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ORIGINAL ARTICLE

Oral anticoagulant use and clinical outcomes in elderly Japanese patients: findings from the SAKURA AF Registry

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Abstract

Direct-acting oral anticoagulants (DOACs) are widely used in aged Japanese patients with atrial fibrillation (AF), but outcome data for such patients are limited. We compared outcomes between 1895 (58.5%) patients aged < 75 years (non-elderly), 1078 (33.3%) 75–84 years (elderly) and 264 (8.2%) ≥ 85 years (very elderly) enrolled in a prospective multicenter registry. Kaplan–Meier analysis (median follow-up: 39.3 months) revealed a significantly high incidence of stroke/systemic embolism (SE) among the very elderly relative to that among the non-elderly or elderly (3.2 vs. 1.2 and 1.5 events per 100 patient-years, $p < 0.001$). Major bleeding in the non-elderly group was significantly infrequent relative to that among the elderly or very elderly group (1.1 vs. 1.6 vs. 1.8 events, $p = 0.033$). After multivariate adjustment, the stroke/SE incidence was comparable between DOAC and warfarin users, regardless of age, but major bleeding decreased significantly among very elderly DOAC users (adjusted HR 0.220, 95% CI 0.042–0.920). The greater increasing incidence of stroke/SE than major bleeding as patients age suggests that stroke prevention should outweigh the bleeding risk when anticoagulants are being considered for aged patients. Our data indicated that DOACs can be a therapeutic option for stroke prevention in very elderly patients.

Keywords Direct oral anticoagulant · Warfarin · Atrial fibrillation · Aged

Disclaimer All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Introduction

Since 2013, Japan has been categorized as a super-aged society, and its population of persons over 65 years of age is now above 25%. Accordingly, the prevalence of atrial fibrillation (AF) in Japan is increasing, with the disorder expected to affect approximately 10 million persons nationwide by 2030 [1]. Direct oral anticoagulants (DOACs) have become a widely accepted alternative to warfarin for treatment of AF because they are easy to use and there are no food or drug interactions [2, 3]. Clinical trials comparing DOACs against warfarin have shown that apixaban and edoxaban reduce the risk of major bleeding and that apixaban, edoxaban, dabigatran, and rivaroxaban reduce the risk of hemorrhagic stroke [4–8]. The reported data have increased enthusiasm for the use of DOACs in elderly patients. Elderly persons are subject to frailty, sarcopenia, and medication non-adherence. Thus, whether oral anticoagulants (OACs) should be administered to elderly patients and, if so, which ones, is an important clinical question for the present and the future aged society. Few data are available regarding clinical outcomes of OAC administration, especially administration of DOACs, among elderly persons in Japan. Therefore, we compared outcomes of warfarin and DOAC administration in non-elderly, elderly, and very elderly patients with AF.

Methods

Study population

Study subjects were from among patients with non-valvular AF who had been enrolled in the SAKURA AF Registry between 1 September 2013 and 31 December 2015 and were subsequently followed up for at least 2 years (with follow-up ending on 31 December 2017). The study design, data collection, and patients' clinical characteristics have been reported previously [2, 9, 10]. The Registry patients, who ranged in age between 33 and 97 years, were all taking an anticoagulant drug for stroke prophylaxis (either newly initiated or not), with 1578 taking warfarin and 1690 taking a DOAC (any of 4 available at the time of enrollment). The total 3268 patients were enrolled by 63 institutions (2 cardiovascular centers, 20 affiliated hospitals or community hospitals, and 41 private clinics) in the Tokyo area. Analysis of the registry data was approved by the Clinical Research Ethics Committee of Nihon University Itabashi Hospital and by the institutional review boards of the other participating institutions. All enrollees provided written informed consent for inclusion in the registry.

Data collection and outcome variables

A web-based registration system, accessed through the SAKURA AF Registry website, was used to collect patient information. Follow-up information, including such laboratory values as the international normalized ratio (INR) for warfarin users, creatinine levels, and hemoglobin concentration, was obtained through a central registry office twice a year (in March and September) [2, 9, 10]. New use of an OAC, defined as OAC therapy initiated within 3 months before the patient's registry enrollment, was noted. For the study described herein, outcomes were assessed especially in terms of stroke [ischemic stroke, hemorrhagic stroke, or transient ischemic attack (TIA)] or systemic embolism (SE) and of major bleeding, defined as a reduction in the hemoglobin concentration of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Cardiovascular events, including heart failure, myocardial infarction, unstable angina, non-fatal stroke and cardiac death, were also assessed, as was death from any cause.

Definitions

Patients were divided into 3 groups on the basis of their age at the time of registry enrollment: <75 years (non-elderly group), 75–84 years (elderly group) and ≥ 85 years (very elderly group). For patients on warfarin, time in therapeutic range (TTR) was calculated by the Rosendaal method [11]. DOACs were administered with respect to specific contraindications and according to the manufacturers' recommended "standard-dose" or "low-dose" regimen or as an "off-label under-dose" or "off-label standard-dose" regimen [2]. We defined under-dosing (off-label low-dose therapy) as administration of a DOAC at low doses despite the standard-dosage criteria being met, except in the case of dabigatran administration, for which we included dosing to 110 mg, bid, as under-dosing, although such dosing is widely recognized for patients under the following indications: CrCl 30–50 mL/min, age ≥ 70 years; and prior bleeding. We defined over-dosing (off-label standard-dose therapy) as administration of a DOAC at standard doses despite the low-dosage criteria being met.

Statistical analysis

Continuous variables are shown as mean $\pm$ SD values, and categorical variables are shown as the number and percentage of patients. Variables were compared between patient groups, with differences in continuous variables subjected

to 2-sample *t* test or one-way ANOVA and differences in categorical variables subjected to χ^2 test. Kaplan–Meier curves were drawn for the cumulative incidence of stroke/SE, major bleeding, cardiovascular events, and all-cause mortality, and between-group differences were analyzed by log-rank test. Cox proportional hazards modeling was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the incident clinical outcomes between DOAC users vs. warfarin users, and between TTR ≥ 60% vs. TTR < 60% among warfarin users per age category. Because of the small number of event outcomes for each age category, a propensity score-adjusted Cox proportional hazard model was performed to assess the relative risk for clinical outcomes of among DOAC users to among warfarin users, and of TTR < 60% to TTR ≥ 60% controlling for the between-group differences. A propensity score was constructed using sex, age, body weight, persistent AF, new use of an OAC, hypertension, diabetes mellitus, heart failure, history of stroke/TIA, vascular disease, creatine clearance (CrCl), and antiplatelet drug use) between treatment groups. All statistical analyses were performed with JMP 14.0.0 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered significant for all analyses.

Results

Patient characteristics

Of the 3268 patients enrolled in the SAKURA AF Registry, 31 were lost to follow-up, leaving 3237 patients, with a median follow-up time of 39.3 months, for our study. One- and 2-year follow-up data were available for 3157 (97.5%) and 2952 (91.2%) patients, respectively. Of the 3237 patients, 1895 (58%) comprised the non-elderly group, 1078 (33.3%) the elderly group, and 264 (8.2%) the very elderly group. Characteristics of the patients at the time of their enrollment are shown per group in Table 1. Age of patients in the non-elderly, elderly, and very elderly groups was 65.9 ± 6.9 years, 78.9 ± 2.8 years, and 87.3 ± 2.5 years, respectively. The proportion of female patients was greatest in the very elderly group, followed by that in the elderly group and that in the non-elderly group (43.8% vs. 31.7% vs. 20.5%, respectively; $p < 0.001$). Height, body weight, and CrCl were significantly lower, and $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were significantly higher in the elderly and very elderly groups than in the non-elderly group ($p < 0.001$ for all). Hypertension, heart failure, vascular disease, and history of stroke/TIA were more prevalent among the elderly and very elderly patients than among the non-elderly patients ($p < 0.001$ for all).

Characteristics of the Warfarin users and DOAC users

Of the 3237 study patients, 1561 were warfarin users and 1676 were DOAC users. Distribution of the TTRs (< 60% vs. ≥ 60%) of the warfarin users is shown per age group in Fig. 1 (left panel), and distribution of the DOAC dosing regimens is also shown per age group in Fig. 1 (right panel). TTR ≥ 60% was significantly more prevalent in the elderly and very elderly groups than in the non-elderly group (69% and 66% vs. 58%, $p < 0.001$). Standard DOAC dosing was most common in the non-elderly group, followed in order by that in the elderly group and that in the very elderly group. Low DOAC dosing was most common in the very elderly group, followed in order by that in the elderly and non-elderly groups. DOAC under-dosing was the same between the non-elderly and elderly groups (23% for each) and significantly less prevalent in the very elderly group (10%). Over-dosing and contraindications for DOAC therapy were documented in only 2–6% of patients, regardless of the age category. Characteristics of warfarin users with TTR ≥ 60% and < 60% are shown by age (< 75 years or ≥ 75 years) in Table 2. In brief, the age was younger and HAS-BLED score was higher among warfarin users with TTR < 60% than those with TTR ≥ 60% in the age < 75 years group, and age was older and HAS-BLED score was higher among warfarin users with TTR < 60% than those with TTR ≥ 60% in the age ≥ 75 years group.

Clinical outcomes per age group

During the median follow-up period of 39.3 (28.5–43.6) months, 134 (4.1%) patients suffered a stroke/SE event, 124 (3.8%) suffered major bleeding, 266 (8.2%) suffered cardiovascular events, and 200 (6.2%) died. Kaplan–Meier curves for stroke/SE, major bleeding, cardiovascular events, and all-cause death are shown per age group in Fig. 2. The incidence of stroke/SE was significantly greater in the very elderly group than in the non-elderly and elderly groups (3.2 vs. 1.2 and 1.5 events per 100 patient-years, $p < 0.001$). Similarly, the incidences of cardiovascular events and death were significantly greater in the very elderly group than in the elderly and non-elderly groups (cardiovascular events, 6.6 vs. 3.6 vs. 2.0, $p < 0.001$; death, 7.1 vs. 2.9 vs. 1.0 events per 100 patient-years, $p < 0.001$). The incidence of major bleeding was significantly low in the non-elderly group but there was no difference between the elderly and very elderly groups (1.1 vs. 1.6 and 1.8 events per 100 patient-years, $p = 0.033$).

Clinical outcomes between the DOAC users versus warfarin users per age group

Results of the Cox regression analysis regarding the risks of stroke/SE, a major bleeding event, and all-cause death in

Table 1 Clinical characteristics of patients, per age group

	Non-elderly (< 75 years) (n = 1895)	Elderly (75–84 years) (n = 1078)	Very elderly (≥ 85 years) (n = 264)	p value[a]
Age (years)	65.9 ± 7.0	78.9 ± 2.8	87.4 ± 2.5	< 0.001
Female sex	387 (20.4)	344 (31.9)	116 (43.9)	< 0.001
Height (cm)	165.3 ± 8.5	159.2 ± 9.2	154.6 ± 9.6	< 0.001
Weight (kg)	67.4 ± 13.0	60.3 ± 11.2	53.2 ± 9.6	< 0.001
BMI (kg/m^2)	24.5 ± 3.9	23.7 ± 3.5	22.2 ± 3.2	< 0.001
AF type				< 0.001
Paroxysmal AF	732 (38.6)	395 (36.6)	74 (28.0)	–
Persistent AF	429 (22.6)	224 (20.8)	59 (22.3)	–
LS-AF	725 (38.3)	445 (41.3)	126 (47.7)	–
Not reported	9 (0.5)	14 (1.3)	5 (1.9)	–
Hypertension	1295 (68.3)	807 (74.9)	206 (78.0)	< 0.001
Diabetes mellitus	442 (23.3)	251 (23.3)	47 (17.8)	0.111
Heart failure	390 (20.6)	243 (22.5)	85 (32.2)	< 0.001
Vascular disease	193 (10.2)	160 (14.8)	46 (17.4)	< 0.001
Stroke or TIA	185 (9.8)	148 (13.7)	33 (12.5)	0.0041
Major bleeding	18 (1.0)	10 (0.9)	3 (1.1)	0.953
AF ablation	244 (12.9)	42 (3.9)	2 (0.8)	< 0.001
Antiplatelet use	263 (13.9)	199 (18.5)	52 (19.7)	0.001
NSAID use	28 (1.5)	22 (2.0)	4 (1.5)	0.515
$CHADS_2$ score	1.32 ± 0.99	2.48 ± 1.01	2.53 ± 1.01	< 0.001
CHA_2DS_2-VASc score	2.30 ± 1.26	3.95 ± 1.19	4.14 ± 1.20	< 0.001
HAS-BLED score	1.31 ± 0.88	1.63 ± 0.76	1.64 ± 0.75	< 0.001
DOAC use	986 (52.0)	569 (52.8)	121 (45.8)	0.121
New OAC use	383 (20.2)	199 (18.5)	49 (18.6)	0.471
OAC duration (months)	36.9 ± 10.1	35.1 ± 10.5	31.4 ± 12.4	< 0.001
CrCl (mL/min)	79 ± 26	55 ± 16	39 ± 14	< 0.001

Values are shown as mean ± SD or n (%)

BMI, body mass index; LS-AF; long-standing persistent AF (AF lasting > 1 year); TIA, transient ischemic attack; NSAID, non-steroidal anti-inflammatory drug; $CHADS_2$, congestive heart failure, hypertension, age ≥ 75 years, diabetes and stroke; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke, vascular disease, age 65–74 years and sex category; HAS-BLED, uncontrolled hypertension (baseline systolic blood pressure > 160 mmHg), abnormal renal function (serum creatinine ≥ 2.26 mg/dL)/liver function [chronic hepatic disease (e.g., cirrhosis) or aspartate aminotransferase and/or alanine aminotransferase > 3 × normal range], stroke, prior major bleeding, elderly (age ≥ 65 years), drug use (alcohol/anti-platelet or NSAID); OAC, oral anticoagulant; DOAC, direct oral anticoagulant; CrCl, creatinine clearance

[a]Comparison between age groups by one-way ANOVA or χ^2 test, as appropriate

DOAC users relative to risks in warfarin users are shown per age group in Table 3. After propensity score adjustment, the risks of stroke/SE and death were statistically equivalent between the DOAC and warfarin users, regardless of age, but the risk of major bleeding was significantly lower for very elderly DOACs users than for very elderly warfarin users (adjusted HR 0.220, 95% CI 0.042–0.920, p = 0.038).

Clinical outcomes between warfarin users with TTR < 60% versus warfarin users with TTR ≥ 60% for patients aged < 75 years or ≥ 75 years

Results of the Cox regression analysis regarding the risks of stroke/SE and a major bleeding event in warfarin users with TTR < 60% relative to risks in warfarin users

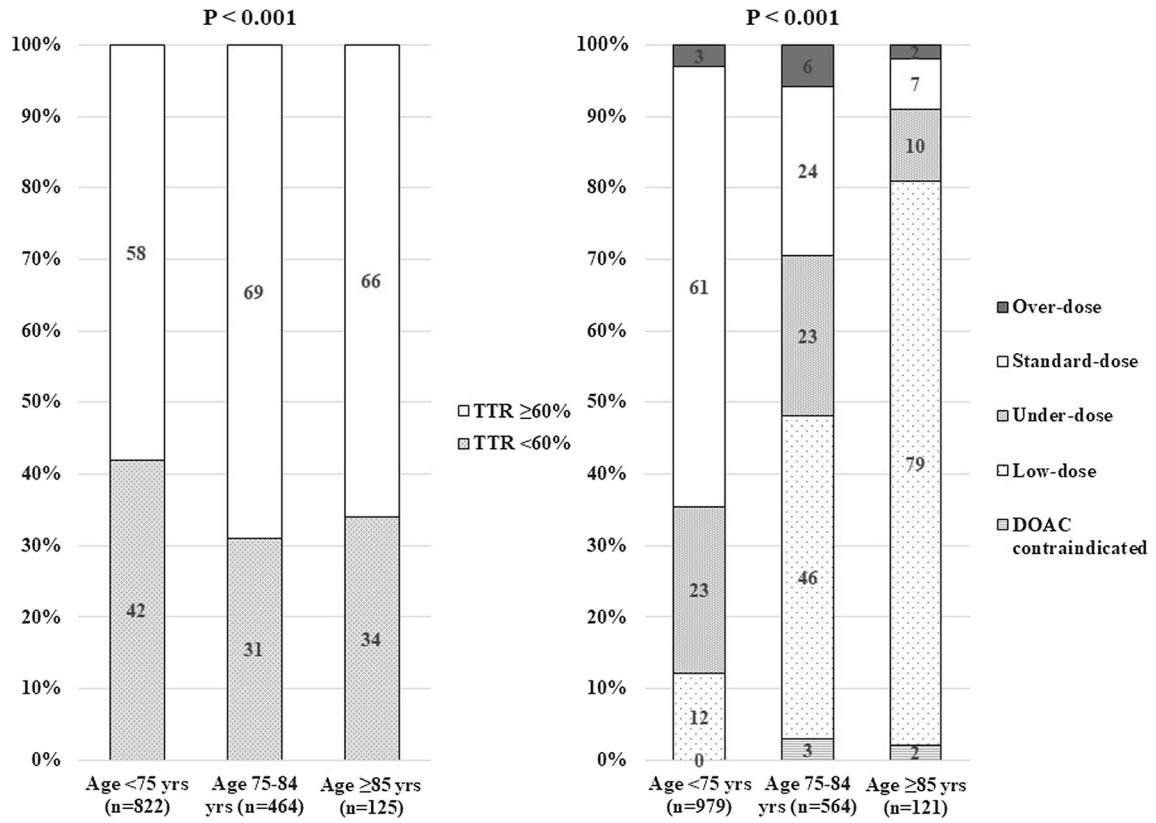

Fig. 1 Percentages of warfarin users, by age, per ≥ 60% or < 60% time in therapeutic range (TTR) (left panel) and of DOAC users, also by age, per dosing regimen (right panel)

with TTR ≥ 60% are shown for patients aged < 75 years or ≥ 75 years in Table 4. Briefly, after propensity score adjustment, re shown: among warfarin users aged ≥ 75 years, risk of stroke/SE was significantly higher in patients with TTR < 60% than in those with TTR ≥ 60% (adjusted HR 3.13, 95% CI 1.42–7.09, $p = 0.005$), but the risks of stroke/SE and major bleeding in patients aged < 75 years were equivalent between those with TTR ≥ 60% and TTR < 60%.

Discussion

Our main study findings were as follows: First, the incidences of stroke/SE, major bleeding, cardiovascular events, and death among patients, regardless of the type of OAC administered, increased with increased age category. Second, overall, there was no significant age-based difference between the warfarin and DOAC users in the incidences of stroke/SE, major bleeding, and death, but among the very elderly, the propensity score-adjusted risk of major bleeding was significantly lower for DOAC users than for warfarin users. Among patients aged ≥ 75 years, the stroke risk was significantly increased for warfarin users with TTR < 60% (vs. TTR ≥ 60%).

The SAKURA AF Registry patient population

Our SAKURA AF Registry-based study involved higher percentages of elderly and very elderly patients (33.3% and 8.2%, respectively) than those previously incorporated in J-RHYTHM Registry-based studies (34.6% and 4.5%, respectively), although J-RHYTHM is the largest registry of AF patients in Japan [12]. Patients over 75 years of age accounted for 53.7% of the Fushimi AF Registry patients [13]. The risk of stroke in elderly patients in our cohort was higher than that in J-RHYTHM registry but lower than that in Fushimi AF registry. It should be noted, however, that both the population and specific characteristics of advanced-age patients in Japan vary, depending on the region and type of hospital from which they come. J-RHYTHM Registry patients came mainly from cardiovascular centers and Fushimi AF registry patients mainly from clinics, whereas a third of our patients came from cardiovascular centers, a third from hospitals, and a third from clinics.

Table 2 Clinical characteristics of warfarin users aged < 75 years and ≥ 75 years and subgrouped by TTR ≥ 60% vs. < 60%

	Age < 75 years		*p* value[a]	Age ≥ 75 years		*p* value[a]
	TTR ≥ 60% (*n* = 479)	TTR < 60% (*n* = 343)		TTR ≥ 60% (*n* = 401)	TTR < 60% (*n* = 188)	
Age (years)	67.4 ± 5.98	64.2 ± 6.6	< 0.001	80.5 ± 4.2	81.1 ± 4.4	0.041
Female sex	81 (16.9)	52 (15.2)	0.501	134 (33.4)	61 (32.5)	0.816
Height (cm)	165.5 ± 8.3	166.3 ± 8.0	0.171	158.6 ± 9.4	158.8 ± 8.7	0.374
Weight (kg)	66.8 ± 12.2	67.9 ± 12.7	0.233	59.6 ± 11.2	58.9 ± 10.4	0.752
BMI (kg/m^2)	24.3 ± 3.6	24.5 ± 4.0	0.539	23.6 ± 3.3	23.3 ± 3.3	0.830
AF type						
Paroxysmal AF	146 (30.5)	106 (30.9)	0.482	111 (27.7)	67 (35.6)	0.197
Persistent A	111 (23.2)	91 (26.5)		94 (23.4)	35 (18.6)	
LS-AF	218 (45.5)	145 (42.3)		190 (47.4)	82 (43.6)	
Not reported	4 (0.8)	1 (0.3)		6 (1.5)	4 (2.1)	
Hypertension	330 (68.9)	237 (69.1)	0.951	317 (79.1)	146 (77.7)	0.702
Diabetes mellitus	113 (23.6)	96 (28.0)	0.154	105 (26.2)	32 (17.0)	0.012
Heart failure	105 (21.9)	96 (28.0)	0.047	112 (27.9)	47 (25.0)	0.453
Vascular disease	52 (10.9)	43 (12.5)	0.459	64 (15.9)	28 (14.9)	0.739
Stroke or TIA	60 (12.5)	36 (10.5)	0.369	53 (13.2)	24 (12.8)	0.879
Major bleeding	4 (8.4)	4 (1.2)	0.636	4 (1.0)	1 (0.5)	0.549
AF ablation	53 (11.1)	43 (12.5)	0.518	15 (3.7)	9 (4.8)	0.555
Antiplatelet use	86 (18.0)	55 (16.0)	0.471	91 (22.7)	43 (22.9)	0.962
NSAID use	4 (0.8)	5 (1.5)	0.402	5 (1.3)	4 (2.1)	0.429
$CHADS_2$ score	1.39 ± 1.05	1.46 ± 1.00	0.365	2.59 ± 1.0	2.45 ± 1.0	0.103
CHA_2DS_2-VASc score	2.45 ± 1.32	2.31 ± 1.31	0.130	4.09 ± 1.23	3.93 ± 1.17	0.125
HAS-BLED score	1.46 ± 0.92	1.61 ± 0.92	0.023	1.65 ± 0.79	1.93 ± 0.8	< 0.001
New OAC use	17 (3.5)	17 (5.0)	0.321	13 (3.2)	13 (6.9)	0.051
OAC duration (months)	38.9 ± 8.9	36.9 ± 10.7	0.005	36.3 ± 10.2	35.0 ± 11.1	0.185
CrCl (mL/min)	74 ± 23	79 ± 26	0.003	50 ± 17	49 ± 17	0.5211

Values are shown as mean ± SD or *n* (%)

TTR, time within therapeutic range. Other abbreviations are as in Table 1

[a]For comparison between the two groups by *t* test or χ^2 test, as appropriate

Clinical outcomes for non-elderly, elderly, and very elderly patients

Our registry data revealed age-related increases in stroke/SE, major bleeding, cardiovascular events, and death, but the degrees of increase differed per age group, i.e., the incidences of stroke, cardiovascular events, and death were markedly and significantly increased in the elderly and very elderly groups in comparison to that in the non-elderly group, but the incidence of major bleeding was equivalent between the elderly and very elderly patients, despite a slight increase in bleeding risk for patients aged ≥ 75 years (vs. < 75 years). In contrast, data from the ENGAGE AF-TIMI 48 Trial revealed twofold and threefold increases in stroke events and major hemorrhagic complications, respectively, in warfarin users aged ≥ 75 years [14]. This pattern was also evident from sub-analyses of elderly patients in other randomized control trials (RCTs) comparing DOACs and warfarin in patients with AF [15–17] and in a recently reported cohort of patients given vitamin K antagonists [18]. Therefore, the bleeding risk faced by elderly patients seems to be higher than the stroke risk. In contrast, data similar to ours were obtained from PREvention oF thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF) [19], a prospective, real-world registry of 7228 AF patients. The data pointed to stroke risk as the major concern in elderly patients rather than the propensity for bleeding related to anticoagulant treatment. Discrepancies between the RCT, PREFER in AF, and our findings might be due to under-dosing of warfarin or of DOACs that occurs in clinical practice. We found an increased incidence of stroke/SE but equivalent incidence of major bleeding in warfarin users aged ≥ 75 years with TTR < 60% vs. TTR ≥ 60%. Nonetheless, we previously reported that the incidence of stroke/SE and major bleeding did not differ statistically between the standard-dose DOAC users and under-dose DOAC users in this study cohort [20]. Further, the percentage of under-dose DOAC users was relatively low in the very elderly group.

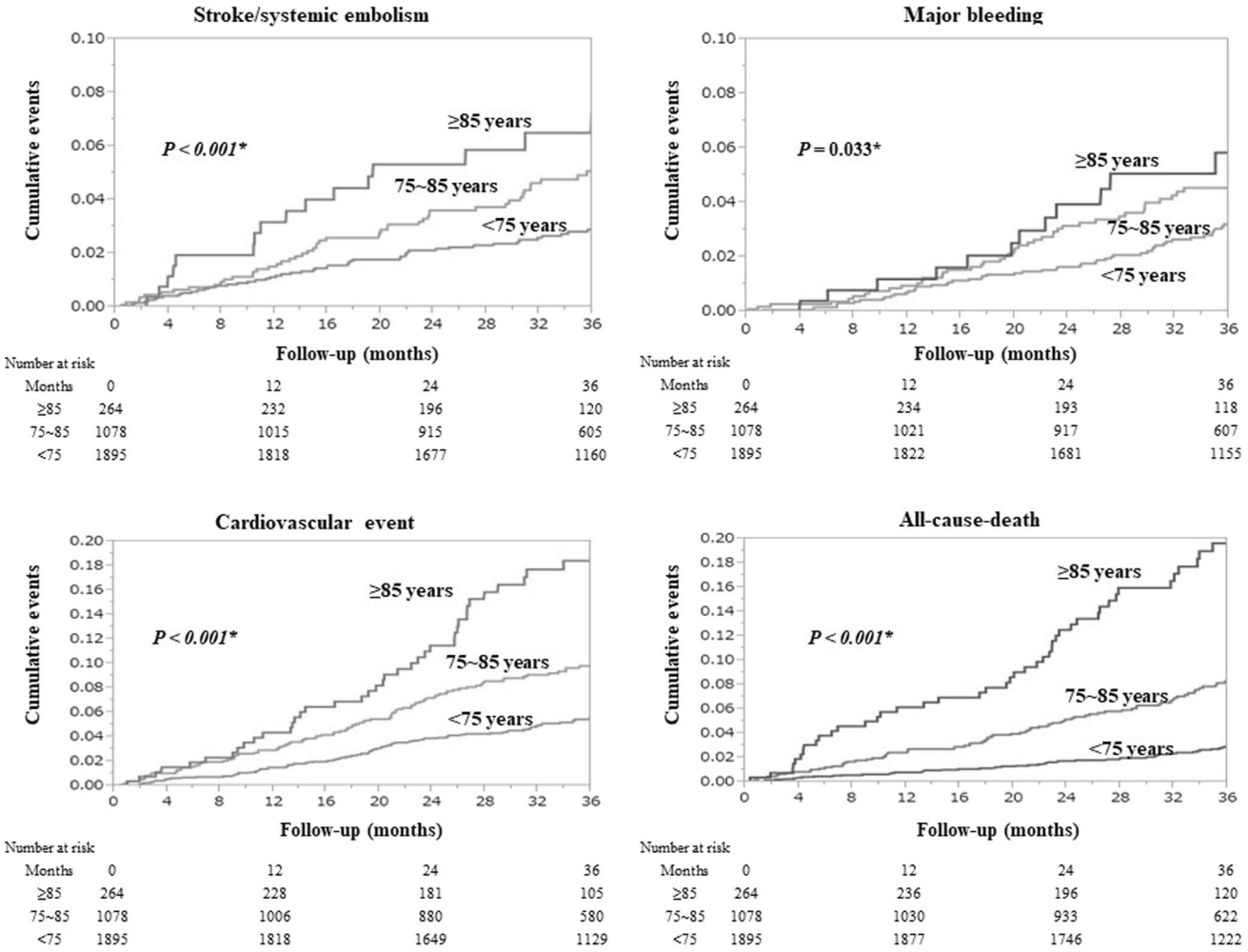

Fig. 2 Kaplan–Meier curves for the occurrence of stroke or systemic embolism (SE), major bleeding, cardiovascular events, and all-cause mortality in each of the three age-based patient groups. (Asterisk) By log-rank test

Therefore, in our cohort, the impact of under-dosing as an explanation for the stroke risk outweighing the bleeding risk may be greater among warfarin users than among DOAC users. Another possible influence was the OAC adherence factor. Adherence is known to be important for stroke prevention, but reports have indicated that adherence to a DOAC regimen tends to decrease after its initiation, and this decline is strongly associated with increased stroke risk [21–23]. In clinical practice, non-adherence is sometimes seen among patients of advanced age because of lack of support, lack of disease knowledge, confusion, physical difficulties, polypharmacy, and/or costs [24–26]. Nevertheless, although multiple underlying factors existed in our cohort, our data suggest that for patients of advanced age stroke prevention is of greater importance than bleeding risk conferred by OAC therapy. Our data are in keeping previous reports of a significant benefit from OAC therapy (vs. antiplatelet or no anti-thrombotic therapy) regardless of age but with the oldest patients receiving the greatest benefit [19, 21]. Therefore, careful attention should be paid when physicians decide whether OAC therapy should be avoided or not, even in very elderly patients.

With one exception that the risk of major bleeding was significantly lower for DOAC users than for warfarin users among the very elderly, we found equivalence between DOAC and warfarin users in stroke/SE and bleeding and death events. Similarly, in sub-analyses of the 4 RCTs regarding the elderly people aged > 75 years also indicated that the risk of major bleeding appeared lower in DOAC than in warfarin, and stroke or death events were even lower in DOAC than in warfarin, especially in apixaban and edoxaban [4–7]. In real-world cohort studies, DOACs (vs. warfarin) yielded equivalent stroke events but significantly reduced the risk of intracranial hemorrhage in very elderly patients with AF [19, 27]. Our study showed the incidences of cardiovascular events and death to be markedly increased in elderly and very elderly patients with a comorbidity such as renal impairment, heart failure, or vascular disease. Such

Table 3 Results of Cox proportional hazards modeling for risk of stroke/SE, major bleeding, and death among DOAC users (aged < 75, ≥ 75–84, or > 85 years) relative to that of counterpart warfarin users

	DOAC Event rate per 100 patient-years	Warfarin Event rate per 100 patient-years	Crude HR (95% CI) (vs. warfarin)	*p* value	[a]Adjusted HR (95% CI) (vs. warfarin)	*p* value
Stroke/SE						
Age < 75 year	1.009	1.011	1.007 (0.599–1.692)	0.980	0.915 (0.510–1.634)	0.765
Age 75–84 years	2.237	1.559	1.465 (0.875–2.493)	0.147	1.299 (0.731–2.328)	0.372
Age ≥ 85 years	2.314	2.631	0.931 (0.333–2.500)	0.887	0.484 (0.146–1.560)	0.224
Major bleeding						
Age < 75 years	0.973	1.149	0.872 (0.524–1.444)	0.596	0.824 (0.497–1.436)	0.497
Age 75–84 years	1.720	1.559	1.122 (0.646–1.958)	0.683	1.107 (0.610–2.008)	0.736
Age ≥ 85 years	0.985	2.382	0.396 (0.088–1.328)	0.139	**0.220 (0.042–0.920)**	**0.038**
Death						
Age < 75 years	0.835	1.219	0.700 (0412–1.172)	0.176	0.706 (0.389–1.255)	0.238
Age 75–84 years	3.129	2.691	1.191 (0.791–1.804)	0.402	1.272 (0.921–1.973)	0.281
Age ≥ 85 years	5.833	8.104	0.748 (0.409–1.329)	0.325	0.674 (0.333–1.326)	0.256

Bold values indicate a statistical significance

HR, hazard ratio; 95%CI, 95% confidence interval

[a]Adjusted by propensity score calculated by sex, age, body weight, persistent AF, new use, hypertension, diabetes mellitus, heart failure, history of stroke/TIA, vascular disease, creatinine clearance, and antiplatelet drug use

patients can often suffer from frailty, sarcopenia and/or dementia, which are known to increase the risk of bleeding events, stroke, and even death [26]. Our previous report obtained from the data of this study cohort showed a lower HAS-BLED score in DOAC users than in warfarin users [2, 9], which may partially be related to lower major bleeding events for DOAC users among very elderly patients. Nevertheless, recent studies together with our data suggest that DOACs can be used as a therapeutic option for stroke prevention for elderly and very elderly patients, but not without the physical and mental statuses of these patients taken into account.

Limitations

Because our study was an observational study, selection bias could have been introduced and not compensated for by the Cox proportional hazards modeling. Also, the study patients were mainly from Tokyo, therefore, the data might not be reflective of patients in other parts of the country. The study did not include a large enough number of users of each of the 4 DOACs for outcome analyses with multivariate adjustment; thus we grouped the DOAC users together.

Table 4 Results of Cox proportional hazards modeling for risk of stroke/SE and major bleeding events in warfarin users (aged < 75 or ≥ 75 years) with a TTR < 60% relative to that of counterpart warfarin users with a TTR ≥ 60%

	TTR <60% Event rate per 100 patient-years	TTR ≥60% Event rate per 100 patient-years	Crude HR	*p* value	Adjusted HR*	*p* value
Stroke/SE						
Age <75	0.908	0.841	1.11 (0.47–2.54)	0.798	1.85 (0.75–4.47)	0.178
Age ≥75 years	2.885	0.907	**3.13 (1.46–6.93)**	**0.003**	**3.13 (1.42–7.09)**	**0.005**
Major bleeding						
Age <75 years	1.090	1.036	1.05 (0.48–2.20)	0.904	1.21 (0.54–2.63)	0.637
Age ≥75 years	2.152	1.157	1.85 (0.84–4.01)	0.123	1.83 (0.82–4.02)	0.135

Bold values indicate a statistical significance

Hazard ratios (HRs) are shown as 95% confidence intervals. *Adjusted by propensity score calculated by sex, age, body weight, persistent AF, new OAC use, hypertension, diabetes mellitus, heart failure, history of stroke/TIA, vascular disease, creatinine clearance, and antiplatelet drug use

Conclusions

AF-associated stroke/SE events appear to increase more dramatically than major bleeding events as patients age. Stroke/SE, major bleeding, and all-cause mortality appear to be equivalent between warfarin users and DOAC users of advanced age, whereas major bleeding rates appear to be significantly lower in DOAC users than in warfarin users among patients aged ≥ 85 years. Our data suggest that stroke prevention should outweigh the bleeding risk when anticoagulants are being considered for patients of advanced age and that DOACs can be an alternative option to warfarin, especially for very elderly patients.

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Compliance with ethical standards

Conflict 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-Meyers Squibb, Boehringer Ingelheim, Pfizer, Boston Scientific Corporation, Hokushin Medical, and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Meyers 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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