Clinical Characteristics and Treatment Patterns in Japanese Patients with Nonvalvular Atrial Fibrillation and a $CHADS_2$ Score＝0, Including Those with Cancer

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ABSTRACT

Background: Epidemiological data on Japanese patients with nonvalvular atrial fibrillation（NVAF）and a low risk of stroke（$CHADS_2$ score＝0）are limited. The objective of this study was to explore the characteristics of patients with NVAF and a $CHADS_2$ score＝0, including those with cancer, and oral anticoagulant（OAC）treatment patterns in Japanese clinical settings.

Methods: This retrospective cohort study was conducted using the Medical Data Vision data from January 1, 2013, to December 31, 2022. Eligible patients were aged 20–74 years at the time of the index date（date of the first confirmed diagnosis of NVAF）.

Results: Of the 35,954 patients（with cancer: 9107, without cancer: 26,847）included in the analysis, 65.2% were men, 57.5% were aged 65–74 years, and 19.2% weighed ＜50 kg. Overall, 23.4% and 37.4% of patients had CHA_2DS_2-VASc and CHA_2DS_2-VA scores of 0, respectively. The most common comorbidity was any cancer（25.3%）. Of the 32,600 patients, excluding those diagnosed with venous thromboembolism, 10,302（31.6%）patients initiated an OAC within 14 days after the index date. There was an increasing trend in the rate of OAC use in patients with a $CHADS_2$ score＝0 across the years during the study period, whereas, the rate of warfarin use was gradually decreasing. In the non-OAC group, the proportion of patients with comorbid cancer was slightly higher than in the direct OAC groups（25.4% vs. 18.3%–21.5%）.

Conclusion: Among NVAF patients with a $CHADS_2$ score＝0, cancer was the most common comorbidity and the rate of OAC use gradually increased over the years.

Key words: Cancer, $CHADS_2$ score, Nonvalvular atrial fibrillation, Oral anticoagulant, Stroke

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Clinical Characteristics and Treatment Patterns in Japanese Patients with Nonvalvular Atrial Fibrillation and a $CHADS_2$ Score＝0, Including Those with Cancer: がん患者を含めた $CHADS_2$ スコア 0 点の日本人非弁膜症性心房細動の臨床的特徴と治療パターン

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INTRODUCTION

Nonvalvular atrial fibrillation (NVAF) accounts for approximately 95% of all atrial fibrillation (AF) cases and is a significant risk factor for fatal and disabling ischemic stroke[1]. Vitamin K antagonists (VKAs), mainly warfarin, were previously the standard of care for patients with NVAF[1,2]. Direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, have shown to reduce the incidence of stroke in patients with NVAF and demonstrated a lower or similar incidence of stroke and major bleeding events relative to warfarin in clinical trials[3–6].

The $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used for thromboembolism and stroke risk stratification in patients with NVAF[7]. $CHADS_2$ assigns scores as follows: congestive heart failure, hypertension, age ≧75 years, and diabetes (1 point each) and previous history of stroke or transient ischemic attack (2 points; total score=6)[8]. A total $CHADS_2$ score of 0 is considered as low risk, 1 as intermediate risk, and ≧2 as high risk[2]. Compared with the $CHADS_2$ score, the CHA_2DS_2-VASc score includes 3 additional factors: vascular diseases, including myocardial infarction, aortic plaque, and peripheral arterial disease; age 65–74 years; and sex category (female sex)[7,9]. In the United States and Europe, the CHA_2DS_2-VASc score is widely used for stroke risk stratification in patients with NVAF[10,11]. The recent 2024 European Society of Cardiology (ESC) guidelines recommend the use of the CHA_2DS_2-VA score, which excludes sex category as a criterion[12]. The guideline recommends a CHA_2DS_2-VA score of ≧2 as an indicator of elevated thromboembolic risk for initiating oral anticoagulant (OAC)[12]. In contrast, the Japanese Circulation Society (JCS)/Japanese Heart Rhythm Society 2020 Guideline on Pharmacotherapy for the Management of Cardiac Arrhythmias recommends using the $CHADS_2$ score for stroke risk assessment in patients with NVAF, based on a pooled analysis of 3 Japanese AF registries (J-RHYTHM Registry, Fushimi AF Registry, and Shinken Database), in which the additional VASc factors in the CHA_2DS_2-VASc score were not identified as significant risk factors for ischemic stroke in Japanese patients with NVAF not receiving OAC[2,13]. Risk factors not included in the $CHADS_2$ score (e.g., cardiomyopathy, age 65–74 years, vascular disease [prior MI, aortic plaque, and peripheral arterial disease], persistent and permanent AF, renal dysfunction, body weight ≦50 kg, and left atrial diameter [LAD]>45 mm) are considered as "other risks" when considering anticoagulation therapy[2]. Current Japanese treatment guidelines recommend initiating an OAC for all patients with a $CHADS_2$ score ≧1 and those with a $CHADS_2$ score=0 after considering other risk factors[2,14].

On the other hand, the number of NVAF patients with a $CHADS_2$ sore=0 is not small. Indeed, the proportion of these patients was reported to be 15.6% in the J-RHYTHM Registry[15], 11.2% in the Fushimi AF Registry[16], and 34.0% in the Shinken Database[17]. Therefore, patients with a $CHADS_2$ score=0 cannot be ignored in terms of anticoagulation therapy in real-world clinical settings. However, there are limited data on the risk-benefit profile of anticoagulation therapy for patients with a $CHADS_2$ score=0[18,19]. In addition, OAC treatment patterns in patients with NVAF having a $CHADS_2$ score=0 in real-world settings remain unclear.

Accumulating evidence suggests an association between cancer and AF[20–23]. AF could also be triggered by the use of alkylating agents, anthracyclines, and some targeted therapies[20]. AF has frequently been observed and investi-

gated extensively as a postoperative complication in certain types of cancer (e.g., lung and esophagus)[20]. The 2022 ESC Guidelines on cardio-oncology recommend the assessment of thromboembolic risk, bleeding risk, patient preferences, and drug availability when initiating anticoagulation therapy in patients with cancer-associated venous thrombosis[24]. Moreover, the DOAC use in patients with AF and concurrent cancer is supported by current real-world evidence[25].

There are epidemiological studies in patients with a low risk of stroke, including those with cancer[18,19,26]; however, Japanese data are limited[27,28]. Cancer-related data have not been collected in most Japanese epidemiological studies for AF, and data on cancer-associated NVAF remain unclear. Therefore, we conducted an epidemiological survey to understand the characteristics of NVAF patients with a $CHADS_2$ score=0, including those with cancer. Then, this survey clarified OAC treatment patterns in such patients in Japan.

METHODS

1 Study design

This retrospective cohort study analyzed data from a longitudinal database provided by Medical Data Vision Co. Ltd.(MDV; Tokyo, Japan). At the time of data extraction, there were 43.2 million patients from 475 registered hospitals(8.5% of all hospitals and 27.0% of Diagnosis Procedure Combination [DPC] hospitals in Japan). Patient data were analyzed for the period registered in the database. Data were extracted from patients registered in the MDV database between January 1, 2013, and December 31, 2022. The index date was defined as the date of the first confirmed diagnosis of AF after January 1, 2013. The baseline time interval was set at 180 days prior to the index date. The month of diagnosis and prior 6 months were included because the information on diagnosis is recorded monthly in the claims data. This study extracted data that existed in an anonymized structured format and did not contain any personal information of patients. According to applicable legal requirements, such data are not subject to privacy laws. According to the Ethical Guidelines for Human Life Science and Medical Research in Japan, informed consent is not required for studies that use nonlinkable, anonymized data. Therefore, obtaining informed consent from the patients and institutional review board approval were not required.

2 Patients

Eligible patients were aged 20-74 years at the time of the index date and with a confirmed diagnosis of AF (International Classification of Diseases 10th revision[ICD-10]: I48) during the study period. Patients without a visit in the baseline period prior to the index date; with a confirmed diagnosis of valvular AF (I48.9), postoperative AF(I48.9, Z95.2, and so on), or rheumatic valvular disease (I05.0 and so on); and with records of mechanical valve replacement(T82.0) were excluded (**Table S1**). Patients who had received any OAC (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) during the baseline period and those with any disease, which is a component of the $CHADS_2$ score, prior to the index date were also excluded. Patients were stratified as follows: with and without a cancer diagnosis during the baseline period (Population 1). Population 2 comprised patients from Population 1 who were not diagnosed with venous thromboembolism (including pulmonary embolism and deep vein thrombosis) during the study period. Patients who had a record of ≧2 OACs on the index date were excluded. Patients in Population 2 were broadly divided into 2 groups: those who did not start OAC therapy(non-OAC group)

and those who started an OAC (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) within 2 weeks of the index date (OAC group, **Table S2**). Patient demographics and clinical characteristics were described for Populations 1 and 2. Both the CHA_2DS_2-VASc and CHA_2DS_2-VA scores were determined in this study. For patients with cancer, cancer-related information, such as the location of cancer and treatment, was recorded. For patients who had received an OAC, the median initial dose of the OAC was recorded.

3 Statistical analysis

This epidemiological study employed a descriptive approach to assess the characteristics of patients with NVAF and a $CHADS_2$ score=0. Due to the large number of patients and possibility of detecting meaningless differences, no intergroup comparisons were made. Continuous variables are presented as mean±standard deviation (SD) and/or median (interquartile range [IQR]). Categorical variables are expressed as frequency and proportions. Temporal trend in the proportion of patients with cancer and the rates of OAC use were evaluated using the Cochran-Armitage test, with a significance level of 0.05. All analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1 Patient disposition

Of the 1,138,953 patients whose data were extracted from the MDV database, 1,100,707 had a diagnosis of AF after the follow-up start date (**Fig. 1**). A total of 441,175 patients were aged 20-74 years at the index date, of whom 35,954 were included in Population 1 (with cancer: 9107 and without cancer: 26,847). The distribution of patients in Population 2 (n=32,600) was as follows: non-OAC (n=22,298), warfarin (n=676), dabigatran (n=931), rivaroxaban (n=2739), apixaban (n=2447), and edoxaban (n=3509; **Fig. 1**).

2 Demographics and patient characteristics (Population 1)

Between 2013 and 2022, the index year in which the maximum number of patients (13.1% of the overall Population 1) were recruited was 2019 (**Table S3**). No significant trend was observed in the proportion of cancer comorbidity between 2013 and 2022 (p=0.606 for trend; **Fig. 2** and **Table S3**). Demographics and patient characteristics in Population 1 are summarized in **Table 1**. The type of AF was paroxysmal (26.0%), nonparoxysmal (including persistent and permanent: 5.7%), and unknown (68.3%). Most patients were men (65.2%), and the mean age was 62.5±11.5 years; 57.5% were aged 65-74 years. Overall, 23.4% and 37.4% of patients had a CHA_2DS_2-VASc and CHA_2DS_2-VA score of 0, respectively. The most common comorbidity was any cancer (25.3%) followed by cardiac conduction failure (17.2%), gastritis (14.4%), and peptic ulcer (12.0%). The most commonly prescribed drug class was nonsteroidal anti-inflammatory drugs (15.0%), followed by antiarrhythmics (7.9%). Among the prescribed anticancer drugs, the most commonly prescribed drug class was antimetabolites (2.5%), followed by platinum (2.2%; **Table 1**).

3 Clinical characteristics and management of patients with cancer

Among patients with cancer, 70.5% were aged 65-74 years, and the prevalence of comorbidities was generally higher than that reported in the overall population (**Table 1**). Of the 9107 patients with cancer, 6443 (70.7%) were men (**Table 1**). Cancer-related information in patients with cancer is summarized in **Table 2**. Metastatic solid tumors were the most common cancer reported in both men (20.7%) and women

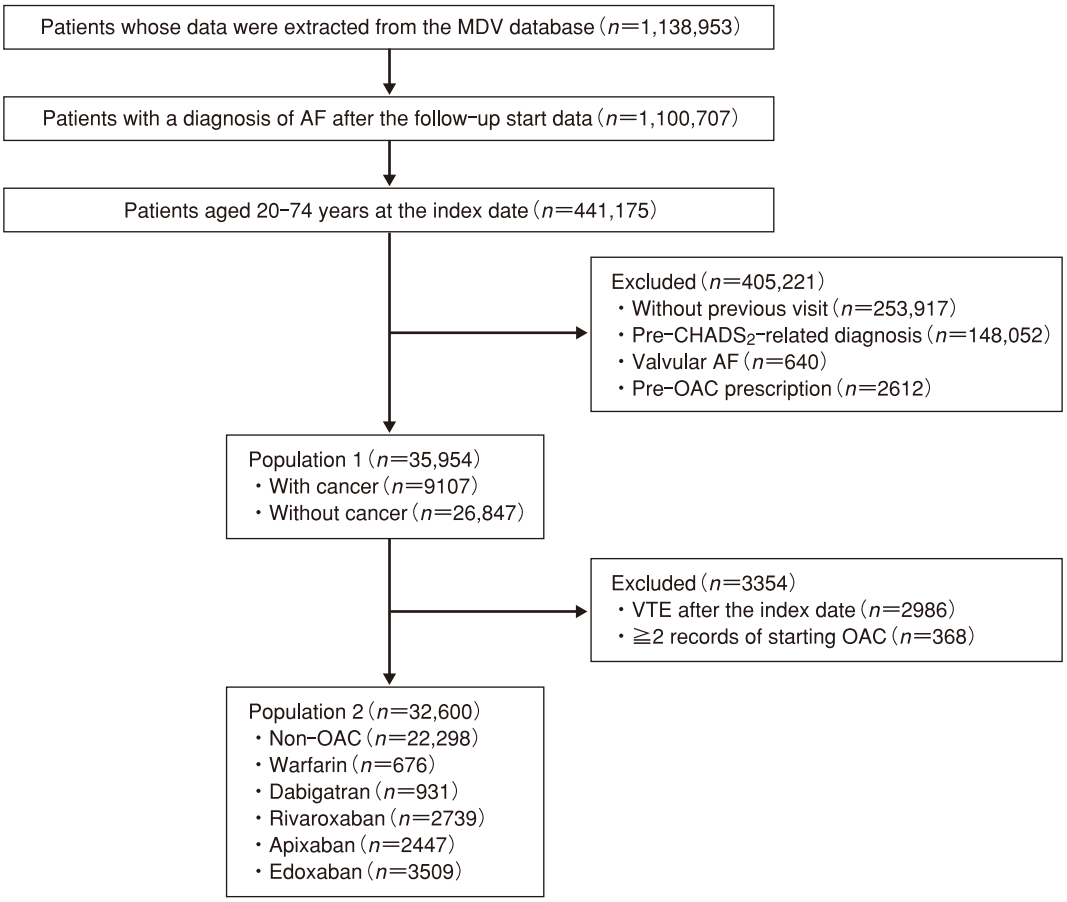

Fig. 1 Patient disposition
AF: atrial fibrillation, MDV: Medical Data Vision, OAC: oral anticoagulant, VTE: venous thromboembolism

(26.3%). Intestinal cancer was the most common (19.5%), followed by lung (18.8%) and stomach (13.4%) cancer. Antimetabolites were the most commonly prescribed drug class (9.8%), followed by platinum (8.8%) and microtubule inhibitors (5.3%). Surgery for cancer was performed in 12.9% of patients, and radiotherapy for cancer administered to 3.9% of patients.

4 Demographics and patient characteristics (Population 2)

A total of 10,302/32,600 (31.6%) patients were prescribed an OAC within 14 days after the index date, and 22,298/32,600 (68.4%) patients were not prescribed any OAC. In 2013, 22.8% of patients were prescribed any OAC, whereas 77.2% were not (**Fig. 3** and **Table S3**). There was a significant increasing trend in the rate of OAC use in patients with a $CHADS_2$ score=0 across the years during the study period ($p<0.001$ for trend, **Fig. 3** and **Table S3**); whereas the rate of warfarin use was gradually decreasing (**Table S3**). Patient characteristics without OAC (non-OAC) and with each OAC in Population 2 are summarized in **Table 3**. In the overall Population 2, the distribution of patients by type of AF was as follows: paroxysmal (26.7%),

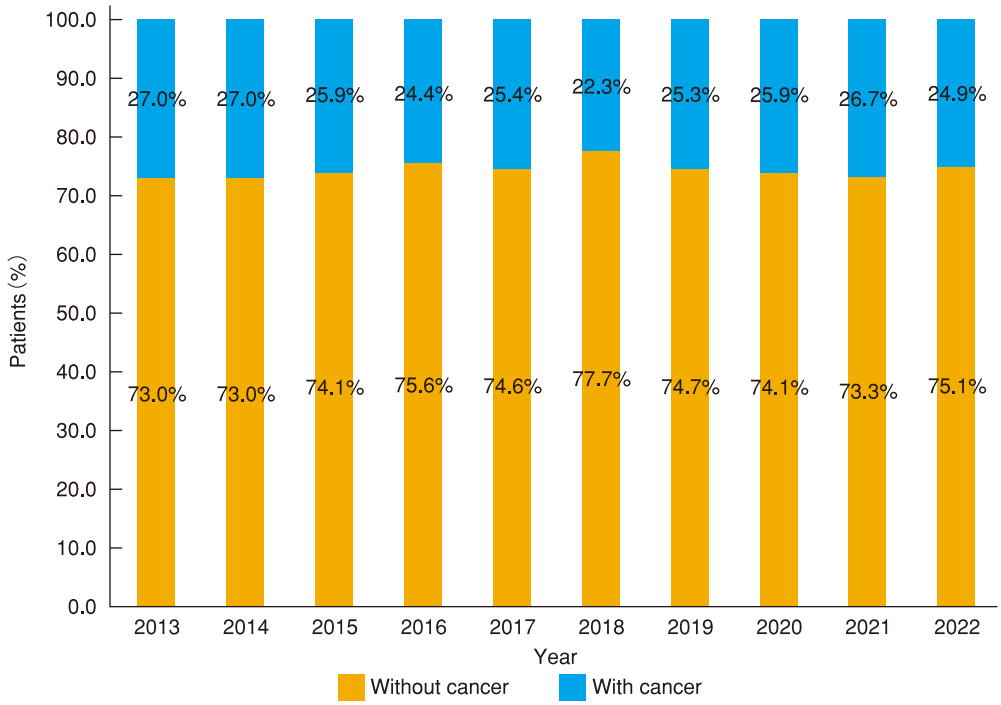

Fig. 2 Temporal trend in the proportion of patients with cancer

nonparoxysmal (5.6%), and unknown (67.7%). Most patients were men (65.7%), and the mean age was 62.4±11.5 years; 57.4% were aged 65–74 years. Older patients (aged 65–74 years) were more prevalent in all OAC groups (59.6%–70.7%) than in the non-OAC group (53.7%), especially in warfarin (70.7%) and apixaban (68.0%) groups. The percentage of patients weighing <50 kg varied by OAC, with the highest being in the edoxaban group (20.1%) and lowest in the dabigatran group (9.6%). The proportion of patients with renal disease was 2.5%, 11.5%, and 0.6%–1.2% in the non-OAC, warfarin, and DOAC groups, respectively. The proportion of patients with comorbid cancer was slightly higher in the non-OAC group vs. the DOAC groups (25.4% vs. 18.3%–21.5%). The proportion of patients with CHA_2DS_2-VASc and CHA_2DS_2-VA scores of 0 was 23.5% and 37.4%, respectively. The most common comorbidity was any cancer (23.8%), followed by cardiac conduction failure (17.7%) and gastritis (14.0%). Among patients with any cancer (n=7762), OAC was not prescribed to 5659 (72.9%) patients, whereas among those without cancer (n=24,838), OAC was not prescribed to 16,639 (67.0%) patients. No apparent differences in concomitant medications were observed among groups (**Table 3**).

DISCUSSION

This study assessed the characteristics of Japanese patients diagnosed with NVAF with a $CHADS_2$ score=0, including those with cancer, and analyzed the treatment patterns of OACs. Approximately 25% of patients in this study had cancer, approximately 20% had a body weight <50 kg, and approximately 2% had renal disease. Approximately 30% of patients initiated an

Table 1　Demographics and patient characteristics（Population 1）

	Total (*N*=35,954)	With cancer (*n*=9107)	Without cancer (*n*=26,847)
Type of AF			
Paroxysmal	9358 (26.0)	2058 (22.6)	7300 (27.2)
Nonparoxysmal[a]	2046 (5.7)	550 (6.0)	1496 (5.6)
Unknown	24,550 (68.3)	6499 (71.4)	18,051 (67.2)
Sex, men	23,453 (65.2)	6443 (70.7)	17,010 (63.4)
Age, years	62.5±11.5	66.1±8.0	61.2±12.2
20–64 years	15,272 (42.5)	2685 (29.5)	12,587 (46.9)
65–74 years	20,682 (57.5)	6422 (70.5)	14,260 (53.1)
Body weight	16,001 (44.5)	6050 (66.4)	9951 (37.1)
＜50 kg	3069 (19.2)	1258 (20.8)	1811 (18.2)
≧50 kg	12,932 (80.8)	4792 (79.2)	8140 (81.8)
CHA_2DS_2-VASc score＝0	8401 (23.4)	1595 (17.5)	6806 (25.4)
CHA_2DS_2-VA score＝0	13,455 (37.4)	2454 (26.9)	11,001 (41.0)
Comorbidities[b,c]			
Any cancer	9107 (25.3)	9107 (100.0)	0 (0.0)
Metastatic solid tumor	2036 (5.7)	2036 (22.4)	0 (0.0)
Coagulopathy	1348 (3.7)	608 (6.7)	740 (2.8)
Hyperthyroidism	1313 (3.7)	143 (1.6)	1170 (4.4)
Dyslipidemia	3526 (9.8)	739 (8.1)	2787 (10.4)
Hyperuricemia/gout	254 (0.7)	61 (0.7)	193 (0.7)
Stress	74 (0.2)	29 (0.3)	45 (0.2)
Sleep disorder	3476 (9.7)	1404 (15.4)	2072 (7.7)
Sleep apnea syndrome	325 (0.9)	41 (0.5)	284 (1.1)
Valvular disease	1919 (5.3)	566 (6.2)	1353 (5.0)
Angina	3541 (9.8)	704 (7.7)	2837 (10.6)
Myocardial infarction	432 (1.2)	107 (1.2)	325 (1.2)
Atheroma	595 (1.7)	83 (0.9)	512 (1.9)
Peripheral vascular disease	1063 (3.0)	198 (2.2)	865 (3.2)
Peripheral thrombosis	1832 (5.1)	630 (6.9)	1202 (4.5)
Pulmonary embolism	398 (1.1)	168 (1.8)	230 (0.9)
Deep vein thrombosis	1469 (4.1)	555 (6.1)	914 (3.4)
Pregnancy	143 (0.4)	15 (0.2)	128 (0.5)
Pericarditis	474 (1.3)	144 (1.6)	330 (1.2)
Cardiomyopathy	319 (0.9)	71 (0.8)	248 (0.9)
Cardiac conduction failure	6187 (17.2)	944 (10.4)	5243 (19.5)
Chronic pulmonary disease	3255 (9.1)	1333 (14.6)	1922 (7.2)
Peptic ulcer	4316 (12.0)	1908 (21.0)	2408 (9.0)
Gastritis	5190 (14.4)	1866 (20.5)	3324 (12.4)
Mild liver dysfunction	2749 (7.6)	1064 (11.7)	1685 (6.3)
Moderate/severe liver dysfunction	203 (0.6)	89 (1.0)	114 (0.4)
Rheumatic disease	758 (2.1)	148 (1.6)	610 (2.3)
Renal disease	816 (2.3)	228 (2.5)	588 (2.2)
Polyuria	154 (0.4)	59 (0.6)	95 (0.4)

Table 1 Demographics and patient characteristics (Population 1) (continued)

	Total (N=35,954)	With cancer (n=9107)	Without cancer (n=26,847)
Drugs			
Heparin	1513 (4.2)	690 (7.6)	823 (3.1)
LMWH	94 (0.3)	69 (0.8)	25 (0.1)
Fondaparinux	5 (<0.1)	2 (<0.1)	3 (<0.1)
Antiplatelets	993 (2.8)	160 (1.8)	833 (3.1)
Thrombolytics	26 (0.1)	7 (0.1)	19 (0.1)
Antiarrhythmics	2848 (7.9)	493 (5.4)	2355 (8.8)
ACEi/ARB	245 (0.7)	140 (1.5)	105 (0.4)
MRA	116 (0.3)	53 (0.6)	63 (0.2)
Beta-blocker	895 (2.5)	163 (1.8)	732 (2.7)
CCB	1729 (4.8)	418 (4.6)	1311 (4.9)
Statin	881 (2.5)	238 (2.6)	643 (2.4)
Female hormones[d]	220 (0.6)	28 (0.3)	192 (0.7)
NSAIDs	5398 (15.0)	1866 (20.5)	3532 (13.2)
Digoxin	79 (0.2)	41 (0.5)	38 (0.1)
Anticancer drugs			
Alkylating agents	181 (0.5)	173 (1.9)	8 (<0.1)
Antimetabolites	905 (2.5)	888 (9.8)	17 (0.1)
Microtubule inhibitors	479 (1.3)	479 (5.3)	0 (0.0)
Cytotoxic antibiotics	365 (1.0)	363 (4.0)	2 (<0.1)
PK inhibitors	121 (0.3)	120 (1.3)	1 (<0.1)
Monoclonal antibody	450 (1.3)	448 (4.9)	2 (<0.1)
Platinum	800 (2.2)	800 (8.8)	0 (0.0)
Other antineoplastic drugs	119 (0.3)	111 (1.2)	8 (<0.1)
Hormones	148 (0.4)	137 (1.5)	11 (<0.1)
Hormone antagonists	148 (0.4)	288 (3.2)	3 (<0.1)

Data are presented as n (%) or mean±SD, unless otherwise specified

[a]Includes persistent and permanent AF

[b]One patient may have been counted in multiple categories

[c]From the day before the index date till 180 days ago

[d]Estrogen and progesterone

ACEi: angiotensin-converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, LMWH: low-molecular-weight heparin, MRA: mineralocorticoid receptor antagonist, NSAID: nonsteroidal anti-inflammatory drug, PK: protein kinase, SD: standard deviation

OAC within 14 days of AF diagnosis. These results indicate that while patients with a $CHADS_2$ score=0 generally have a low risk for stroke, those who have any additional risk factors may require OAC after thorough clinical evaluation.

The mean age of patients in Population 1 in this study (62.5 years) was lower than that recorded in the J-RHYTHM (69.7 years) and Fushimi AF (74.2 years) registries but higher than that reported in the Shinken Database (60.6 years)[15-17]. The proportion of men in this study (65.2%) was lower than that in the J-RHYTHM Registry (68.9%) and higher than that in the

Table 2　Cancer-related information in patients with cancer

	Total (N=9107)	Men (n=6443)	Women (n=2664)
Location of cancer			
Oral	361 (4.0)	317 (4.9)	44 (1.7)
Esophagus	703 (7.7)	616 (9.6)	87 (3.3)
Stomach	1219 (13.4)	995 (15.4)	224 (8.4)
Intestine	1776 (19.5)	1301 (20.2)	475 (17.8)
Liver	418 (4.6)	343 (5.3)	75 (2.8)
Pancreas	251 (2.8)	163 (2.5)	88 (3.3)
Lung	1711 (18.8)	1298 (20.1)	413 (15.5)
Thymus/heart	49 (0.5)	33 (0.5)	16 (0.6)
Bone/joint	16 (0.2)	10 (0.2)	6 (0.2)
Skin	122 (1.3)	81 (1.3)	41 (1.5)
Breast	648 (7.1)	5 (0.1)	643 (24.1)
Female reproductive	371 (4.1)	0 (0.0)	371 (13.9)
Male reproductive	868 (9.5)	868 (13.5)	0 (0.0)
Kidney	756 (8.3)	639 (9.9)	117 (4.4)
CNS	46 (0.5)	27 (0.4)	19 (0.7)
Endocrine	174 (1.9)	79 (1.2)	95 (3.6)
Lymph/blood	663 (7.3)	439 (6.8)	224 (8.4)
Metastatic solid tumor	2036 (22.4)	1336 (20.7)	700 (26.3)
Anticancer drugs			
Alkylating agents	173 (1.9)	70 (1.1)	103 (3.9)
Antimetabolites	888 (9.8)	598 (9.3)	290 (10.9)
Microtubule inhibitors	479 (5.3)	274 (4.3)	205 (7.7)
Cytotoxic antibiotics	363 (4.0)	207 (3.2)	156 (5.9)
PK inhibitors	120 (1.3)	57 (0.9)	63 (2.4)
Monoclonal antibody	448 (4.9)	270 (4.2)	178 (6.7)
Platinum	800 (8.8)	563 (8.7)	237 (8.9)
Other antineoplastic drugs	111 (1.2)	68 (1.1)	43 (1.6)
Hormones	137 (1.5)	124 (1.9)	13 (0.5)
Hormone antagonists	288 (3.2)	131 (2.0)	157 (5.9)
Treatment for cancer			
Surgery	1179 (12.9)	827 (12.8)	352 (13.2)
Stem cell transplant	0 (0.0)	2 (<0.1)	1 (<0.1)
Lymphadenectomy	17 (0.2)	7 (0.1)	10 (0.4)
Radiotherapy	352 (3.9)	259 (4.0)	93 (3.5)

Data are presented as n (%)
CNS: central nervous system, PK: protein kinase

Fushimi AF Registry (59.3%) and Shinken Database (61.0%)[15-17]. Approximately 60% of patients in this study had advanced age (65-74 years). While advanced age was reported as a significant risk factor for stroke in Western studies[29,30], age (65-74 years) was not found to be a significant risk factor for thromboembolism in a pooled analysis of 3 Japanese AF registries[13] or 5 Japanese AF registry studies (J-RISK AF)[31].

Low body mass index (BMI) < 18.5 kg/m^2 is

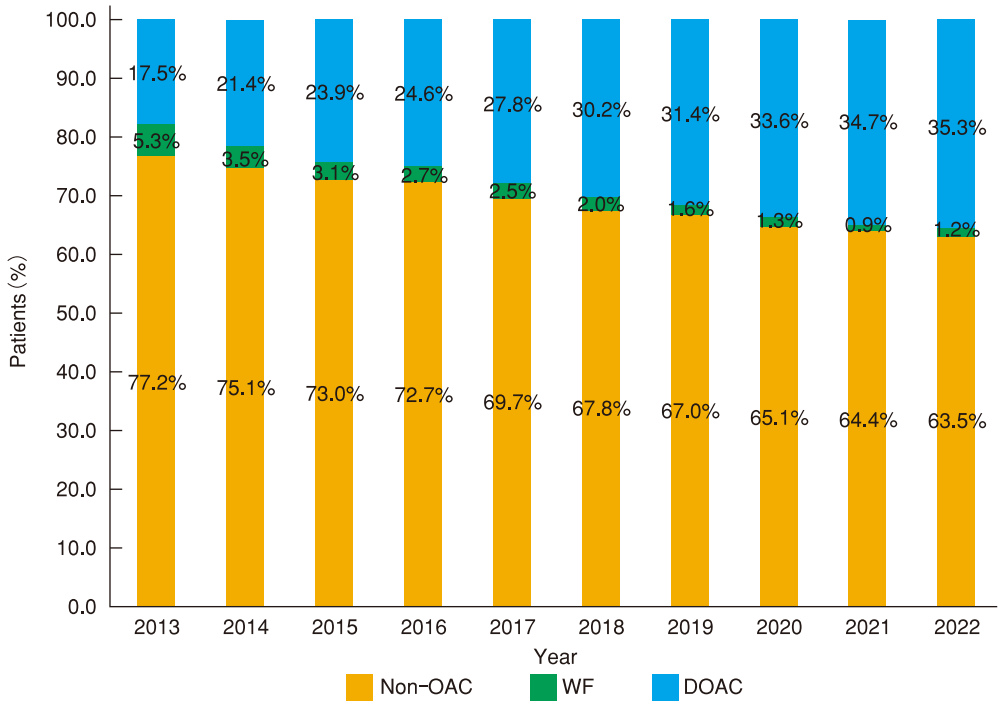

Fig. 3 Temporal trend in the rates of OAC use
OAC: oral anticoagulant, WF: warfarin, DOAC: direct oral anticoagulant

a risk factor for ischemic stroke in Japanese patients[2,31]. Body weight information was available for approximately half of all patients in this study based on MDV database, and approximately 20% weighed ＜50 kg. In the Fushimi AF Registry, patients weighing ≦50 kg were associated with a nearly 2-fold increased risk of stroke/systemic embolism (SE), worse mortality rate, and higher incidence of stroke/SE/all-cause death than non-low-body-weight patients[32].

The type of AF (persistent and permanent AF) is also identified as a risk factor for ischemic stroke in Japanese patients[2,31]. However, it was impossible to correctly determine the type of AF from the ICD-10 coding in the present study; thus, the proportion of unknown AF was approximately 70% of patients each in Populations 1 and 2. Therefore, most patients with persistent and permanent AF deemed to be included in the unknown AF group. In contrast, paroxysmal AF was reported in approximately 26% of patients in this study. The detection of paroxysmal AF is challenging; however, the widespread use of wearable devices and artificial intelligence is making it more feasible, which is beneficial to patients[33].

Although the $CHADS_2$ and CHA_2DS_2-VASc scores are widely used for risk assessment of ischemic stroke, a novel Japanese-specific scoring system that includes low BMI and type of AF, the HELT-E_2S_2 score, which assigns scoring based on the following risk factors: hypertension, elderly (aged 75-84 years), low BMI ＜18.5 kg/m^2, and type of AF (persistent/permanent) (1 point each), and extreme elderly (aged

Table 3 Patient characteristics without anticoagulation therapy and with each oral anticoagulant in Population 2

	Total (*N*=32,600)	Non-OAC (*n*=22,298)	Warfarin (*n*=676)	Dabigatran (*n*=931)	Rivaroxaban (*n*=2739)	Apixaban (*n*=2447)	Edoxaban (*n*=3509)
Type of AF							
Paroxysmal	8705 (26.7)	6352 (28.5)	119 (17.6)	226 (24.3)	610 (22.3)	592 (24.2)	806 (23.0)
Nonparoxysmal[a]	1839 (5.6)	1216 (5.5)	97 (14.3)	56 (6.0)	138 (5.0)	133 (5.4)	199 (5.7)
Unknown	22,056 (67.7)	14,730 (66.1)	460 (68.0)	649 (69.7)	1991 (72.7)	1722 (70.4)	2504 (71.4)
Sex, men	21,416 (65.7)	14,306 (64.2)	507 (75.0)	701 (75.3)	2033 (74.2)	1702 (69.6)	2167 (61.8)
Age	62.4±11.5	61.2±12.3	66.0±8.8	63.6±10.0	64.8±9.0	65.4±9.0	65.2±8.7
20–64 years	13,878 (42.6)	10,320 (46.3)	198 (29.3)	376 (40.4)	977 (35.7)	782 (32.0)	1225 (34.9)
65–74 years	18,722 (57.4)	11,978 (53.7)	478 (70.7)	555 (59.6)	1762 (64.3)	1665 (68.0)	2284 (65.1)
Body weight	14,081 (43.2)	9683 (43.4)	494 (73.1)	335 (40.0)	1068 (39.0)	955 (39.0)	1546 (44.1)
＜50 kg	2728 (19.4)	1995 (20.6)	73 (14.8)	32 (9.6)	154 (14.4)	163 (17.1)	311 (20.1)
≧50 kg	11,353 (80.6)	7688 (79.4)	421 (85.2)	303 (90.4)	914 (85.6)	792 (82.9)	1235 (79.9)
Initial dose of OAC[b]							
Mean±SD	—	—	3.6±11.0	261.5±164.6	14.9±8.4	10.5±5.1	43.2±31.2
Median (IQR)	—	—	2.5 (2.0, 3.0)	220 (220, 300)	15 (15, 15)	10 (10, 10)	30 (30, 60)
CHA_2DS_2-VASc score＝0	7665 (23.5)	5489 (24.6)	127 (18.8)	246 (26.4)	644 (23.5)	468 (19.1)	691 (19.7)
CHA_2DS_2-VA score＝0	12,205 (37.4)	9146 (41.0)	161 (23.8)	319 (34.3)	841 (30.7)	649 (26.5)	1089 (31.0)
Comorbidities[c,d]							
Any cancer	7762 (23.8)	5659 (25.4)	144 (21.3)	170 (18.3)	540 (19.7)	495 (20.2)	754 (21.5)
No cancer	24,838 (76.2)	16,639 (74.6)	532 (78.7)	761 (81.7)	2199 (80.3)	1952 (79.8)	2755 (78.5)
Metastatic solid tumor	1609 (4.9)	1188 (5.3)	34 (5.0)	28 (3.0)	97 (3.5)	103 (4.2)	159 (4.5)
Coagulopathy	1080 (3.3)	761 (3.4)	48 (7.1)	26 (2.8)	75 (2.7)	58 (2.4)	112 (3.2)
Hyperthyroidism	1236 (3.8)	991 (4.4)	13 (1.9)	30 (3.2)	67 (2.4)	65 (2.7)	70 (2.0)
Dyslipidemia	3186 (9.8)	1919 (8.6)	93 (13.8)	119 (12.8)	350 (12.8)	292 (11.9)	413 (11.8)
Hyperuricemia/gout	229 (0.7)	128 (0.6)	10 (1.5)	13 (1.4)	20 (0.7)	28 (1.1)	30 (0.9)
Stress	65 (0.2)	38 (0.2)	3 (0.4)	0 (0.0)	7 (0.3)	6 (0.2)	11 (0.3)
Sleep disorder	2981 (9.1)	2067 (9.3)	66 (9.8)	69 (7.4)	220 (8.0)	228 (9.3)	331 (9.4)
Sleep apnea syndrome	301 (0.9)	202 (0.9)	4 (0.6)	10 (1.1)	27 (1.0)	24 (1.0)	34 (1.0)
Valvular disease	1703 (5.2)	1141 (5.1)	69 (10.2)	40 (4.3)	153 (5.6)	121 (4.9)	179 (5.1)
Angina	3238 (9.9)	2111 (9.5)	88 (13.0)	113 (12.1)	323 (11.8)	299 (12.2)	304 (8.7)
Myocardial infarction	391 (1.2)	260 (1.2)	20 (3.0)	2 (0.2)	33 (1.2)	43 (1.8)	33 (0.9)

Table 3 Patient characteristics without anticoagulation therapy and with each oral anticoagulant in Population 2 (continued)

	Total (*N*=32,600)	Non-OAC (*n*=22,298)	Warfarin (*n*=676)	Dabigatran (*n*=931)	Rivaroxaban (*n*=2739)	Apixaban (*n*=2447)	Edoxaban (*n*=3509)
Atheroma	515 (1.6)	296 (1.3)	23 (3.4)	13 (1.4)	54 (2.0)	62 (2.5)	67 (1.9)
Peripheral vascular disease	930 (2.9)	564 (2.5)	42 (6.2)	26 (2.8)	96 (3.5)	95 (3.9)	107 (3.0)
Peripheral thrombosis	372 (1.1)	157 (0.7)	45 (6.7)	24 (2.6)	42 (1.5)	49 (2.0)	55 (1.6)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	125 (0.4)	117 (0.5)	1 (0.1)	0 (0.0)	4 (0.1)	1 (<0.1)	2 (0.1)
Pericarditis	410 (1.3)	283 (1.3)	15 (2.2)	9 (1.0)	32 (1.2)	31 (1.3)	40 (1.1)
Cardiomyopathy	298 (0.9)	196 (0.9)	15 (2.2)	4 (0.4)	19 (0.7)	26 (1.1)	38 (1.1)
Cardiac conduction failure	5781 (17.7)	3959 (17.8)	72 (10.7)	202 (21.7)	496 (18.1)	451 (18.4)	601 (17.1)
Chronic pulmonary disease	2874 (8.8)	2021 (9.1)	46 (6.8)	80 (8.6)	214 (7.8)	212 (8.7)	301 (8.6)
Peptic ulcer	3726 (11.4)	2402 (10.8)	109 (16.1)	138 (14.8)	312 (11.4)	314 (12.8)	451 (12.9)
Gastritis	4568 (14.0)	3137 (14.1)	100 (14.8)	114 (12.2)	371 (13.5)	331 (13.5)	515 (14.7)
Mild liver dysfunction	2391 (7.3)	1693 (7.6)	50 (7.4)	60 (6.4)	186 (6.8)	161 (6.6)	241 (6.9)
Moderate/severe liver dysfunction	153 (0.5)	117 (0.5)	6 (0.9)	1 (0.1)	7 (0.3)	11 (0.4)	11 (0.3)
Rheumatic disease	644 (2.0)	409 (1.8)	17 (2.5)	19 (2.0)	52 (1.9)	42 (1.7)	105 (3.0)
Renal disease	722 (2.2)	551 (2.5)	78 (11.5)	6 (0.6)	22 (0.8)	29 (1.2)	36 (1.0)
Polyuria	139 (0.4)	89 (0.4)	1 (0.1)	5 (0.5)	13 (0.5)	13 (0.5)	18 (0.5)
Drugs							
Heparin	1222 (3.7)	830 (3.7)	62 (9.2)	16 (1.7)	95 (3.5)	76 (3.1)	143 (4.1)
LMWH	69 (0.2)	54 (0.2)	2 (0.3)	0 (0.0)	3 (0.1)	2 (0.1)	8 (0.2)
Fondaparinux	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (0.1)
Antiplatelets	878 (2.7)	565 (2.5)	24 (3.6)	24 (2.6)	102 (3.7)	71 (2.9)	92 (2.6)
Thrombolytics	15 (<0.1)	7 (<0.1)	2 (0.3)	1 (0.1)	1 (<0.1)	1 (<0.1)	3 (0.1)
Antiarrhythmics	2678 (8.2)	1875 (8.4)	31 (4.6)	75 (8.1)	254 (9.3)	199 (8.1)	244 (7.0)
ACEi/ARB	219 (0.7)	139 (0.6)	2 (0.3)	5 (0.5)	21 (0.8)	17 (0.7)	35 (1.0)
MRA	93 (0.3)	67 (0.3)	1 (0.1)	4 (0.4)	2 (0.1)	6 (0.2)	13 (0.4)
β-blocker	836 (2.6)	593 (2.7)	8 (1.2)	24 (2.6)	87 (3.2)	47 (1.9)	77 (2.2)
CCB	1617 (5.0)	1107 (5.0)	18 (2.7)	41 (4.4)	153 (5.6)	123 (5.0)	175 (5.0)
Statin	792 (2.4)	512 (2.3)	13 (1.9)	22 (2.4)	76 (2.8)	73 (3.0)	96 (2.7)
Female hormones[e]	185 (0.6)	144 (0.6)	4 (0.6)	2 (0.2)	10 (0.4)	10 (0.4)	15 (0.4)

Table 3 Patient characteristics without anticoagulation therapy and with each oral anticoagulant in Population 2 (continued)

	Total (N=32,600)	Non-OAC (n=22,298)	Warfarin (n=676)	Dabigatran (n=931)	Rivaroxaban (n=2739)	Apixaban (n=2447)	Edoxaban (n=3509)
NSAIDs	4630 (14.2)	3237 (14.5)	84 (12.4)	124 (13.3)	363 (13.3)	317 (13.0)	505 (14.4)
Digoxin	73 (0.2)	58 (0.3)	1 (0.1)	2 (0.2)	4 (0.1)	6 (0.2)	2 (0.1)
Anticancer drugs							
Alkylating agents	146 (0.4)	114 (0.5)	2 (0.3)	3 (0.3)	6 (0.2)	5 (0.2)	16 (0.5)
Antimetabolites	678 (2.1)	541 (2.4)	8 (1.2)	10 (1.1)	22 (0.8)	40 (1.6)	57 (1.6)
Microtubule inhibitors	376 (1.2)	302 (1.4)	5 (0.7)	10 (1.1)	13 (0.5)	14 (0.6)	32 (0.9)
Cytotoxic antibiotics	272 (0.8)	205 (0.9)	2 (0.3)	6 (0.6)	12 (0.4)	15 (0.6)	32 (0.9)
PK inhibitors	96 (0.3)	69 (0.3)	0 (0.0)	1 (0.1)	8 (0.3)	8 (0.3)	10 (0.3)
Monoclonal antibody	339 (1.0)	266 (1.2)	2 (0.3)	6 (0.6)	7 (0.3)	21 (0.9)	37 (1.1)
Platinum	616 (1.9)	490 (2.2)	5 (0.7)	9 (1.0)	22 (0.8)	34 (1.4)	56 (1.6)
Other antineoplastic drugs	102 (0.3)	79 (0.4)	0 (0.0)	1 (0.1)	4 (0.1)	9 (0.4)	9 (0.3)
Hormones	139 (0.4)	106 (0.5)	2 (0.3)	5 (0.5)	11 (0.4)	4 (0.2)	11 (0.3)
Hormone antagonists	260 (0.8)	168 (0.8)	5 (0.7)	8 (0.9)	24 (0.9)	21 (0.9)	34 (1.0)

Data are presented as n (%) or mean±SD, unless otherwise specified

[a]Includes persistent and permanent AF

[b]Data are presented as mean±SD and/or median IQR mg/day

[c]One patient may have been counted in multiple categories

[d]From the day before the index date till 180 days ago

[e]Estrogen and progesterone

ACEi: angiotensin-converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, IQR: interquartile range, LMWH: low-molecular-weight heparin, MRA: mineralocorticoid receptor antagonist, NSAID: nonsteroidal anti-inflammatory drug, OAC: oral anticoagulant, PK: protein kinase, SD: standard deviation

≧85 years) and previous stroke (2 points each; total score=7), can estimate the risk of ischemic stroke more effectively[34].

Vascular disease is listed as "other risks" for thromboembolism in patients with NVAF in the Japanese guidelines[2]. In Population 1, vascular diseases such as angina, MI, atheroma, and peripheral vascular disease were observed in 9.8%, 1.2%, 1.7%, and 3.0% of patients, respectively. Cardiomyopathy, which is also included in other risks for thromboembolism in patients with NVAF in Japanese guidelines[2], was observed in 0.9% of patients in this study. Cardiomyopathy was reportedly an independent risk factor for stroke in Japanese patients with NVAF[35]. However, it was not detected as a significant risk factor for ischemic stroke in the J-RISK AF[31]. Renal disease was observed as a comorbidity in 2.3% of patients in Population 1. Although renal dysfunction was reportedly an independent risk factor for thromboembolism in Japanese patients with NVAF[36,37], renal function could not be evaluated in this study because this was an ICD-10 code-based analysis. Cancer was observed in 25.3% of patients in Population 1 and 23.8% in Population 2 and was the most common comorbidity in both populations.

Patients with a $CHADS_2$ score=0 have been excluded from several randomized controlled trials of DOACs performed to date, such as ROCKET AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF-TIMI 48 (edoxaban) trials[4-6]. The RE-LY trial (dabigatran) included approximately 30% of patients with a $CHADS_2$ score=0 or 1[3]. Nonetheless, data on the risk-benefit profile of OAC therapy for patients with a $CHADS_2$ score=0 are scarce[18,19].

AF and cancer are closely related due to their bidirectional nature and shared risk factors, such as advanced age, obesity, diabetes, and smoking[38-40]. Management of patients with coexisting AF and cancer is difficult due to the high risk of bleeding and thrombosis[41,42]. However, data on patients with AF and cancer are limited, as several Japanese registries have excluded patients with cancer. The All Nippon AF In the Elderly (ANAFIE) registry includes patients with cancer but is limited to elderly patients with NVAF aged ≧75 years and active cancer (primary cancer-bearing), defined as patients diagnosed with primary gastric, colorectal, lung, breast, uterine, ovarian, pancreatic, or other cancers who are treatment-naïve, planned to undergo, or currently undergoing cancer treatment, including chemotherapy, radiotherapy, or surgery, for cancer resection and those who have a life expectancy of ≧1 year at the time of providing informed consent[43]. In this study, the most common location of cancer was the intestine (19.5%), followed by the lung (18.8%) and stomach (13.4%), which is in agreement with Japanese cancer epidemiology data for 2022[44].

A complex issue in patients with cancer with new AF is risk stratification for stroke/SE, and the ESC cardio-oncology guidelines recommend the use of the CHA_2DS_2-VASc score; however, the CHA_2DS_2-VASc score has not been extensively validated in patients with cancer[24]. Other conventional risk scores, such as $CHADS_2$ and HAS-BLED scores, also do not consider cancer as a risk factor for stroke and bleeding in patients win NVAF[39]. In a Danish real-world study that included patients with a CHA_2DS_2-VASc score=0, the 2-year cumulative incidence of thromboembolism in patients with and without recent cancer was 1.7% and 1.2%, respectively[45], thus further emphasizing the need to consider cancer as a risk factor when initiating OAC in patients apparently at a low risk of stroke estimated by conventional risk scores.

In the present study, the OAC use in NVAF

patients with $CHADS_2$ score＝0 showed a significant increasing trend across the years; and among OACs, there was a decreasing trend in the warfarin use and an increasing trend in the DOAC use. Nevertheless, to our best knowledge, no studies have evaluated the efficacy and safety of DOACs in specific patients with a $CHADS_2$ score ＝0. Therefore, additional research is needed to better understand the benefits of DOACs in patients with a $CHADS_2$ score＝0, including those with cancer.

In Population 2, the proportion of patients aged 65–74 years (70.7%) and those with comorbid renal disease (11.5%) was the highest in the warfarin group, suggesting that warfarin was favorably prescribed to elderly Japanese patients with renal impairment rather than DOACs. When an OAC is being considered in patients with NVAF for stroke prevention, DOACs are the preferred option compared with VKAs in Asian than in non-Asian patients, because the efficacy and safety of DOACs in Asians are more profound than in non-Asians[46,47]. Despite the elevated bleeding risk, DOACs have a significant benefit in terms of reducing the stroke risk in individuals with AF and cancer[48]. Although DOACs have not been evaluated in dedicated randomized controlled trials in patients with cancer, secondary analyses of seminal DOAC trials and observational data suggest better safety and at least similar effectiveness of DOACs compared with VKAs in patients with AF and cancer[49–52]. Therefore, a careful assessment of the individual's risk-benefit profile is needed to initiate a DOAC. Atterman, et al demonstrated that patients with AF and active cancer, and at least an intermediate stroke risk who were treated with an OAC had a lower risk of adverse events, including death[53]. In this study, a higher proportion of patients with cancer did not receive any OAC than those without cancer and nearly 75% of patients with any cancer did not receive any OAC. This rate is comparable with a real-world study conducted in the United States from 2010 to 2016 where nearly 70% of NVAF patients with cancer did not initiate anticoagulation therapy[54]. Despite studies demonstrating that DOACs are effective and generally safe in patients with NVAF and cancer[49–52], their uptake in this population is limited due to increased bleeding risk, prothrombotic state associated with cancer and anticancer therapies, lack of a well-validated risk score specifically for patients with cancer, and potential drug-drug interactions[39,55]. Additionally, patients with AF and cancer are less likely to see a cardiologist or fill anticoagulant prescriptions[56]. Furthermore, similar to the findings of the current study, the warfarin use declined, whereas DOAC use increased during the study period[54].

The strength of this study is that the findings are based on the MDV database, which includes a nationwide population and an elderly population. However, there are some limitations. First, the MDV database consists of inpatient and outpatient data derived from only DPC hospitals. The prevalence of comorbidities or other factors among patients treated at DPC hospitals may be higher than those seen among patients diagnosed with NVAF by general practitioners and the general population. Second, although valvular AF is defined as rheumatic mitral valve diseases (predominantly mitral stenosis) and mechanical prosthetic valves in Japanese guidelines[2], some patients with NVAF may have been classified as valvular AF and excluded from the present analysis. Third, because only patients with baseline data were included, patients who had a suspected diagnosis of NVAF at clinics and were then diagnosed with NVAF at the first visit at any of the DPC hospitals were not included. Patients with a $CHADS_2$ score＝0 were identified

using the ICD-10 code to exclude those with heart failure, hypertension, diabetes mellitus, or history of stroke. However, the study population included patients who were prescribed treatment for hypertension or heart failure, such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and mineralocorticoid receptor antagonists. Although the precise reasons for the prescription of these drugs were unknown, the proportion of patients prescribed these drugs was limited to 1.0% and, therefore, might not affect the overall results. Fourth, the "other risks" for ischemic stroke described in Japanese guidelines[2] were not sufficiently evaluated. Body weight was obtained only from approximately 50% of patients. Although LAD >45 mm is reportedly an additional risk factor for ischemic stroke in patients with NVAF[57], echocardiographic findings were not available in this study. Fifth, diseases that could not be adequately assessed in the DPC database should be investigated in detail using other data sources, such as registries. A detailed survey that includes patients with cancer is warranted to identify unknown risks for stroke and investigate the optimal pharmacotherapy for patients with a $CHADS_2$ score=0. Finally, clinical outcomes, such as the incidence of thromboembolism and major bleeding, were not assessed in this study. Therefore, it is unknown whether OAC use is really beneficial in NVAF patients with a $CHADS_2$ score=0, including those with cancer.

CONCLUSION

This study highlights the clinical characteristics and treatment patterns of Japanese NVAF patients with a $CHADS_2$ score=0, including those with cancer. In this study, patients with a $CHADS_2$ score=0 had the highest rate of comorbid cancer. The proportion of NVAF patients with cancer was consistent during the study period, while the proportion of patients receiving OAC treatment increased yearly. Further studies are needed to determine if OACs are really beneficial in NVAF patients with a $CHADS_2$ score=0, including those with concurrent cancer.

CONFLICT OF INTEREST

Eitaro Kodani has received remuneration from Daiichi-Sankyo. Miki Imura and Susumu Hirose are employees of Pfizer Japan Inc.

ETHICS APPROVAL

Since this is an epidemiological study and did not evaluate the efficacy or safety of any drug, it was not reviewed by an institutional review board. This study extracted data that existed in an anonymized structured format and did not contain any personal information of patients. According to applicable legal requirements, such data are not subject to privacy laws. According to the Ethical Guidelines for Human Life Science and Medical Research in Japan, informed consent is not required for studies that use nonlinkable, anonymized data. Therefore, obtaining informed consent from the patients and institutional review board approval were not required.

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AUTHORSHIP

All authors listed in this article fulfill the criteria set by the International Committee of Medical Journal Editors (ICMJE) for authorship, take responsibility for the integrity of the work, and have provided their consent for the publication of this version.

AUTHOR CONTRIBUTIONS

Eitaro Kodani interpreted the data, critically reviewed the literature, and reviewed and edited the final manuscript. Miki Imura designed the study, managed the project, interpreted the data, critically reviewed the literature, and prepared and edited the final manuscript. Susumu Hirose interpreted the data, critically reviewed the literature, and reviewed and edited the final manuscript. All authors read and approved the final manuscript.

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Supplementary material

Table S1 Definition of excluding factors/excluded diseases and procedures

Code 1[a]	Code 2[b]	Names
Valvular AF		
I48.9	8846941	Valvular atrial fibrillation
I48.9	8847772	Postoperative atrial fibrillation
Mechanical-valvular		
T82.0	8835595	Mechanical complications of artificial heart valve
T82.0	8842773	Artificial heart valve failure
Rheumatic valvular disease		
I05.0	8836695	Mitral valve stenosis
I05.1	8840946	Rheumatic mitral valve incompetence
I05.2	3942006	Mitral stenosis and insufficiency
I05.8	3949003	Papillary mitral insufficiency
I05.8	8836698	Mitral valve insufficiency
I05.9	3949001	Mitral valvular disease
I05.9	4240009	Mitral valvular disease
I05.9	4240018	Mitral valve disease
I05.9	8836697	Mitral valve endocarditis
I05.9	8840945	Rheumatic mitral valve disease
I06.0	8840947	Rheumatic aortic stenosis disease
I06.0	8849007	Rheumatic aortic valve stenosis disease
I06.1	8840950	Rheumatic aortic valve incompetence
I06.2	8840948	Rheumatic aortic valve stenosis and insufficiency
I06.9	8840949	Rheumatic aortic valve disease
I08.0	8848940	Mitral stenosis, insufficiency, and aortic valve stenosis
I08.0	8848941	Mitral stenosis and insufficiency and aortic valve incompetence
I08.0	8848956	Aortic valve stenosis and insufficiency and mitral valve stenosis
I08.0	8848957	Aortic valve stenosis and insufficiency and mitral valve incompetence
I08.0	8848960	Aortic valve stenosis and mitral valve stenosis
I08.0	8848962	Aortic valve stenosis and mitral valve incompetence
I08.0	8848967	Aortic valve incompetence and mitral valve stenosis
I08.0	8848969	Aortic valve incompetence and mitral valve incompetence
I08.1	8848942	Mitral valve stenosis and tricuspid stenosis
I08.1	8848943	Mitral valve stenosis and tricuspid valve incompetence
I08.1	8848945	Mitral valve incompetence and tricuspid stenosis
I08.1	8848946	Mitral valve incompetence and tricuspid valve incompetence
I08.2	8848958	Aortic valve stenosis and tricuspid stenosis
I08.2	8848959	Aortic valve stenosis and tricuspid valve incompetence
I08.2	8848965	Aortic valve incompetence and tricuspid stenosis
I08.2	8848966	Aortic valve incompetence and tricuspid valve incompetence
I08.3	8848961	Aortic valve stenosis and mitral valve stenosis and tricuspid valve incompetence
I08.3	8848963	Aortic valve stenosis and mitral valve incompetence and tricuspid valve incompetence
I08.3	8848968	Aortic valve incompetence and mitral valve stenosis and tricuspid valve incompetence
I08.3	8848970	Aortic valve incompetence and mitral valve incompetence and tricuspid valve incompetence
Z95.2	8842927	Heart valve replacement postoperative
Z95.2	8844545	Post-aortic valve replacement
Z95.4	8842956	Post-mitral valve replacement
Z95.4	8844305	Post-allogenic valve replacement

[a]ICD-10 code [b]Japanese claims code ICD-10: International Classification of Diseases 10th revision

Table S2 Definition of OACs

EPhMRA ATC classification	General name	Claims code	Drug name
B01A0	Warfarin potassium	610450012	Warfarin K tablets 1 mg
B01A0	Warfarin potassium	610460002	Warfarin K tablets 1 mg "F"
B01A0	Warfarin potassium	610462024	Warfarin K tablets 0.5 mg "HD"
B01A0	Warfarin potassium	610462025	Warfarin K tablets 2 mg "HD"
B01A0	Warfarin potassium	610463227	Warfarin K tablets 0.5 mg
B01A0	Warfarin potassium	610463228	Warfarin K tablets 2 mg
B01A0	Warfarin potassium	613330001	Warfarin K tablets 1 mg
B01A0	Warfarin potassium	613330002	Warfarin K tablets 5 mg
B01A0	Warfarin potassium	613330003	Warfarin tablets 1 mg
B01A0	Warfarin potassium	613330004	Warfarin tablets 5 mg
B01A0	Warfarin potassium	620000731	Warfarin K tablets 1 mg "HD"
B01A0	Warfarin potassium	620002332	Warfarin tablets 0.5 mg
B01A0	Warfarin potassium	620002472	Warfarin tablets 0.5 mg
B01A0	Warfarin potassium	620002473	Warfarin tablets 1 mg
B01A0	Warfarin potassium	620811502	Warfarin K tablets 1 mg "F"
B01A0	Warfarin potassium	620811503	Warfarin K tablets 1 mg "Nissin"
B01A0	Warfarin potassium	620811507	Warfarin K tablets 1 mg "TEVA"
B01A0	Warfarin potassium	620811510	Warfarin K tablets 1 mg "TOWA"
B01A0	Warfarin potassium	620811511	Warfarin K tablets 1 mg "NP"
B01A0	Warfarin potassium	621480504	Warfarin K tablets 0.5 mg "TEVA"
B01A0	Warfarin potassium	621480506	Warfarin K tablets 0.5 mg "Towa"
B01A0	Warfarin potassium	621480507	Warfarin K tablets 0.5 mg "NP"
B01A0	Warfarin potassium	621480509	Warfarin K tablets 0.5 mg "NIG"
B01A0	Warfarin potassium	621480604	Warfarin K tablets 2 mg "NP"
B01A0	Warfarin potassium	621938101	Warfarin K granules 0.2% "NS"
B01A0	Warfarin potassium	621940901	Warfarin K granules 0.2% "YD"
B01A0	Warfarin potassium	622122601	Warfarin granules 0.2%
B01E0	Dabigatran etexilate methanesulfonate	622043301	Prazaxa capsules 75 mg
B01E0	Dabigatran etexilate methanesulfonate	622043401	Prazaxa capsules 110 mg
B01F0	Apixaban	622224901	Eliquis tablets 2.5 mg
B01F0	Apixaban	622225001	Eliquis tablets 5 mg
B01F0	Edoxaban tosylate hydrate	622080901	LIXIANA tablets 15 mg
B01F0	Edoxaban tosylate hydrate	622081001	LIXIANA tablets 30 mg
B01F0	Edoxaban tosylate hydrate	622375201	LIXIANA tablets 60 mg
B01F0	Edoxaban tosylate hydrate	622576001	LIXIANA OD tablets 15 mg
B01F0	Edoxaban tosylate hydrate	622576101	LIXIANA OD tablets 30 mg
B01F0	Edoxaban tosylate hydrate	622576201	LIXIANA OD tablets 60 mg
B01F0	Rivaroxaban	622068301	Xarelto tablets 10 mg
B01F0	Rivaroxaban	622068401	Xarelto tablets 15 mg
B01F0	Rivaroxaban	622449101	Xarelto fine granules 10 mg
B01F0	Rivaroxaban	622449201	Xarelto fine granules 15 mg
B01F0	Rivaroxaban	622829001	Xarelto OD tablets 10 mg
B01F0	Rivaroxaban	622829101	Xarelto OD tablets 15 mg
B01F0	Rivaroxaban	622919801	Xarelto tablets 2.5 mg

ATC: Anatomical Therapeutic Chemical, EPhMRA: European Pharmaceutical Market Research Association, OAC: oral anticoagulant, OD: once daily

Table S3 Ten-year trends in the population of cancer in Population 1 and the rate of OAC use in Population 2

Index year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	*p* for trend*
Population 1											
Number	1526	2448	2901	3329	3766	4234	4716	4300	4637	4097	
With cancer (*n*=9107)	412 (27.0)	662 (27.0)	752 (25.9)	811 (24.4)	957 (25.4)	945 (22.3)	1195 (25.3)	1115 (25.9)	1236 (26.7)	1022 (24.9)	0.606
Population 2											
Number	1395	2221	2632	2934	3366	3823	4288	3933	4227	3781	
OAC use (*n*=10,302)	318 (22.8)	552 (24.9)	711 (27.0)	800 (27.3)	1020 (30.3)	1229 (32.2)	1415 (33.0)	1374 (34.9)	1503 (35.6)	1380 (36.5)	<0.001
Non-OAC (*n*=22,298)	1077 (77.2)	1669 (75.1)	1921 (73.0)	2134 (72.7)	2346 (69.7)	2594 (67.8)	2873 (67.0)	2559 (65.1)	2724 (64.4)	2401 (63.5)	
Warfarin (*n*=676)	74 (5.3)	77 (3.5)	81 (3.1)	79 (2.7)	84 (2.5)	76 (2.0)	68 (1.6)	53 (1.3)	37 (0.9)	47 (1.2)	<0.001
DOAC (*n*=9626)	244 (17.5)	475 (21.4)	630 (23.9)	721 (24.6)	936 (27.8)	1153 (30.2)	1347 (31.4)	1321 (33.6)	1466 (34.7)	1333 (35.3)	
Dabigatran (*n*=931)	104 (7.5)	104 (4.7)	78 (3.0)	56 (1.9)	96 (2.9)	132 (3.5)	112 (2.6)	102 (2.6)	95 (2.2)	52 (1.4)	
Rivaroxaban (*n*=2739)	135 (9.7)	192 (8.6)	229 (8.7)	223 (7.6)	285 (8.5)	300 (7.8)	391 (9.1)	327 (8.3)	344 (8.1)	313 (8.3)	
Apixaban (*n*=2447)	4 (0.3)	175 (7.9)	276 (10.5)	289 (9.9)	255 (7.6)	275 (7.2)	289 (6.7)	290 (7.4)	315 (7.5)	279 (7.4)	
Edoxaban (*n*=3509)	1 (<0.1)	4 (0.2)	47 (1.8)	153 (5.2)	300 (8.9)	446 (11.7)	555 (12.9)	602 (15.3)	712 (16.8)	689 (18.2)	

Proportion of patients were calculated within each index year.

*Cochran-Armitage test

DOAC: direct oral anticoagulant, OAC: oral anticoagulant