



Original article

Current status of clinical background of patients with atrial fibrillation in a community-based survey: The Fushimi AF Registry

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ABSTRACT

Background: Atrial fibrillation (AF) increases the risks of stroke and death, and the prevalence of AF is increasing significantly. Until recently, warfarin was the only oral anticoagulant for stroke prevention, but novel anticoagulants are now under development.

Methods and results: The Fushimi AF Registry is a community-based survey of AF patients. We aimed to enroll all of the AF patients in Fushimi-ku, which is located at the southern end of the city of Kyoto. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. On the basis of the general prevalence of AF in the Japanese (0.6%), we estimated the total number of AF patients as 1700. A total of 76 institutions, a large proportion of which were private clinics, participated in the study. At present, we have enrolled 3183 patients from March 2011 to June 2012 (approximately 1.12% of total population). The mean age was 74.2 ± 11.0 years, and 59.3% of subjects were male. The mean body weight was 58.5 ± 13.2 kg, and the proportions with a body weight of less than 50 kg and 60 kg were 25.7% and 55.0%, respectively. The type of AF was paroxysmal in 46.0%, persistent in 7.3%, and permanent in 46.7%. Major co-existing diseases were hypertension (60.6%), heart failure (27.9%), diabetes (23.2%), stroke (19.4%), coronary artery disease (15.0%), myocardial infarction (6.4%), dyslipidemia (42.4%), and chronic kidney disease (26.4%). The mean CHADS2 score was 2.09 ± 1.35 : 0 in 11.8% of patients, 1 in 27.1%, and 2 in 29.1%. Warfarin was prescribed in only 48.5% of patients, whereas anti-platelet drugs, mainly aspirin, were prescribed for more than 30% of the patients. **Conclusions:** The Fushimi AF Registry provides a unique snapshot of current AF management in an urban community in Japan.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in developed countries, and increases the risks for stroke and death [1]. The number of patients with AF is gradually and steadily increasing in Japan because of the aging of the Japanese population [2].

The Fushimi AF Registry is a community-based survey of AF patients. In this registry, we aimed to enroll all the AF patients in

Fushimi-ku. Fushimi-ku is located at the southern end of the city of Kyoto and is one of its eleven wards; it has prospered through various types of business and industry, and was therefore assumed to represent a typical urban community in Japan. In fact, the age distribution of the population in Fushimi-ku is similar to that in the city of Kyoto, as well as that in Japan. Fushimi-ku is densely populated, with a total population of 283,000. On the basis of the general prevalence of AF in the Japanese (0.6%) [3], a rough estimate of the number of patients with AF in Fushimi-ku is 1700. However, taking into consideration that many of the patients with AF are asymptomatic, we assumed that the actual prevalence of AF might be even higher.

Vitamin K antagonists (mainly warfarin) are highly effective to reduce the risk of stroke, and have been the sole choice for stroke prevention during the last 50 years; however, their use is limited

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for a number of reasons: narrow therapeutic range, drug and food interactions, need for monitoring, and risk of bleeding [4]. Novel oral anticoagulants have recently been shown to be equivalent or superior to warfarin in preventing stroke or systemic embolism [5–7]. These new-generation drugs may provide better alternatives to warfarin for stroke prevention in patients with AF.

The purpose of this study is to demonstrate the current status of the clinical background of AF patients in a community-based clinical setting. In the Fushimi AF Registry, a total of 76 institutions, a large proportion of which were private clinics of general practitioners, participated in the registry. Most of the previous epidemiological data on AF were derived from databases of patients enrolled at highly specialized cardiovascular centers, but many AF patients are under the management of primary-care physicians in community-based clinical settings.

Methods

The inclusion criterion for the registry is the documentation of AF on 12-lead electrocardiogram (ECG) or Holter monitoring at any time. There are no exclusion criteria.

A total of 76 institutions, all of which are members of Fushimi-Ishikai (Fushimi Medical Association), participated in the registry. They consist of 2 cardiovascular centers (National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital), 10 small- and medium-sized hospitals (<400 beds), and 64 primary care clinics.

The enrollment of patients was started in March 2011. All the participating institutions tried to enroll all consecutive patients with AF under regular outpatient care or under admission. We did not include the address of patients as an inclusion or exclusion criterion; this database is the accumulation of the AF patients who visited the participating medical institutions in Fushimi-ku.

Clinical background data, including underlying diseases, medications, and laboratory data, were collected using an electronic case report form of a web-based database system (<https://edmsweb16.eps.co.jp/edmsweb/002001/FAF/top.html>). Data were automatically checked for missing or contradictory entries and values out of the normal range. Additional editing checks were performed by clinical research coordinators at the general office of the registry. Data collected at the registry are expressed as mean \pm SD.

Patients were categorized into three clinical types of AF: paroxysmal, persistent, or permanent, based on the physician's perception of the AF at the time of enrollment. The definitions of the types of AF are as follows:

Paroxysmal AF: Recurrent AF that terminates spontaneously and lasts ≤ 7 days;

Persistent AF: recurrent AF or sustained AF lasting > 7 days that can be terminated by either pharmacological therapy or electrical cardioversion;

Permanent AF: AF that has been present for a long time. Pharmacological or electrical cardioversion has not been performed, or one or several attempts have failed to restore sinus rhythm.

A patient with first-diagnosed episode of AF was followed for a period of time before the registration, and was classified into one of the above-mentioned three types of AF.

The risk of stroke was evaluated by CHADS2 score [8] and CHA2DS2-VASc score [9].

Heart failure was diagnosed if the patient had a history of hospitalization for heart failure, if the patient had symptoms due to heart failure (New York Heart Association functional class ≥ 2), or if the left ventricular ejection fraction was $< 40\%$. Hypertension was diagnosed if peripheral blood pressure was $> 140/90$ mmHg or if

the patient was taking medication for hypertension. The presence of diabetes was diagnosed using HbA1c (JDS) 6.5% as the standard or was assumed if the patient was taking medication for the treatment of diabetes. Dyslipidemia was diagnosed if total cholesterol was > 220 mg/dL, if low-density lipoprotein cholesterol was > 140 mg/dL, if triglyceride was > 150 mg/dL, if high-density lipoprotein cholesterol was < 40 mg/dL, or if the patient was taking statins. Chronic kidney disease (CKD) was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate (eGFR) was < 60 mL/min/1.73 m² for more than 3 months. Major bleeding was defined as a reduction in the hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. All other bleeding was considered minor.

The study protocol was approved by the ethical committees of National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital. Since the present research belongs to an observational study not using human biological specimens, written informed consent was not obtained from each patient according to the ethical guidelines for epidemiological research issued by Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan. However, we have published all relevant details regarding this study to be carried out and provide each patient an opportunity to refuse inclusion in this research by posting the details at every participating clinic and at the homepages of our institutions. We also held a public meeting with citizens in Fushimi-ku to demonstrate outlines of the present study.

Results

As of June 2012, we have enrolled 3183 patients from 76 institutions (Appendix A), which is more than we anticipated from the population size; 2317 patients were enrolled from cardiovascular centers and 866 from small- or medium-sized hospitals or primary care clinics.

Baseline characteristics of registered patients

The baseline clinical characteristics of all registered AF patients are summarized in Table 1; 59.3% were male, and the mean age was 74.2 years. The type of AF was paroxysmal in 46.0%, persistent in 7.3%, and permanent in 46.7%. Compared with studies in Europe or North America, the Japanese patients were much leaner and smaller; the proportions with a body weight of less than 50 kg and 60 kg were 25.7% and 55.0%, respectively. Almost half of the patients were asymptomatic. Table 2 shows co-morbidities. Hypertension was by far the most prevalent associated medical condition, exceeding 60%. Other risk factors for atherosclerotic diseases were remarkably frequent: 23.2% of patients were diabetic, 42.4% had dyslipidemia, and 26.4% had CKD. Coronary artery disease and heart failure were present in 15.0% and 27.9%, respectively. Of all patients, 21.9% had previously suffered from stroke, transient ischemic attack (TIA), or systemic embolic events, and the vast majority of these cases were of ischemic stroke (17.8%). A small number (1.7%) of patients had a history of major bleeding, and 8.6% had undergone pacemaker device implantation.

Age groups and types of AF

The prevalence of the types of AF varied between the age groups (Fig. 1). Paroxysmal AF was the predominant type in the younger patients, but the proportions with persistent/permanent AF increased with increasing age, and more than 50% of patients had persistent/permanent AF among those ≥ 70 years old.

Table 1
Baseline characteristics of the patients.

<i>n</i>	3183
Male (%)	1887 (59.3%)
Age (years)	74.2 ± 11.0
20–29	7 (0.2%)
30–39	21 (0.7%)
40–49	66 (2.1%)
50–59	159 (5.0%)
60–69	711 (22.3%)
70–79	1163 (36.5%)
80–89	870 (27.3%)
90–	186 (5.8%)
≥70	2219 (69.7%)
≥75	1708 (53.7%)
≥80	1056 (33.2%)
Range	21–104
Type of atrial fibrillation	
Paroxysmal	1463 (46.0%)
Persistent	233 (7.3%)
Permanent	1487 (46.7%)
Height (cm)	159.6 ± 10.1
Weight (kg)	58.5 ± 13.2
<50	699 (25.7%)
<60	1493 (55.0%)
Body mass index (kg/m ²)	22.8 ± 3.9
<18.5	320 (12.2%)
18.5–25	1619 (61.6%)
≥25	691 (26.3%)
Systolic BP (mmHg)	124.7 ± 19.1
Diastolic BP (mmHg)	70.3 ± 12.9
Heart rate (bpm)	77.8 ± 15.6
Asymptomatic	1602 (50.3%)
Symptomatic	1581 (49.7%)
Palpitation	1096 (34.4%)
Shortness of breath	474 (14.9%)
Easy fatigue	326 (10.2%)
Chest pain	87 (2.7%)
Faintness	173 (5.4%)

Data are number (%) or mean ± SD; BP, blood pressure.

CHADS2 score and stroke risk

Table 3 shows the CHADS2 score and the CHA2DS2-VASc score. The mean CHADS2 and CHA2DS2-VASc scores were 2.09 and 3.43, respectively. Fig. 2 shows a histogram of CHADS2 and CHA2DS2-VASc scores. CHADS2 score = 2 was the most common subpopulation (Fig. 2A). With increasing age, CHADS2 score gradually increased as well, and patients with a CHADS2 score ≥ 2 constituted more than 70% in elderly patients (≥70 years old).

Drugs used in AF patients

Table 4 shows the drugs prescribed at baseline. Anticoagulation drugs, mostly warfarin, were prescribed for 50.5%. Anti-platelet drugs, including aspirin, were prescribed for more than 30% of the patients in the registry. Many patients were taking multiple anti-thrombotic drugs. A combination of warfarin and aspirin was prescribed to a total of 10.4% of patients.

Rate control drugs were used in 45.5%; more than half of them were beta blockers. Rhythm control drugs were used in 20.3%, mainly class Ic anti-arrhythmic drugs. Since many patients had co-existing hypertension, anti-hypertensive drugs were widely prescribed. Angiotensin receptor blockers were the most commonly used class of anti-hypertensive drugs. Catheter ablation and electronic defibrillation were performed in 5.3% and 3.2% of patients, respectively. Here, the procedures performed for other arrhythmias (such as paroxysmal supraventricular tachycardia) were not included.

Fig. 3 shows the distribution of warfarin and aspirin therapies according to CHADS2 score, age of the patients, and the type of AF. In

Table 2
Co-morbidities.

Stroke/TIA/SEE	697 (21.9%)
Stroke	619 (19.4%)
Ischemic	566 (17.8%)
Hemorrhagic	57 (1.8%)
Unknown	9 (0.3%)
TIA	75 (2.4%)
SEE	40 (1.3%)
Upper limbs	2 (0.1%)
Lower limbs	15 (0.5%)
Coronary artery	4 (0.1%)
Renal artery	5 (0.2%)
Eye	3 (0.1%)
Pulmonary	5 (0.2%)
Others	7 (0.2%)
Heart failure	889 (27.9%)
Hospitalization	536 (16.8%)
NYHA ≥ 2	505 (15.9%)
EF < 40%	144 (4.5%)
Valvular heart disease	576 (18.1%)
Mitral stenosis	45 (1.4%)
Valve surgery	146 (4.6%)
Cardiomyopathy	95 (3.0%)
Hypertrophic	37 (1.2%)
Dilated	53 (1.7%)
Others	5 (0.2%)
Hypertension	1928 (60.6%)
Diabetes mellitus	737 (23.2%)
Dyslipidemia	1350 (42.4%)
Coronary artery disease	479 (15.0%)
Previous myocardial infarction	203 (6.4%)
Previous PCI	241 (7.6%)
Previous CABG	88 (2.8%)
Peripheral artery disease	138 (4.3%)
Previous PTA	53 (1.7%)
Previous bypass surgery	21 (0.7%)
Chronic kidney disease	841 (26.4%)
Hemodialysis	93 (2.9%)
COPD	156 (4.9%)
Major bleeding	55 (1.7%)
Device implantation	273 (8.6%)
Pacemaker	238 (7.5%)
ICD	18 (0.6%)
CRT	7 (0.2%)
CRT-D	10 (0.3%)

Data are number (%). TIA, transient ischemic attack; SEE, systemic embolic events; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PTA, percutaneous transluminal angioplasty; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator.

the current guidelines, warfarin is recommended for patients with CHADS2 score ≥ 2, but warfarin was underused for those high-risk patients, and also overused for low- to intermediate-risk patients with CHADS2 score 0–1 (Fig. 3A). Use of warfarin increased as CHADS2 score increased, but reached a plateau at CHADS2 score ≥ 4. In the same way, use of warfarin increased with increasing age, but declined in the over-80s (Fig. 3B). The rate of warfarin prescription was lower in paroxysmal-type AF than in persistent or permanent AF, in all CHADS2 score subclasses (Fig. 3C).

Examination results in AF patients

Table 5 shows the examination data. A total of 17.9% of patients were anemic (hemoglobin <11 mg/dL). Mean eGFR and creatinine clearance levels were 60.9 and 63.4, respectively and 11.4% of patients had a creatinine clearance <30 mL/min. Echocardiography was performed in 2453 patients: left ventricular end-diastolic diameter/end-systolic diameter 46.6/30.6, left ventricular ejection fraction 63.1%, left atrial diameter 43.9 mm. Left ventricular asyn-chrony was detected in 23.1% of patients.

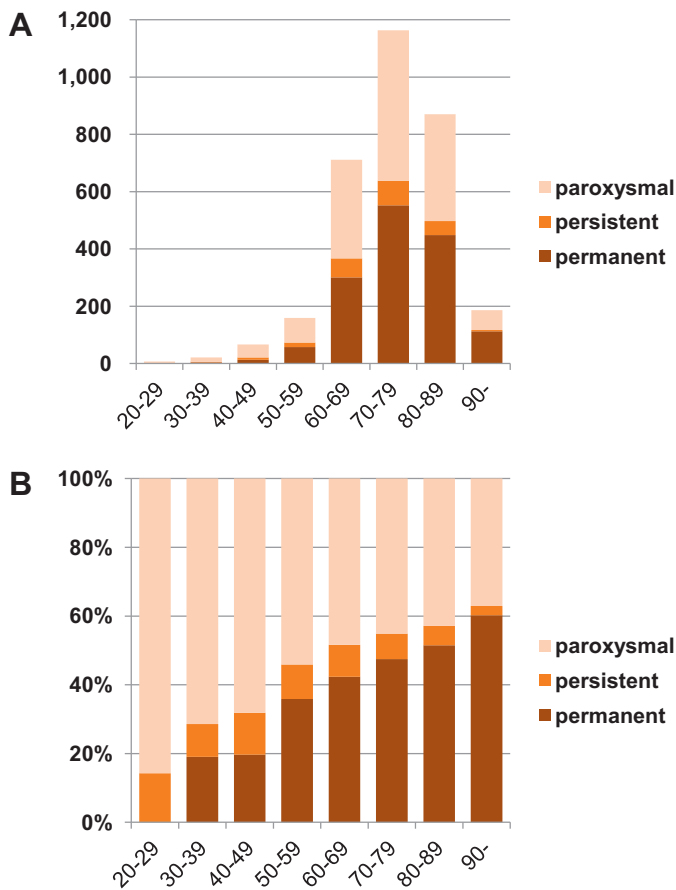


Fig. 1. Age groups and types of atrial fibrillation (A and B).

Table 3
CHADS2 and CHA2DS2-VASc scores.

CHADS2 score	2.09 ± 1.35
0	357 (11.2%)
1	817 (25.7%)
2	880 (27.6%)
3	617 (19.4%)
4	352 (11.1%)
5	142 (4.5%)
6	18 (0.6%)
CHA2DS2-VASc score	3.43 ± 1.71
0	129 (4.1%)
1	313 (9.8%)
2	510 (16.0%)
3	704 (22.1%)
4	686 (21.6%)
5	484 (15.2%)
6	232 (7.3%)
7	100 (3.1%)
8	24 (0.8%)
9	1 (0.0%)

Data are number (%) or mean ± SD.

Discussion

The Fushimi AF Registry provides a unique snapshot of current AF management in an urban community in Japan. The registry demonstrates that the AF patients have higher risk profiles and receive a lower level of anticoagulation drugs for stroke prevention than previously reported.

Fushimi-ku is a typical urban district in Japan, located in the south of the city of Kyoto; it has prospered from a variety of business and industry, and is also famous for its historical heritage and culture spots. It has a population of 283,000, making it the largest among the eleven wards of Kyoto. The age distribution of Fushimi-ku is similar to that of Kyoto city, as well as that of the entire country.

Since many AF patients are asymptomatic and have episodes of AF intermittently, comprehensive data on the clinical profiles of AF

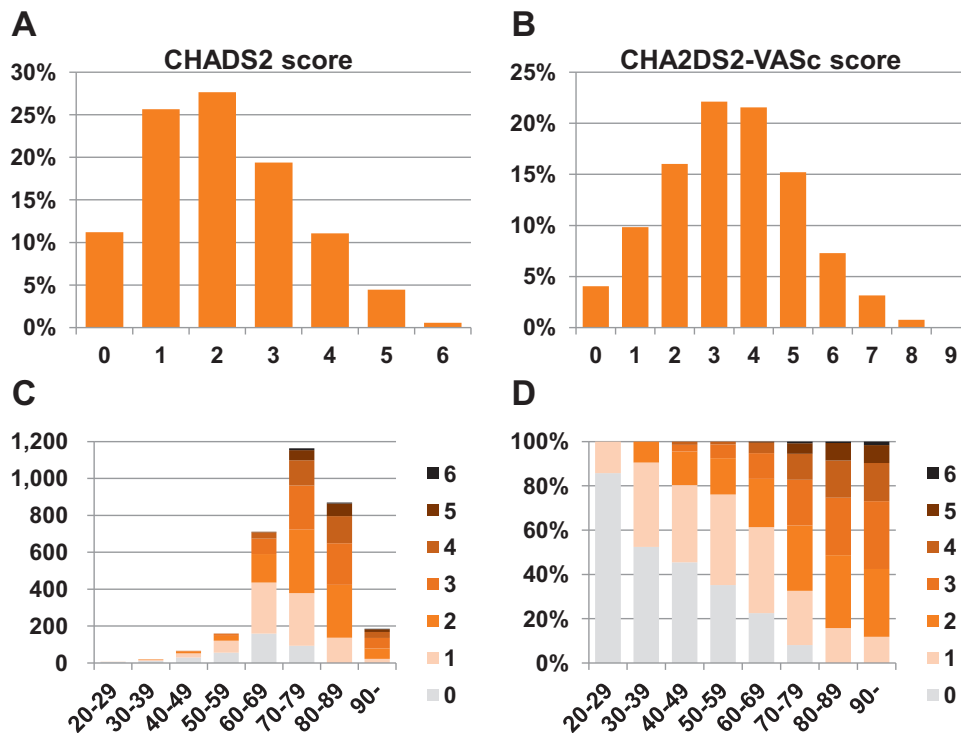


Fig. 2. The histograms of CHADS2 (A) and CHA2DS2-VASc (B) scores. Age groups and CHADS2 score (C and D).

Table 4
Drugs and treatment.

Anti-coagulation drugs	1609 (50.5%)
Warfarin	1543 (48.5%)
Dabigatran (300 mg)	21 (0.7%)
Dabigatran (220 mg)	45 (1.4%)
Dabigatran	66 (2.1%)
Anti-platelet drugs	990 (31.1%)
Aspirin	833 (26.2%)
Clopidogrel	131 (4.1%)
Ticlopidine	60 (1.9%)
Cilostazol	94 (3.0%)
Others	37 (1.2%)
Rate-control drugs	1447 (45.5%)
Digitalis	470 (14.8%)
Verapamil	344 (10.8%)
Diltiazem	119 (3.7%)
β blockers	846 (26.6%)
Rhythm-control drugs	646 (20.3%)
Class Ia	178 (5.6%)
Class Ib	31 (1.0%)
Class Ic	412 (12.9%)
Amiodarone	16 (0.5%)
Bepidil	49 (1.5%)
Anti-hypertensive drugs	1743 (54.8%)
ARB	1127 (35.4%)
ACEI	292 (9.2%)
Aliskiren	6 (0.2%)
Eplerenone	31 (1.0%)
CCB	954 (30.0%)
Diuretics	915 (28.7%)
Loop	733 (23.0%)
Spironolactone	322 (10.1%)
Thiazides	125 (3.9%)
Statins	709 (22.3%)
Ethyl icosapentate	43 (1.4%)
Insulin	103 (3.2%)
Oral hypoglycemic drugs	298 (9.4%)
Catheter ablation	168 (5.3%)
Electronic defibrillation	101 (3.2%)

Data are number (%). ARB, angiotensin receptor blockers; ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers.

patients in Japan have not been fully characterized. The prevalence of AF in the Japanese general population is reportedly 0.6%, based on the data from periodic health examinations in 2003 [3]. Since that study was based on the data obtained from periodic health examination and not from the medical records of hospitals or clinics, the presence of paroxysmal type of AF may have been underestimated. Indeed, the Fushimi AF Registry data suggest that the prevalence of AF in Japanese may have already exceeded 1.0%.

We compared our data with the J-RHYTHM Registry [10,11], the largest database of Japanese AF patients. In the Fushimi AF Registry, a total of 76 institutions, a large proportion of which were private clinics of general practitioners, participated in the study. In contrast, the J-RHYTHM Registry recruited patients only from highly specialized cardiovascular centers or clinics throughout Japan, and not from general practitioner clinics. Therefore, it is assumed that the registered patients in the J-RHYTHM Registry were a highly selected class of patients. The Fushimi AF patients were older than the J-RHYTHM patients: 74 versus 69 years in terms of mean age. In particular, the proportion of patients aged over 80 years was much greater in the Fushimi AF (33.2% vs. 16.0%). Various co-morbidities were more prevalent in Fushimi AF: hypertension (60.6% vs. 59.1%), diabetes (23.2% vs. 18.2%), stroke/TIA (21.9% vs. 14.0%), and coronary artery disease (15.0% vs. 10.1%). As a result, the CHADS2 score was substantially higher in Fushimi AF: 2.1 versus 1.7. In J-RHYTHM, the proportion with a low- to intermediate-risk CHADS2 score of 0–1 was almost 50%, and CHADS 1 was the most frequent subclass; however, in the Fushimi AF, the proportion with a CHADS2 score 0–1 was 38.9%, and CHADS 2 was the most common type. Despite the higher risk profiles in the Fushimi AF patients, they

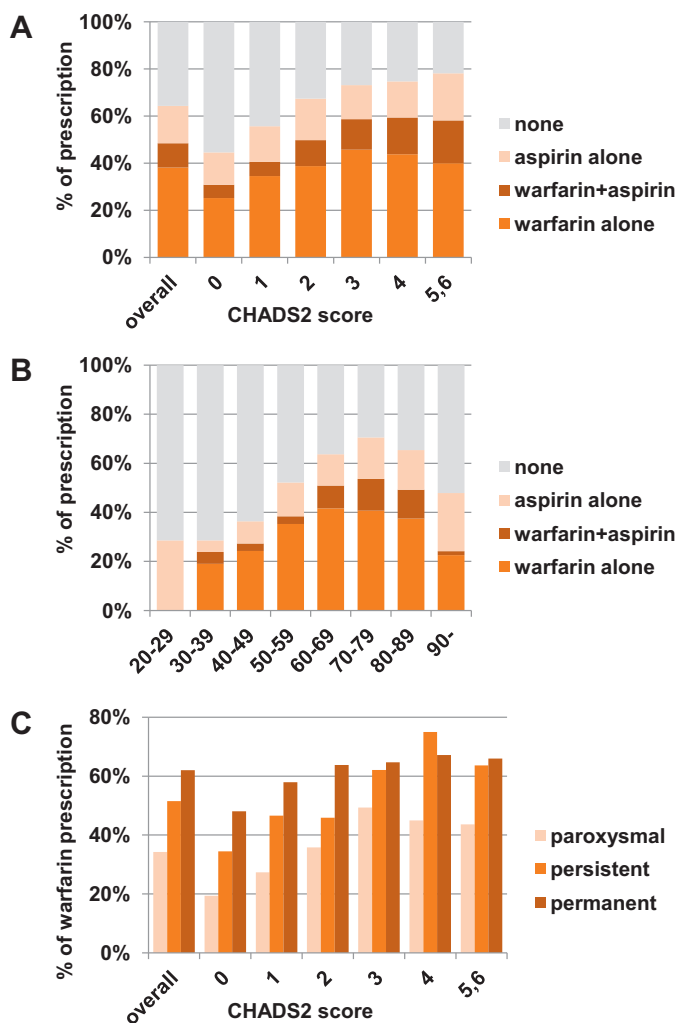


Fig. 3. Distribution of anti-thrombotic therapies, according to CHADS2 score (A) and age groups (B). Rate of warfarin prescription in each type of atrial fibrillation, according to CHADS2 score (C).

received warfarin prescriptions at a much lower rate: 48.5% (warfarin or dabigatran 50.5%) vs. 89%. Thus, the Fushimi AF patients were older, had higher risk profiles with more co-morbidities, but received warfarin prescriptions at a lower rate.

Warfarin is difficult to use for a number of reasons: narrow therapeutic range, drug and food interactions, the need for monitoring, and a risk of bleeding [4]. Therefore, it is underused, as shown in this study, or aspirin is prescribed in many cases as a substitute for warfarin. The current Japanese guidelines for the pharmacological management of AF [12,13] do not recommend aspirin use, on the basis of the results of the JAST study [14] in which aspirin was neither effective nor safe in AF patients. A previous study revealed that patients with paroxysmal AF have a risk of thromboembolic events similar to that in patients with sustained (persistent or permanent) AF [15], and current guidelines recommend the use of warfarin irrespective of the type of AF. However, the rate of warfarin prescription was considerably lower in paroxysmal AF. Thus, discordance between the guidelines and real-world clinical practice was found for several issues, especially in stroke prevention, but this is not limited to Fushimi-ku: it was also the case in another cohort study in Japan [16], as well as in other countries [17–19]. Guideline nonadherence and undertreatment with antithrombotic agents are suggested to be associated with a high risk of stroke and mortality [20]. These limitations of

Table 5
Examination results.

		No. performed
Blood test		2995
White blood cell (/μL)	6060 ± 2348	2965
Platelet (×10 ⁴ /μL)	20.1 ± 7.0	2957
Hemoglobin (g/dL)	12.9 ± 2.1	2965
Hematocrit (%)	38.7 ± 5.9	2952
Anemia (n)	509 (17.0%)	
NT-pro BNP (pg/mL)	1914 ± 5193	746
BNP (pg/mL)	245 ± 967	454
Creatinine (mg/dL)	1.09 ± 1.19	2955
BUN (mg/dL)	20.4 ± 11.5	2906
eGFR (mL/min/1.73 m ²)	60.9 ± 24.0	2955
<60	1458 (49.3%)	
≥60	1497 (50.7%)	
Creatinine clearance (mL/min)	63.4 ± 31.6	2579
<30	294 (11.4%)	
30–50	625 (24.2%)	
≥50	1660 (64.4%)	
Total cholesterol (mg/dL)	179 ± 39	1950
Triglycerides (mg/dL)	126 ± 100	2489
HDL cholesterol (mg/dL)	57 ± 17	2249
LDL cholesterol (mg/dL)	105 ± 32	2158
Glucose (mg/dL)	117 ± 41	2826
HbA1c (JDS) (%)	5.9 ± 2.5	1597
Chest X-ray		2644
CTR (%)	54.5 ± 7.5	2615
Echocardiography		2453
LV diastolic diameter (mm)	46.6 ± 6.6	2388
LV systolic diameter (mm)	30.6 ± 7.0	2365
LV ejection fraction (%)	63.1 ± 11.7	2406
IVS thickness (mm)	9.5 ± 1.8	2360
PW thickness (mm)	9.4 ± 1.6	2356
LA diameter (mm)	43.9 ± 8.6	2377
Local asynergy	564 (23.1%)	2441

Data are number (%) or mean ± SD. Anemia was defined as hemoglobin level <11.0 g/dL. BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; CTR, cardio-thoracic ratio; LV, left ventricle; IVS, inter-ventricular septum; PW, posterior wall; LA, left atrium.

warfarin have encouraged efforts to develop new oral anticoagulants that are effective, safe, and convenient to use [21]. In Japan, dabigatran and rivaroxaban have been approved and become available, and apixaban and edoxaban are now under development. The Fushimi AF Registry is expected to reveal the balance between effectiveness and risk before and after the appearance of the new anticoagulants.

In conclusion, the Fushimi AF Registry provides a unique snapshot of current real-world AF management in an urban community in Japan. Our ultimate goal is to minimize the occurrence of embolic stroke in AF patients.

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Disclosures

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Appendix A.

The following is a list of the institutions participating in the registry.

Chief investigator: Akao M (National Hospital Organization Kyoto Medical Center).

Vice-chief investigator: Chun YH (Ijinkai Takeda General Hospital).

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