, a number of reasons were reported for doing so in the present study (Table 2). Medication switching from an index NOAC occurs in one in five patients with NVAF in the United States and is therefore not uncommon[30]; however, the reasons behind switching have not been well studied, and practical clinical guidelines for switching between NOACs are lacking. Our findings, therefore, provide some insight into the real-world experience in switching between NOACs in Japan.

4.4 | Limitations

This study had some limitations. First, the single-cohort design prevented comparisons with warfarin or other NOACs. Second, 37.8% of the patients discontinued apixaban treatment or were lost to follow during the 104-week follow-up period. Discontinuation of periodical visits and transfer to other hospitals/clinics accounted for 51% of these patients for whom the follow-up was discontinued. This rate seemed a little higher, but the clinical status of these patients at the discontinuation of apixaban was determined, yielding a mean follow-up period of 17.4 months. This result was similar to that of a previous Japanese PMS of another NOAC, which was designed to follow the patients for 104 weeks, but yielded a mean follow-up period of approximately 15 months.[31] The shorter follow-up period than designed would have underestimated event rates in the present study as well as in that PMS study.[31] Third, as a result of the inherent limitations of a noninterventional design, this study may not have generated unbiased relative risk estimates or absolute incidence rates. Fourth, since some of the reasons for switching from other anticoagulants to apixaban are subjective, the possibility of selection bias and confounding bias cannot be ruled out. Fifth, possible misclassifications of events cannot be ruled out since events were assessed by treating physicians and were not confirmed by an independent adjudication committee. Sixth, adherence of prescribing apixaban was not evaluated in

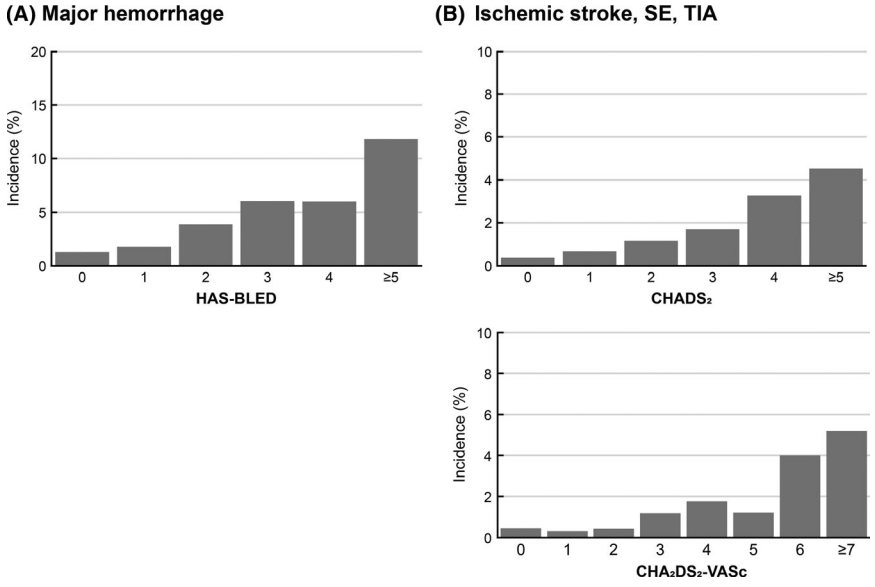

FIGURE 3 Incidence of (A) major hemorrhage by baseline HAS-BLED score and (B) ischemic stroke, SE, and TIA by baseline $CHADS_2$ score and CHA_2DS_2-VASc score. SE, systemic embolism; TIA, transient ischemic attack

TABLE 5 Incidence rate of thromboembolic events

	Overall (n = 6286)	Apixaban initiators (n = 3093)	From warfarin (n = 2034)	From other NOACs (n = 1118)	*P* value for trend[a]
Ischemic stroke/SE/TIA	89 (1.00)	42 (1.01)	33 (1.05)	13 (0.80)	0.686
Ischemic stroke	79 (0.88)	36 (0.87)	30 (0.96)	12 (0.74)	0.717
Atherothrombotic	8 (0.09)	6 (0.14)	2 (0.06)	0 (0)	NA
Cardioembolic	45 (0.50)	19 (0.46)	17 (0.54)	8 (0.49)	0.836
Lacunar	7 (0.08)	5 (0.12)	0 (0)	2 (0.12)	NA
Cryptogenic	9 (0.10)	4 (0.10)	4 (0.13)	1 (0.06)	NA
Unknown	6 (0.07)	2 (0.05)	3 (0.10)	1 (0.06)	NA
Others	5 (0.06)	1 (0.02)	4 (0.13)	0 (0)	NA
SE	3 (0.03)	2 (0.05)	0 (0)	1 (0.06)	NA
TIA	8 (0.09)	4 (0.10)	4 (0.13)	0 (0)	NA

Note: Number of patients (% per year).
Abbreviations: NA, not assessed due to lower event rates; NOACs, non-vitamin K oral anticoagulants; SE, systemic embolism; TIA, transient ischemic attack.
[a]Comparison among three subgroups.

the present study. Seventh, upon comparison of patient background and incidence rates, safety and effectiveness among the three subgroups categorized by prior anticoagulation therapy, power was not considered for the *P* value calculation. Finally, changes in apixaban doses were not considered in the course of treatment, and event rates were determined using the baseline apixaban doses. Approximately 900 patients did not meet ≥2 dose reduction criteria but received 2.5 mg BID apixaban, so-called underdose. The association of apixaban doses and dose reduction criteria with outcome events seems clinically relevant, but is not reported herein. This will be reported separately.

5 | CONCLUSIONS

No new safety signals of apixaban were identified in Japanese NVAF patients. The safety and effectiveness profile for apixaban was consistent with that in the ARISTOTLE study. There was no notable difference in safety or effectiveness event rates among apixaban initiators, patients switched from warfarin, and those switched from other NOACs.

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CONFLICT OF INTEREST

HI has received remuneration from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer Healthcare, and Daiichi Sankyo. MY has received remuneration from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer Healthcare, and Daiichi Sankyo. MU,

TY, and AK are employees of Bristol-Myers Squibb. HH is an employee of Pfizer Japan. This study is registered as ClinicalTrials.gov ID: NCT02007655.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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