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Different determinants of vascular and nonvascular deaths in patients with atrial fibrillation: A SAKURA AF Registry substudy



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ABSTRACT

Background: The incidence and causes of death among patients in Japan treated for atrial fibrillation (AF), a major determinant of strokes and death, with direct oral anticoagulants (DOACs) are unclear. This study's aim was two-fold: to compare the incidence and causes of death between DOAC and warfarin users in Japan and to identify the factors associated with vascular and nonvascular death in the Japanese AF population.

Methods: The study was based on the SAKURA AF registry, in which clinical events were tracked in 3267 enrollees from 63 institutions for 2–4 years. Enrollees included warfarin users ($n = 1577$) and users of any of 4 DOACs ($n = 1690$). The incidence, cause, and major determinants of death were analyzed.

Results: During a median 39.3-month follow-up, 200 patients died, with most succumbing to cardiac death (25%), malignancies (21%), or respiratory infections (20%). There was no significant difference in deaths from any cause between warfarin and DOAC users (108 vs. 92 patients, $p = 0.34$). An age ≥ 75 years was found to be a major determinant of death, but the relative risk (vs. <75 years) was greater for nonvascular death (hazard ratio: 2.85 and 4.97 for age 75–84 and ≥ 85 years, respectively) than vascular death (2.14 and 2.98 for 75–84 and ≥ 85 years, respectively). Heart failure, renal dysfunction, and the type of institution were major determinants of vascular death, and a male sex, weight <50 kg, and anemia were major determinants of nonvascular death.

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Conclusions: The results of our AF registry-based study, in which two thirds of the enrolled patients succumbed to cardiac death, malignancies, or respiratory infections within 2–4 years and use of DOACs rather than warfarin did not reduce the mortality, indicated that a management of AF that includes prophylaxis for vascular and nonvascular events in addition to strokes is warranted.

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Introduction

Atrial fibrillation (AF), one of the most common arrhythmias, is associated with thromboembolisms, a reduced cardiac output, heart failure, and symptoms such as palpitations and dyspnea on exertion [1–3]. The incidence of AF is increasing, and the number of patients in Japan is expected to reach over 1 million by 2050 [4]. AF is a major determinant of strokes and death. We generally recommend anticoagulation therapy to prevent strokes in patients with AF. Anticoagulants are of two types: direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), primarily warfarin, and the available DOACs are of two classes, with dabigatran being a direct thrombin inhibitor and rivaroxaban, apixaban, and edoxaban being factor Xa inhibitors. The benefits of DOACs over warfarin in reducing the risk of vascular events and especially of major bleeding in patients with AF have been substantiated in randomized controlled trials (RCTs) [5–8]. In comparison to warfarin, which is known to interact with multiple foods and drugs and requires frequent laboratory monitoring, DOACs are convenient to use. DOACs are rapidly replacing warfarin; a DOAC is now used initially for anticoagulation therapy in a reported 61% of patients with AF [9]. The large-scale registries in Japan, such as the J-RHYTHM Registry [10,11], Fushimi AF Registry [12], and Shinken Database [13], have included few DOAC users because those registries were established before or soon after the initial approval of DOAC use in Japan. In a previous meta-analysis, the all-cause mortality associated with DOAC use was shown to be lower than that associated with warfarin use, mainly due to a reduction in the incidence of fatal bleeding [14]. Nonetheless, whether DOAC use will reduce the mortality among Japanese patients or change the distribution of the causes of death among Japanese patients remains uncertain. Further, there is a need to clarify the determinants of vascular death and nonvascular death so that we can improve the management of AF. Thus, using data from the SAKURA AF Registry, we conducted a study to first clarify the incidence and cause of death among warfarin users and among DOAC users in Japan, and then to identify the factors associated with vascular and nonvascular death in these patients.

Methods

Our investigation was conducted as a substudy of the SAKURA AF Registry (UMIN000014420) [15,16], which was set up to support multicenter prospective observational research by tracking the clinical events in AF patients for at least 2 years and up to 4 years after their enrollment. Patients were enrolled between September 2013 and December 2015 and were eligible for inclusion if they were ≥ 20 years of age, diagnosed with nonvalvular AF, and were beginning or had already begun anticoagulation therapy for stroke prevention. The analysis of the Registry data was approved by the Nihon University School of Medicine Itabashi Hospital institutional review board (IRB) and the IRBs of the hospitals where the patients were being treated. All enrollees had provided written informed consent for their inclusion in the Registry. The total enrollment was 3267 patients treated with warfarin ($n = 1577$) or any of 4 DOACs ($n = 1690$). These patients were from 63 institutions (2 cardiovas-

cular centers, 13 affiliated hospitals or community hospitals, and 48 private clinics) in the Tokyo area (Appendix). A website was created for the SAKURA AF Registry and is currently being used to collect patient data through a web-based registration system. Follow-up information, including such laboratory values as the prothrombin time/international normalized ratio (PT-INR) in warfarin users, creatinine clearance (CrCl), and hemoglobin (Hb) concentration, was collected through a central registry office twice a year (in March and September). The time in a therapeutic range (TTR) was calculated by the Rosendaal method [17]. We calculated the TTR assuming a PT-INR of 1.6–2.6 and PT-INR of 2.0–3.0 were the therapeutic ranges for Japanese AF patients aged ≥ 70 years and those aged < 70 years, respectively, according to the 2013 Japanese Circulation Society guidelines [18]. Good PT-INR control was defined arbitrarily as a TTR $> 60\%$. New use of an OAC, defined as an OAC therapy initiated within 3 months before the patient's enrollment, was noted.

In the substudy described herein, we examined the cause of death. Each death was attributed to a specific cause by an adjudication committee that was set up for this study. A death was first classified as vascular, nonvascular, or of unknown cause. Vascular death included sudden cardiac death, heart failure, myocardial infarctions, ischemic stroke/systemic embolisms (SEs), hemorrhagic strokes, and extracranial bleeding. Nonvascular death included malignancies, respiratory infections, other infections, and all other causes of death. Patients who died within 30 days of the onset of a myocardial infarction or stroke were classified as having those causes, but those who died after 30 days of the onset of those were classified as a subsequent cause of death including respiratory infections or heart failure. Difficult adjudication cases were discussed and classified into a specific cause by the adjudication committee.

Statistical analysis

The values are shown as the mean \pm SD or median (interquartile range). The normality of the distribution was assessed by

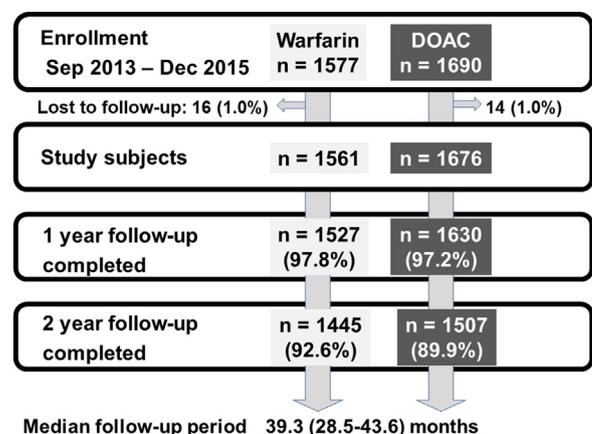


Fig. 1. Flow diagram of the enrollment and follow-up of patients in the SAKURA AF Registry. DOACs, direct oral anticoagulants.

the Kolmogorov–Smirnov test. Differences in categorical variables were analyzed by a chi-squared test, and differences in continuous variables were analyzed by a Student's *t*-test or Mann–Whitney U test, as appropriate. Kaplan–Meier curves were drawn for the time to events and analyzed by a log-rank test. Cox proportional hazards modeling was used to assess the association between the clinical variables and death, with a hazard ratio (HR) and 95% confidence interval (CI) computed for each variable after an adjustment for patient comorbidities that existed at the time of enrollment. A two-sided *p*-value <0.05 was considered statistically significant. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [19].

Results

A total of 3267 patients with nonvalvular AF were enrolled in the Registry, and 30 were lost to follow-up; thus, 3237 patients were included in the analysis described herein (Fig. 1). The characteristics of the patients at the time of enrollment are shown in Table 1. Of the total 3237 patients, 1561 (48.2%) were warfarin users, and 1676 (51.8%) DOAC users [dabigatran, *n* = 456 (14.1%), rivaroxaban, *n* = 761 (23.5%), apixaban, *n* = 428 (13.2%), or edoxaban, *n* = 31 (1.0%)]. As for the age distribution, 1895 (58.5%)

patients were aged <75 years, 1078 (33.3%) aged 75–84 years, and 264 (8.2%) aged ≥85 years, respectively. DOACs were over-dosed in 66 (4.0%) patients who were defined as being administered with a standard-dose of DOACs despite the low-dose regimen criteria being met. DOACs were used at the appropriate standard-dose in 746 (45.0%) patients. The follow-up time ranged from 28.5 to 43.6 months. The TTR was available in 1441 (92.3%) of the 1561 warfarin users. The mean TTR was 65.4 ± 31.1%. The PT-INR control was considered good in 877 (62.2%) of those 1441 warfarin users.

There was no difference in the age distribution, body weight, or body mass index, but the sex, body height, systolic blood pressure, prevalence of paroxysmal AF, CHADS₂ score, CHA₂DS₂-VASC score, CrCl, hypertension, dyslipidemia, history of heart failure, type of institution, use of antiplatelet and antiarrhythmic (class) drugs, and new use of an OAC differed significantly between the warfarin users and DOAC users. During the median follow-up period of 39.3 months, 134 (4.1%) stroke/SE events, 124 (3.8%) major bleeding events, and 200 (6.2%) deaths occurred [14]. Major bleeding events were significantly higher in the over-dose group than standard-dose group [5 (7.6%) vs. 26 (3.5%), *p* = 0.042]. Fifty (25%) of the deaths were cardiac deaths [attributed to sudden cardiac death, *n* = 15 (7.5%); heart failure, *n* = 28 (14%); and myocardial infarction, *n* = 7 (3.5%)]. Other deaths were attributed to malignancies [*n* = 42 (21%)], respiratory infections [*n* = 40 (20%)], ischemic strokes/SEs

Table 1
Characteristics of the warfarin users and DOAC users at the time of enrollment in the Sakura AF Registry.

	Total	Warfarin users	DOAC users	<i>p</i> -Value
Number of patients	<i>n</i> = 3237	<i>n</i> = 1561	<i>n</i> = 1676	
Age (years)	71.98 ± 9.39	72.19 ± 9.27	71.79 ± 9.50	0.229
<75	1895 (58.5)	909 (58.2)	986 (58.8)	0.122
75–84	1078 (33.3)	509 (32.6)	569 (33.9)	
≥85	264 (8.2)	143 (9.2)	121 (7.2)	
Female sex	847 (26.2)	367 (23.5)	480 (28.6)	0.001
Body height (cm)	162.42 ± 9.58	162.83 ± 9.37	162.03 ± 9.76	0.018
Body weight (kg)	63.84 ± 13.01	63.98 ± 12.52	63.72 ± 13.45	0.565
BMI (kg/m ²)	24.06 ± 3.77	24.01 ± 3.59	24.10 ± 3.93	0.547
SBP (mmHg)	127.54 ± 16.02	126.77 ± 15.99	128.26 ± 16.01	0.008
DBP (mmHg)	74.55 ± 11.29	74.19 ± 11.03	74.90 ± 11.53	0.073
Heart rate (beats/min)	73.65 ± 15.35	73.89 ± 14.83	73.43 ± 15.82	0.388
Paroxysmal AF	1201 (37.1)	492 (31.5)	709 (42.3)	<0.001
Current smoker	391 (12.1)	187 (12.0)	204 (12.2)	0.885
Institution type				
Center	1303 (40.3)	655 (42.0)	648 (38.7)	<0.001
Hospital	1178 (36.4)	596 (38.2)	582 (34.7)	
Clinic	756 (23.4)	310 (19.9)	446 (26.6)	
Medical history				
Hypertension	2308 (71.3)	1145 (73.4)	1163 (69.4)	0.013
Dyslipidemia	1253 (38.7)	640 (41.0)	613 (36.6)	0.01
Diabetes	740 (22.9)	378 (24.2)	362 (21.6)	0.079
Heart failure	718 (22.2)	399 (25.6)	319 (19.0)	<0.001
Stroke/TIA	366 (11.3)	190 (12.2)	176 (10.5)	0.134
CHADS ₂ score	1.80 ± 1.15	1.89 ± 1.16	1.72 ± 1.14	<0.001
CHA ₂ DS ₂ -VASC score	3.00 ± 1.49	3.08 ± 1.51	2.92 ± 1.46	0.003
Antiplatelet use	386 (11.9)	231 (14.8)	155 (9.2)	<0.001
Beta blocker use	1460 (45.1)	722 (46.3)	738 (44.0)	0.216
NSAID use	54 (1.7)	21 (1.3)	33 (2.0)	0.173
Antiarrhythmic drug class	387 (12.0)	166 (10.6)	221 (13.2)	0.026
Bepiridil	326 (10.1)	148 (9.5)	178 (10.6)	0.293
Amiodarone	32 (1.0)	20 (1.3)	12 (1.0)	0.112
New use (OAC therapy duration >3 months)	631 (19.5)	78 (5.0)	553 (33.0)	<0.001
CrCl (ml/min)	67.90 ± 26.63	65.30 ± 25.66	70.31 ± 27.29	<0.001

Values are the mean ± SD or number (%) of patients. AF, atrial fibrillation; BMI, body mass index; Center, cardiovascular center; CHADS₂, Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, prior Stroke or TIA (doubled); CHA₂DS₂-VASC, Congestive heart failure, Hypertension, Age >75 years (doubled), Diabetes mellitus, prior Stroke, TIA, or thromboembolic event (doubled), Vascular disease, Age 65–74 years, sex category, CrCl, creatinine clearance; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; Hospital, affiliated hospital or community hospital; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; SBP, systolic blood pressure; TIA, transient ischemic attack.

Table 2

Causes of death and the results of Cox proportional hazards modeling for patients taking DOACs versus warfarin users.

Number of patients	All patients n = 3237	DOAC users n = 1676	Warfarin users n = 1561	HR (vs. WF), 95% CI	p-Value
All-cause death	200	92 (5.5)	108 (6.9)		
Vascular death	76	34 (2.0)	42 (2.7)	0.81 [0.51, 1.27]	0.36
Sudden cardiac death	15	10 (0.6)	5 (0.3)	1.96 [0.67, 5.75]	0.22
Heart failure	28	12 (0.7)	16 (1.0)	0.75 [0.36, 1.59]	0.46
Myocardial infarction	7	2 (0.1)	5 (0.3)	0.42 [0.08, 2.18]	0.30
Ischemic stroke/SE	11	4 (0.2)	7 (0.4)	0.55 [0.16, 1.90]	0.35
Hemorrhagic stroke	8	5 (0.3)	3 (0.2)	1.62 [0.39, 6.78]	0.51
Extracranial hemorrhage	7	1 (0.1)	6 (0.4)	0.17 [0.02, 1.43]	0.10
Nonvascular death	97	43 (2.6)	54 (3.5)	0.83 [0.56, 1.24]	0.36
Malignancy	42	19 (1.1)	23 (1.5)	0.84 [0.46, 1.54]	0.57
Respiratory infection	40	18 (1.1)	22 (1.4)	0.88 [0.47, 1.65]	0.70
Other infections	5	2 (0.1)	3 (0.2)	0.65 [0.11, 3.87]	0.63
Other	10	4 (0.2)	6 (0.4)	0.70 [0.20, 2.47]	0.58
Cause unknown	27	15 (0.9)	12 (0.8)	1.31 [0.61, 2.79]	0.49

CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; WF, warfarin; SE, systemic embolism.

[n = 11 (5.5%)], hemorrhagic strokes [n = 8 (4%)], extracranial bleeding [n = 7 (3.5%)], other infections [n = 5 (2.5%)], and other causes [n = 10 (5%)], which included suicide, traffic accidents, and asphyxia. The deaths were recorded as “of an unknown cause” in the remaining 27 cases (Table 2).

The number of deaths did not differ significantly between DOAC users and warfarin users (92 vs. 108 patients, $p = 0.34$; Fig. 2). There was no difference in any of the causes of death between the DOAC users and warfarin users (Table 2). Regarding the sex-differences in death, a male sex had a modestly higher prevalence of myocardial infarctions, extracranial hemorrhages, and malignancies, but a female sex had deaths caused significantly by heart failure (Table 3). An age 75–84 years and ≥ 85 years (vs. age <75 years), male sex, weight <50 kg, history of congestive heart failure, renal dysfunction, anemia (Hb <12 g/dL), and the center (vs. clinic) were shown to be independently associated with death from any cause, but DOAC use was not (HR, 1.04; 95% CI: 0.76–1.43, $p = 0.79$ vs. warfarin use; Table 4).

Of the total 200 deaths, 76 (38%) were classified as a vascular death, 97 (48.5%) as a nonvascular death, and 27 (13.5%) as that of an unknown cause. The Hb level in the patients who died due to malignancies was significantly lower than that of other causes (12.5 ± 1.65 g/dL vs. 13.8 ± 1.68 g/dL, $p < 0.001$). A Cox proportion-

al hazards modeling showed the major determinants of vascular death to be an age ≥ 85 years and 75–84 years (vs. age <75 years), history of congestive heart failure, renal dysfunction, and the center (vs. clinic) (Table 5), and the major determinants of nonvascular death to be an age ≥ 85 years and 75–84 years (vs. age <75 years), male sex, body weight <50 kg, and anemia (Hb <12 g/dL) (Table 6). Old age (i.e. age ≥ 85 years) was a stronger independent predictor of nonvascular death than of vascular death, but the relative risk (vs. <75 years) differed between vascular death (HR: 2.35 and 3.51 for 75–84 and ≥ 85 years) and nonvascular death (2.91 and 5.09 for 75–84 and ≥ 85 years) (Tables 5 and 6).

Discussion

The major findings from this study were as follows: First, death was most frequently due to cardiac death (25%; including sudden cardiac death, heart failure, and myocardial infarctions), and this was followed by malignancies (21%), and respiratory infections (20%); strokes and bleeding were not major causes of death. Second, an age ≥ 75 years, male sex, body weight <50 kg, history of heart failure, renal dysfunction, anemia, and the institution type were significantly associated with an increased risk of death from any cause, but use of a DOAC (vs. warfarin) was not. Third, the major determinants of vascular death and nonvascular death differed slightly.

The SAKURA AF Registry is a large-scale registry designed to collect data that can be used for a prospective evaluation of the outcomes among AF patients in Japan who are treated with a DOAC or warfarin. In the substudy described herein, we clarified the incidences and causes of death among the users of warfarin and users of a DOAC. Although previous RCTs [5–8] and a meta-analysis [14] have revealed better clinical outcomes under DOAC therapy than under warfarin therapy, especially in terms of fatal bleeding and all-cause death, Japanese patients represented only 2.3% of the patients (1672 of 71,683 patients) included in those RCTs [5–8,20–22]. The life expectancy of Japanese persons is greater than that of persons in most other countries [23], and the Japanese social insurance system, which is a universal health insurance system, differs from that of other countries. Thus, the reported data cannot be understood as data reflecting the real-world clinical practice in Japan. Indeed, an overall death rate of 4.63%/year (6206 of 71,590 patients) was reported from a meta-analysis [14], whereas that documented in our registry was much lower at 2.55%/year (200 of 3237 patients). Because the enrollment period for our registry was

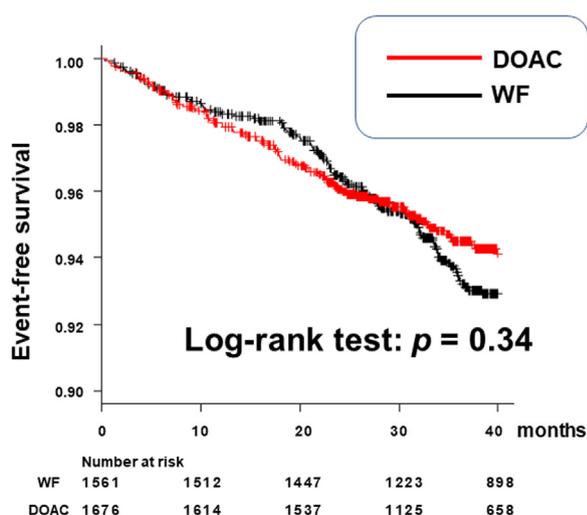


Fig. 2. Kaplan-Meier curves for the event-free survival. DOAC, direct oral anticoagulant; WF, warfarin.

Table 3

Causes of death and the results of Cox proportional hazards modeling for males versus females.

Number of patients	All patients n = 3237	Male n = 2390	Female n = 847	HR (vs. female), 95% CI	p-Value
All-cause death	200	152 (6.4)	48 (5.7)	1.09 [0.78, 1.50]	0.62
Vascular death	76	50 (2.1)	26 (3.1)	0.67 [0.42, 1.07]	0.10
Sudden cardiac death	15	8 (0.3)	7 (0.8)	0.40 [0.14, 1.10]	0.08
Heart failure	28	16 (0.7)	12 (1.4)	0.46 [0.22, 0.98]	0.04
Myocardial infarction	7	7 (0.3)	0	N/A	
Ischemic stroke/SE	11	7 (0.3)	4 (0.5)	0.61 [0.18, 2.09]	0.43
Hemorrhagic stroke	8	5 (0.2)	3 (0.4)	0.59 [0.14, 2.46]	0.47
Extracranial hemorrhages	7	7 (0.3)	0	N/A	
Nonvascular death	97	79 (3.3)	18 (2.1)	1.49 [0.89, 2.49]	0.13
Malignancies	42	37 (1.5)	5 (0.6)	2.54 [1.00, 6.46]	0.051
Respiratory infections	40	33 (1.4)	7 (0.8)	1.59 [0.70, 3.59]	0.27
Other infections	5	5 (0.2)	0	N/A	
Other	10	4 (0.2)	6 (0.7)	0.23 [0.06, 0.80]	0.02
Cause unknown	27	23 (1.0)	4 (0.5)	1.95 [0.67, 5.63]	0.22

CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; N/A, not applicable; WF, warfarin; SE, systemic embolism.

Table 4

Results of the multivariable analysis performed to identify the determinants of death from any cause.

	HR	95% CI min	95% CI max	p-Value
DOAC (vs warfarin)	1.04	0.76	1.43	0.79
Age				
<75 years (reference)	1.00			
75–84 years	2.32	1.61	3.35	<0.001
≥85 years	3.79	2.37	6.05	<0.001
Male	2.20	1.49	3.24	<0.001
Body weight <50 kg	1.57	1.06	2.33	0.03
History of CHF	1.08	1.02	1.13	0.005
History of stroke/TIA	1.01	0.95	1.06	0.80
History of IHD	1.17	0.79	1.75	0.43
DM	1.10	0.94	1.30	0.23
HTN (systolic BP >160 mmHg)	1.11	0.54	2.27	0.78
CrCl <50 ml/min	1.84	1.29	2.63	<0.001
Hb <12 g/dl	2.17	1.57	3.01	<0.001
New use (OAC therapy duration <3months)	1.16	0.78	1.72	0.46
Institution type				
Center (reference)	1.00			
Hospital	0.79	0.58	1.08	0.14
Clinic	0.48	0.30	0.77	0.002

BP, blood pressure; Center, cardiovascular center; CHF, congestive heart failure; CI, confidence interval; CrCl, creatinine clearance; DM, diabetes mellitus; DOAC, direct oral anticoagulant; Hb, hemoglobin; Hospital, affiliated hospital or community hospital; HR, hazard ratio; HTN, hypertension; IHD, ischemic heart disease; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischemic attack.

Table 5

Results of the multivariable analysis performed to identify the determinants of vascular death.

	HR	95% CI min	95% CI max	p-Value
Age				
<75 years (reference)	1.00			
75–84 years	2.35	1.29	4.31	0.006
≥85 years	3.51	1.61	7.64	0.002
Male	1.22	0.68	2.20	0.50
Body weight <50 kg	1.63	0.87	3.08	0.13
History of CHF	1.12	1.04	1.22	0.005
History of stroke/TIA	1.04	0.96	1.13	0.32
CrCl <50 ml/min	2.10	1.16	3.08	0.015
Hb <12 g/dl	1.26	0.73	2.18	0.41
Institution type				
Center (reference)	1.00			
Hospital	0.66	0.40	1.09	0.11
Clinic	0.31	0.14	0.70	0.005

Center, cardiovascular center; CHF, congestive heart failure; CI, confidence interval; CrCl, creatinine clearance; Hb, hemoglobin; Hospital, affiliated hospital or community hospital; HR, hazard ratio; TIA, transient ischemic attack.

Table 6

Results of the multivariable analysis performed to identify the determinants of nonvascular death.

	HR	95% CI min	95% CI max	p-Value
Age				
<75 years (reference)	1.00			
75–84 years	2.91	1.71	4.95	<0.001
≥85 years	5.09	2.60	9.94	<0.001
Male				
Body weight <50 kg	2.09	1.21	3.59	0.008
History of CHF	1.05	0.97	1.13	0.25
History of stroke/TIA	1.01	0.93	1.08	0.89
DM	1.05	0.82	2.26	0.69
CrCl <50 ml/min	1.36	0.82	2.26	0.23
Hb <12 g/dl	2.86	1.83	4.49	<0.001
Institution type				
Center (reference)	1.00			
Hospital	0.96	0.61	1.51	0.86
Clinic	0.74	0.41	1.35	0.33

Center, cardiovascular center; CHF, congestive heart failure; CI, confidence interval; CrCl, creatinine clearance; DM, diabetes mellitus; Hb, hemoglobin; Hospital, affiliated hospital or community hospital; HR, hazard ratio; TIA, transient ischemic attack.

quite recent, the rate of DOAC use was much higher than that reported from previous Japanese observational studies (0% from the J-RHYTHM Registry [10], 7.2% from the FUSHIMI AF Registry [12], and 14.0% from the J-RHYTHM 2 Registry [11]). Therefore, the SAKURA AF Registry is a better reflection of the current status of AF treatment in Japan.

Among registry patients, strokes and bleeding were not major causes of death, with strokes accounting for only 9.5% of the total deaths (5.5% ischemic strokes/SEs and 4% hemorrhagic strokes), a rate that was similar to the rates found in other studies (10.0% in a meta-analysis [14] and 8.4% reported by the Japanese Ministry of Health Labor and Welfare [23]). These data suggest that AF management should focus not only on the risk of a stroke but also on the possibility of a future cardiac event, malignancy, or respiratory infection. Furthermore, the aforementioned meta-analysis showed that DOACs decrease the all-cause mortality typically observed among warfarin users and that the reduction is due to a decreased incidence of fatal bleeding (0.3% vs. 0.7% patients, respectively; $p < 0.001$) [14]. According to our substudy, death from any cause was equivalent between the patients treated with a DOAC and those treated with warfarin. This tendency persisted even after a multivariate adjustment for the covariables related to death. The incidence of extracranial bleeding was somewhat lower among DOAC users than warfarin users [1 (0.1%) vs. 6 (0.4%) patients, respectively; $p = 0.10$], but the incidence of a hemorrhagic stroke was similar between the 2 groups (0.3% vs. 0.2%, respectively; $p = 0.51$). The warfarin users enrolled in our registry had been taking warfarin for a long time, and thus we could assume that the warfarin was well tolerated and controlled as indicated by the relatively good PT-INR control in the majority of study patients. In addition, each of the DOACs was inappropriately underdosed in 20–30% of patients [16]. As a consequence, the number of death-related bleeding events in both groups was not large enough to perform statistically meaningful comparisons.

We found the major determinants of death from any cause and observed a slight difference in the major determinants of vascular death vs. nonvascular death. An age ≥ 75 years, male sex, body weight, history of heart failure, renal dysfunction, anemia, and type of institution were significantly associated with a higher risk of all-cause death, which were consistent with the factors reported from the previous subanalyses [24–27]. The major determinants of vascular death were an age ≥ 75 years, history of congestive heart failure, renal dysfunction, and the clinic (vs. center), suggesting that a periodical physical and laboratory and X-ray examinations to care for those conditions and additional interventions, including antihyper-

tensive, lipid- and glucose-lowering medications, are important to prevent vascular events in older patients with AF. Regarding the sex-difference for death, myocardial infarctions, fatal extracranial hemorrhages, and malignancies were modestly prevalent in the male sex, however, heart failure was frequently seen in the female sex. These sex-specific causes of death should be taken into account, although, the sex-differences were not independently related to the overall vascular deaths. A male sex, body weight <50 kg, and anemia were associated with an increased risk of nonvascular death but not vascular death. Therefore, for patients with AF who are male and aged 75 years or older, have a relatively low body weight, and/or are anemic, additional interventions should be considered to reduce those patients' risk of nonvascular death. Most of the nonvascular deaths that occurred among our Registry patients were the result of a malignancy or respiratory infection; thus, cancer screening and preventing infections, by means of influenza or pneumococcal vaccinations, are needed for patients with AF. We found an interesting finding that being seen at clinics (vs. centers) was independently associated with a decreased risk of vascular death but not of non-vascular death. Generally, the frequency of outpatient visits has become lesser in larger hospitals in Japan. More frequent outpatient visits to clinics than centers would improve the patient consciousness, drug satisfaction, adherence, and control of comorbidities such as hypertension, diabetes, or dyslipidemia [28]. These effects might have led to the reduction in the vascular deaths if the patient background was well-adjusted by our multivariate analysis. Another possibility was that due to unknown multiple residual confounders such as frailty, sarcopenia, dementia, comorbidities, or patient consciousness and adherence. Although this is highly speculative, the patients visiting clinics may have been healthier or adhered to their treatments more strictly than those visiting centers. It is important to note that for very elderly patients (aged 85 years or older) the risk of nonvascular death was shown to be much higher than that of vascular death. "Frailty" has been documented in Japan in 10.0%, 20.4%, and 35.1% of persons aged 75–79, 80–84, and ≥ 85 years, respectively [29]. Thus, for patients with AF who are elderly, special attention should be paid to the risk and any signs of nonvascular disease, and to prevent frailty, interventions, such as exercise training and nutritional supplementation, should be added to the regular OAC therapy.

Study limitations

Because the SAKURA AF Registry was created as a prospective observational registry to evaluate the real-world use of antic-

oagulants by AF patients, patients not taking anticoagulants were not included. In addition, approximately 33% of the DOACs users were new users upon enrollment, whereas only 5% of warfarin users were new users. A multiple adjustment by the patient background may have minimized the patient bias. Nonetheless, as previously described, there was a likelihood of multiple residual confounders, which were not fully adjusted for in the multivariate models and may have biased our results. The registry incorporated only selected institutions within a limited geographical area, and thus we cannot say that our results are reflective of the entire population of AF patients in Japan. We note, however, that patient selection and regional enrollment biases are limitations of all prospective observational studies.

Conclusions

An analysis of the SAKURA AF Registry data showed that cardiac death, malignancies, and respiratory infections accounted for two thirds of the total patient deaths that occurred during a median period of 39.3-months and that all-cause mortality was equivalent between DOAC and well-controlled warfarin users. AF management should focus not only on the patients' risk of a stroke and bleeding but also on their risk of future cardiac events, cancer, and respiratory infections. Additional interventions should be considered to reduce the mortality among AF patients. In very elderly AF patients, attention should be paid especially to the risk of nonvascular disease.

Conflicts of interest

Dr Okumura has accepted remuneration from Daiichi-Sankyo; Dr Hirayama has received research funding from Bayer Healthcare, Daiichi-Sankyo, Otsuka Pharmaceutical, Astellas Pharma, Eisai, Sumitomo Dainippon Pharma, MSD, Nihon Medi-Physics, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Boston Scientific Corporation, Hokushin Medical, and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Myers Squibb, Astellas Pharma, Sanofi, and Takeda Pharmaceutical; Dr Matsumoto has received research funding from Daiichi-Sankyo, Otsuka Pharmaceutical, and Sumitomo Dainippon Pharma, and has accepted remuneration from Nihon Medi-Physics, FUJIFILM RI Pharma, and Biosensors Interventional Technologies Japan.

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Appendix

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