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Age-dependent risk for thromboembolism in atrial fibrillation: The Fushimi AF registry

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ABSTRACT

Background: The risk for thromboembolism depending on the different age subgroups in patients with atrial fibrillation (AF) has not been fully elucidated.
Methods: The Fushimi AF Registry is a community-based prospective survey of patients with AF in Fushimi-ku, Kyoto. Follow-up data were available for 4,466 patients by the end of 2019. Clinical determinants and the description of variables which interact and lead to the incidence of thromboembolism (the composite of ischemic stroke and systemic embolism [SE]) were identified in overall population and in age subgroups (≤64, 65–74, and ≥ 75 years).
Results: A total of 314 patients developed thromboembolism during the median follow-up of 1,610 days (1.56 per 100 person-years). The independent determinants were age advance (per 10 years, hazard ratio [HR]: 1.51, 95% confidence interval [CI]: 1.22–1.86, P < 0.001), low body weight (HR: 1.91, 95% CI: 1.35–2.70, P < 0.001), history of stroke or SE (HR: 2.06, 95% CI: 1.54–2.76, P < 0.001), chronic kidney disease (HR: 1.34, 95% CI: 1.01–1.78, P = 0.043), and left atrial enlargement (HR: 1.57, 95% CI: 1.18–2.10, P = 0.0021). With regard to the age subgroup analysis, diabetes mellitus (P = 0.043), vascular disease (P = 0.005), male sex (P = 0.022), and sustained AF (P = 0.014) indicated significantly relevant interactions between the age subgroups and thromboembolism.
Conclusion: The risk and the impact of baseline characteristics on thromboembolism in patients with AF varied depending on the age subgroups.

1. Introduction

Atrial fibrillation (AF) is recognized as the most common type of cardiac arrhythmia and is a well-established risk factor for thromboembolism including ischemic stroke and systemic thromboembolism (SE) [1]. The risk of AF-related thromboembolism is not homogeneous and depends on the patient's age and comorbidities. This has resulted in the development of clinical scores (i.e., CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, aged 65–74 years, sex category] score) to aid in determining the risk stratification for patients with AF. According to the current definition, the CHA_2DS_2-VASc score assigns 1 point for patients aged 65–74 years and 2 points for those aged ≥ 75 years [2]. This strongly indicates that the AF-related thromboembolic risk should be stratified depending on the different age subgroups. Indeed, the cumulative incidence curves for ischemic stroke in the different age subgroups significantly correlate to the age advance [3]. Therefore, thromboembolic risk management should be comprehensively adjusted depending on patient's age. However, age-specific data on the incidence and risk factors of thromboembolism, especially in a large community-based cohort of AF patients were less evident. The aims of this study were the following: 1) to investigate the clinical determinants of thromboembolism, and 2) to determine the variables whose interactions lead to the incidence of thromboembolism between

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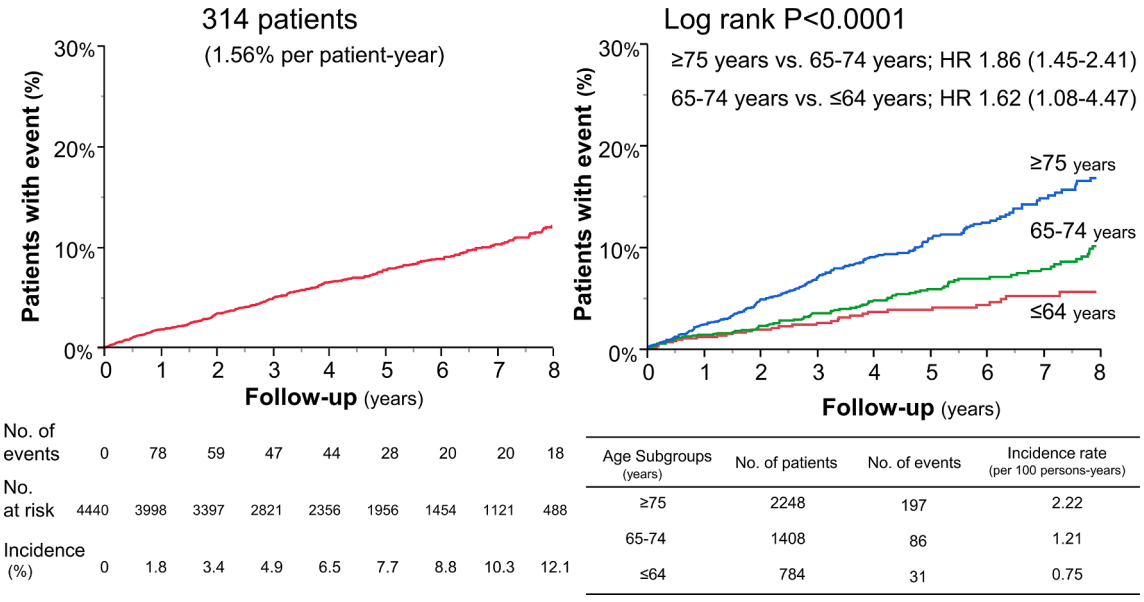

Age Subgroups (years)	No. of patients	No. of events	Incidence rate (per 100 persons-years)
≥75	2248	197	2.22
65-74	1408	86	1.21
≤64	784	31	0.75

Fig. 1. Kaplan-Meier curves and the annual incidence rates for the incidence of thromboembolism. Left; in the entire cohort patients. Right; between the three different age subgroups (≤64, 65–74, and ≥75 years). Comparison data between the age subgroups are presented as HR (95 %CI). HR, hazard ratio; and CI, confidence interval.

the specific age subgroups. Towards these aims, we used data of the Fushimi AF registry, a large community-based prospective survey of Japanese AF patients.

2. Methods

2.1. Study cohort

The Fushimi AF registry is a community-based prospective survey of patients with AF who visited the participating medical institutions in Fushimi-ku, Kyoto, Japan, a densely populated urban area with a total population of 283,000. The detailed study design, patient enrollment, the definition of measurements, and baseline clinical characteristics of the patients in the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834) [4,5]. The inclusion criterion for the registry was any documentation of AF on a 12-lead electrocardiogram or Holter monitoring at any time. There were no exclusion criteria. A total of 81 institutions participated in the registry. Patient enrollment was started on March 2011. All of the participating institutions attempted to enroll all consecutive patients with AF under regular outpatient care or admission to the hospital. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital. Written informed consent was not obtained from patients due to the observational design of the study according to the ethical guidelines for epidemiological research issued by the Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor, and Welfare, Japan.

All of the age data were collected at the time of the entry into the registry. We then classified the entire cohort into three subgroups depending on the age category (≤64, 65–74, and ≥75 years). Baseline clinical characteristics, outcomes and determinants in the entire cohort and between these three subgroups were compared. Clinical variables whose interactions lead to the incidence of thromboembolism were also evaluated.

2.2. Study endpoint and definitions

The clinical endpoint in this analysis was the incidence of thromboembolism; the composite of ischemic stroke or systemic embolism (SE) during the follow-up period. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery. The diagnosis of ischemic or hemorrhagic stroke was confirmed using computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organ. With regard to the comorbidities at the baseline, chronic kidney disease (CKD) was defined as persistent proteinuria or estimated glomerular filtration rate < 60 mL/min/1.73 m2 [6]. Anemia was defined according to the World Health Organization criteria (hemoglobin < 13 g/dl in men, and < 12 g/dl in women) [7]. The type of AF was defined as the followings in accordance with the 2019 AHA/ACC/HRS and 2020 ESC guidelines for the management of patients with AF [8,9]: paroxysmal AF was defined as self-terminating AF within 7 days; persistent AF was defined as AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more; and permanent AF was defined as AF that is accepted by the patients (and physician). Because distinguishing persistent and permanent type is often difficult in daily clinical practice, these two subtypes were combined as sustained AF, as described in our previous reports [10,11]. The definition of pre-existing heart failure (HF) was having one of the following: (1) history of hospitalization for HF prior to enrollment, (2) symptomatic HF (New York Heart Association; NYHA ≥ 2) in association with heart disease. The subtypes of HF, i.e. HF with reduced, mid-range, and preserved ejection fraction (EF) respectively, was classified in accordance with the 2013 ACCF/AHA and 2016 ESC guidelines for the management of patients with HF [12,13].

Oral anticoagulants (OAC) included warfarin and non-vitamin K oral anticoagulants (NOAC: dabigatran, rivaroxaban, apixaban, and edoxaban). Antiplatelet drugs (APD) included aspirin, clopidogrel, prasugrel, ticlopidine, and cilostazol. The values of left ventricular EF and left atrial (LA) diameter in echocardiography were collected at the time of enrollment.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as numbers and percentages, and these variables were

Table 1
Baseline clinical characteristics.

	Entire Cohort	Age Category			P value
		≤64 years	65–74 years	≥75 years	
No.	4,440	784	1,408	2,248	
Baseline characteristics					
Age (years)	73.6 ± 10.9				
Female	1,792 (40.4%)	206 (26.3%)	475 (33.7%)	1,111 (49.4%)	<0.001
Body weight (kg)	59.5 ± 13.5	67.7 ± 15.2	62.4 ± 11.9	54.9 ± 11.9	<0.001
Low body weight (≤50Kg)	1,027 (26.0%)	64 (9.4%)	200 (16.1%)	763 (37.5%)	<0.001
Body mass index (kg/m^2)	23.1 ± 4.0	24.4 ± 4.9	23.6 ± 3.8	22.4 ± 3.8	<0.001
Type of AF					
Paroxysmal	2,195 (49.4%)	477 (60.8%)	678 (48.2%)	1,040 (46.3%)	<0.001
Persistent/ Permanent	2,245 (50.6%)	307 (39.2%)	730 (51.8%)	1,208 (53.7%)	<0.001
LV ejection fraction (%)	62.8 ± 11.7	61.9 ± 12.4	63.4 ± 11.1	62.8 ± 11.7	0.034
LA diameter (mm)	43.5 ± 8.2	42.1 ± 7.7	43.2 ± 8.0	44.1 ± 8.4	<0.001
LA dilatation (≥45 mm)	1,464 (42.2%)	211 (34.5%)	452 (40.5%)	801 (46.0%)	<0.001
Co-morbidities					
$CHADS_2$ score	2.03 ± 1.33	1.11 ± 1.03	1.50 ± 1.14	2.68 ± 1.18	<0.001
CHA_2DS_2-VASc score	3.37 ± 1.69	1.44 ± 1.17	2.93 ± 1.28	4.31 ± 1.35	<0.001
Heart failure	1,214 (27.3%)	143 (18.2%)	301 (21.4%)	770 (34.3%)	<0.001
HFrEF	168/ 1,044 (16.1%)	37/125 (29.6%)	42/264 (15.9%)	89/655 (13.6%)	<0.001
HFmrEF	131/ 1,044 (12.5%)	23/125 (18.4%)	31/264 (11.7%)	77/655 (11.7%)	
HFpEF	745/ 1,044 (71.4%)	65/125 (52.0%)	191/264 (72.4%)	489/655 (74.7%)	
Hypertension	2,798 (63.0%)	404 (51.5%)	921 (65.4%)	1,473 (65.5%)	<0.001
Diabetes mellitus	1,045 (23.5%)	160 (20.4%)	377 (26.8%)	508 (22.6%)	0.0012
Vascular disease	746 (16.8%)	69 (8.8%)	218 (15.5%)	459 (20.4%)	<0.001
Valvular disease	765 (17.2%)	81 (10.3%)	200 (14.2%)	484 (21.5%)	<0.001
Cardiomyopathy	124 (2.8%)	42 (5.4%)	33 (2.3%)	49 (2.2%)	<0.001
Dyslipidemia	1,964 (44.2%)	348 (44.4%)	679 (48.2%)	937 (41.7%)	<0.001
Chronic kidney disease	1,593 (35.9%)	133 (17.0%)	427 (30.3%)	1,033 (46.0%)	<0.001
History of stroke or SE	890 (20.0%)	88 (11.2%)	266 (18.9%)	536 (23.8%)	<0.001
History of major bleeding	200 (4.5%)	25 (3.2%)	55 (3.9%)	120 (5.3%)	0.017
Medications					
OAC	2,475 (55.7%)	339 (43.2%)	850 (60.4%)	1,286 (57.2%)	<0.001
Warfarin	1,834 (41.3%)	240 (30.6%)	606 (43.1%)	988 (44.0%)	<0.001
NOAC	641 (14.4%)	99 (12.6%)	244 (17.3%)	298 (13.2%)	0.001
Antiplatelet drugs	1,196 (26.9%)	153 (19.5%)	341 (24.2%)	702 (31.2%)	<0.001
β-blockers	1,366 (30.8%)	278 (35.5%)	444 (31.5%)	644 (28.7%)	0.0014
Verapamil	430 (9.7%)	65 (8.3%)	141 (10.0%)	224 (10.0%)	0.33
RAS inhibitors	1,974 (44.5%)	295 (37.6%)	641 (45.5%)	1,038 (46.2%)	<0.001
Antiarrhythmic drugs	879 (19.8%)	201 (25.6%)	319 (22.7%)	359 (16.0%)	<0.001
Diuretics	1,268 (28.6%)	141 (18.0%)	335 (23.8%)	792 (35.2%)	<0.001

Categorical data are presented as No. (%), and continuous data are presented as mean ± SD. AF indicates atrial fibrillation; $CHADS_2$, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (1 point), diabetes mellitus (1 point), prior stroke or transient ischemic attack or thromboembolism (2 points); CHA_2DS_2-VASc, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), prior stroke or transient ischemic attack or thromboembolism (2 points), vascular disease (1 point), age 65–74 years (1 point), sex: female (1 point); HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium, LV, left ventricle; OAC, oral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulants; RAS, renin angiotensin system; and SE, systemic embolism.

compared by using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using Student's *t*-test for normally distributed data or Mann–Whitney *U* test for non-normally distributed data. The Kaplan-Meier method was used to estimate the cumulative incidence rate of clinical outcomes. Multivariable analysis using a Cox proportional hazards model was performed to identify the clinical determinants of thromboembolic event. The covariates chosen to be included were age (per 10 years for overall analysis, and not included for each age subgroup analysis), male sex, low body weight (BW:<50 kg), sustained AF, history of stroke or SE, pre-existing heart failure (HF), hypertension, diabetes mellitus, vascular diseases (either having coronary artery disease, peripheral artery disease, or both), CKD, left atrial (LA) enlargement (LA ≥ 45 mm), and OAC prescription at baseline. In addition, statistical tests for interaction were performed to assess the impact of prespecified subgroups on the incidence of thromboembolism between the different age subgroups. The variables as each subgroup chosen to be included were the components of CHA_2DS_2-VASc score (pre-existing heart failure, hypertension, diabetes mellitus, history of stroke or SE, vascular disease, and sex), and other predefined variables, previously reported as an independent risk factor associated with the incidence of thromboembolism (sustained AF, low BW, sustained AF, and CKD) [10,14–16]. We used JMP version 12 (SAS Institute, Cary, NC) to perform all of these analyses. Two-sided P values<0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Of the 4,879 patients enrolled in the registry, follow-up data (collected annually) were available for 4,466 patients (follow-up rate 91.5%) as of December 2019. Of these, 26 patients without prescription data were excluded. Subsequently, the present analysis included 4,440 patients (784 patients at age ≤ 64 years, 1,408 patients at age 65–74 years, and 2,248 patients at age ≥ 75 years) at baseline. During the median follow-up period of 1,610 days [interquartile range, 749–2562 days], 314 patients of the entire cohort developed thromboembolism (1.56% per patient-year). On Kaplan-Meier analysis, the cumulative rate of thromboembolic event was 1.8% at 1 year, and 12.1% at 8 years. With regard to the age subgroups, the annual incidence rate of thromboembolic events became significantly higher depending on the age advance (≤64 vs. 65–74 vs. ≥75 years: 0.75% vs. 1.21% vs. 2.22% per patient-

Table 2
Clinical determinants of thromboembolism during follow-up in entire population, and in 3 age subgroups: Multivariable analysis.

Variables	Entire Cohort			Age Category								
				≤64 years			65–74 years			≥75 years		
	HR	95 %CI	P value	HR	95 %CI	P value	HR	95 %CI	P value	HR	95 %CI	P value
Age (per 10 years)	1.51	1.22–1.86	<0.001									
Male	0.75	0.55–1.04	0.081	4.27	1.10–29.01	0.034	1.83	0.97–3.64	0.062	1.08	0.73–1.61	0.69
Low BW (<50Kg)	1.91	1.35–2.70	<0.001	2.68	0.38–12.08	0.28	2.49	1.17–5.09	0.019	1.68	1.11–2.52	0.013
Sustained AF	0.98	0.73–1.32	0.90	1.52	0.53–4.25	0.43	0.56	0.31–1.00	0.051	1.18	0.81–1.73	0.39
Stroke or SE	2.06	1.54–2.76	<0.001	3.47	0.98–11.09	0.053	1.20	0.60–2.26	0.59	2.36	1.65–3.32	<0.001
Heart failure	1.07	0.79–1.45	0.67	0.22	0.032–0.90	0.033	1.20	0.60–2.31	0.59	1.11	0.77–1.60	0.56
Hypertension	1.03	0.77–1.37	0.86	0.37	0.13–0.98	0.045	1.03	0.59–1.86	0.91	1.12	0.78–1.63	0.55
Diabetes Mellitus	0.98	0.72–1.33	0.88	2.22	0.84–5.63	0.11	1.18	0.65–2.07	0.57	0.81	0.53–1.20	0.30
Organic HD	1.02	0.72–1.43	0.93	1.69	0.44–5.82	0.43	1.40	0.64–2.90	0.39	0.89	0.59–1.33	0.58
Vascular disease	1.14	0.77–1.68	0.52	3.74	0.92–14.84	0.065	0.89	0.38–2.12	0.80	1.11	0.68–1.78	0.67
CKD	1.34	1.01–1.78	0.043	2.48	0.78–7.26	0.12	1.15	0.64–2.03	0.63	1.35	0.95–1.91	0.093
COPD	0.87	0.47–1.62	0.67	0.77	0.04–4.44	0.81	0.73	0.12–2.42	0.66	0.96	0.43–1.87	0.92
Major bleeding	0.86	0.46–1.60	0.62	1.94	0.27–8.52	0.45	0.93	0.15–3.17	0.92	0.73	0.31–1.48	0.41
OAC	0.70	0.53–0.93	0.012	0.42	0.14–1.17	0.098	0.63	0.35–1.10	0.10	0.80	0.56–1.13	0.20
Anemia	1.14	0.86–1.52	0.37	0.51	0.12–1.78	0.30	1.28	0.71–2.25	0.40	1.12	0.80–1.59	0.50
LA ≥ 45 mm	1.57	1.18–2.10	0.0021	1.15	0.42–3.06	0.78	1.56	0.87–2.79	0.14	1.57	1.09–2.25	0.014

AF indicates atrial fibrillation; BW, body weight; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HD, heart disease; HR, hazard ratio; LA, left atrium; OAC, oral anticoagulants; and SE, systemic embolism.

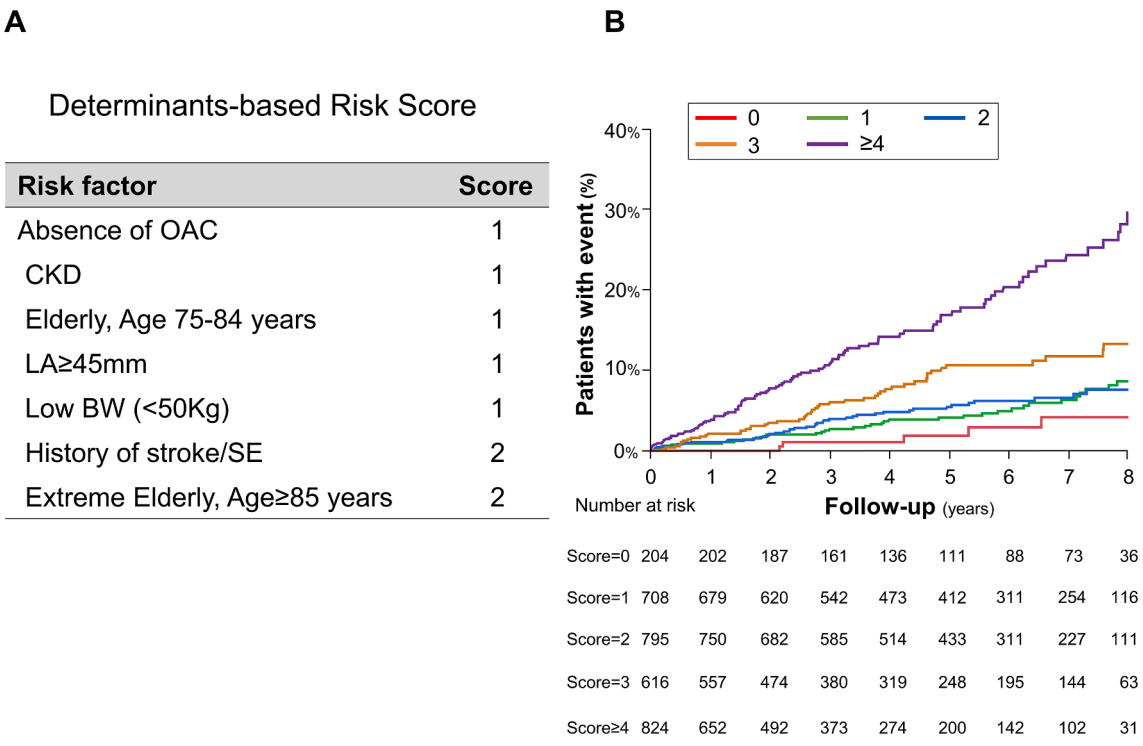

Fig. 2. (A) Variables of determinants-based risk score (full scoring: 0–8) and (B) Kaplan-Meier curves for the incidence of thromboembolism stratified by score assignment (from score 0 group to score ≥ 4 group). BW, body weight; CKD, chronic kidney disease; LA, left atrium; and SE, systemic embolism.

year, respectively, and 65–74 vs. ≤64 years: hazard ratio [HR] 1.62, 95% confidence interval [CI] 1.08–4.47 and ≥75 vs. 65–74 years: HR 1.86, 95 %CI 1.45–2.41, Log rank P < 0.0001, respectively; Fig. 1).

The baseline clinical characteristics of the overall patients, and of the three different age subgroups are shown in Table 1. Among the age subgroups, the proportions of female sex, low BW, sustained AF, and LA enlargement significantly increased with the age advance. These results also applied to the majority of comorbidities, including $CHADS_2$ and CHA_2DS_2-VASc scores (≤64 vs. 65–74 vs. ≥ 75 years: 1.11 ± 1.03 vs. 1.50 ± 1.14 vs. 2.68 ± 1.18, and 1.44 ± 1.17 vs. 2.93 ± 1.28 vs. 4.31 ± 1.35, respectively; P < 0.001). With regard to the medical treatment status, the proportion of APD increased with the age advance, but that of OAC did not, although a significant difference was observed among the age subgroups.

3.2. *Clinical determinants associated with thromboembolism (Multivariable Analysis)*

As shown in Table 2, the independent determinants of thromboembolism among the overall patients using multivariable analysis were age (per 10 years) (HR: 1.51, 95 %CI: 1.22–1.86, P < 0.001), low BW (HR: 1.91, 95 %CI: 1.35–2.70; P < 0.001), history of stroke or SE (HR: 2.06, 95 %CI: 1.54–2.76; P < 0.001), CKD (HR: 1.34, 95 %CI: 1.01–1.78; P = 0.043), and LA enlargement (HR: 1.57, 95 %CI: 1.18–2.10; P = 0.0021).

Table 3
Cumulative incidence rate and hazard ratio of each determinants-based risk score.

Score	Incidence rate (% per patient-year)	HR	95 %CI	P value
0	0.46	Reference		
1	0.98	2.11	0.83–5.37	0.087
2	1.04	2.25	0.89–5.70	0.056
3	1.86	4.02	1.60–10.08	<0.001
≥4	3.92	8.54	3.48–20.97	<0.001

The applied score assignment (full scoring: 0 to 8) were: 1 point to each of age 75–84 years (: elderly), CKD, low BW, LA enlargement, and the absence of OAC, and 2 points to age ≥ 85 years (: extreme elderly), and history of stroke or SE. HR indicates hazard ratio; CI, confidence interval.

Additionally, OAC prescription was significantly associated with lower incidence of thromboembolism (HR: 0.70, 95 %CI: 0.53–0.93; P = 0.012), and therefore the absence of OAC was included as one of the determinants of thromboembolism (HR: 1.42, 95 %CI: 1.08–1.87; P = 0.012, not described in Table). With regard to those between the age subgroups, the male sex in the age ≤ 64 year subgroup, low BW in both age 65–74, and ≥ 75 year subgroups, and history of stroke or SE, and LA enlargement in the age ≥ 75 year subgroup were revealed to be the independent determinants of thromboembolism.

3.3. Determinants-based score assignment and prediction of thromboembolism

Using the variables as the determinants which indicated significant association with the incidence of thromboembolism among the overall patients, a novel risk score assignment was applied. The applied score assignment (full scoring: 0 to 8) were: 1 point to each of age 75–84 years (: elderly), CKD, low BW, LA enlargement, and the absence of OAC, and 2 points to age ≥ 85 years (: extreme elderly), and history of stroke or SE (Fig. 2A). When the patients were stratified by this score assignment, the cumulative incidence rates (% per patient-year) during the follow-up period were 0.46, 0.98, 1.04, 1.85, and 3.92 for scores of 0, 1, 2, 3, and ≥4, respectively. Kaplan-Meier curves for each score indicated that a cumulative incidence of thromboembolism increased with the increase in score (Fig. 2B). Additionally, patients with score of 2 to ≥4 showed significantly, or had a trend toward higher HRs compared to those with a score of 0 as a reference (score 2, 3, and ≥ 4 vs. 0: HR 2.25, 95 %CI 0.89–5.70, P = 0.056; HR 4.02, 95 %CI 1.60–10.08, P < 0.001; and HR 8.54, 95 %CI 3.48–20.97, P < 0.001, respectively) (Table 3).

3.4. Age subgroup analysis

The analysis on the relation of three different age subgroups with the incidence of thromboembolism indicated significant relevant interactions between the patients with diabetes mellitus (≤64 vs. 65–74 vs. ≥ 75 years: HR 2.59, 95 %CI 1.22–5.27 vs. HR 1.33, 95 %CI 0.83–2.07 vs. HR 0.96, 95 %CI 0.69–1.33, respectively; P = 0.043 for interaction), vascular disease (HR 3.96, 95 %CI 1.66–8.49 vs. HR 1.90, 95 %CI 1.14–3.03 vs. HR 1.05, 95 %CI 0.74–1.47, respectively; P = 0.005 for interaction), male sex (HR 2.57, 95 %CI 1.00–8.69 vs. HR 1.37, 95 %CI 0.87–2.23 vs. HR 0.78, 95 %CI 0.59–1.04, respectively; P = 0.022 for interaction), and sustained AF (HR 1.51, 95 %CI 0.74–3.06 vs. HR 0.71, 95 %CI 0.46–1.08 vs. HR 1.50, 95 %CI 1.13–2.01, respectively; P = 0.014 for interaction). For other major subgroups, there was no significance in the interaction between the different age categories (Fig. 3).

4. Discussion

The principal findings from our Japanese community-based AF cohort registry are as follows: (1) the annual thromboembolic event in the entire cohort was 1.56% per patient-year, and it significantly increased depending on the age advance; (2) none of the components of $CHADS_2$ and CHA_2DS_2-VASc scores except the history of stroke or SE and patient's age were independent determinants of thromboembolism in the entire cohort and in the age subgroups; and (3) diabetes mellitus, vascular disease, male sex, and sustained AF, revealed significantly statistical interactions between the age subgroups with regard to the incidence of thromboembolism.

Previous studies had demonstrated that the annual incidence rate of AF-related stroke was approximately 5% [1,17,18]. However, a global, observational, prospective study of patients with AF who were enrolled from ≥ 30 countries worldwide found that the annual incidence rate was considerably lower at 1.25% (95 %CI; 1.13–1.38) per patient-year [19]. The recent database from several observational studies was also consistent with our present study [20–22], which closely reflected the current status of thromboembolic event in the clinical practice.

4.1. Determinants associated with thromboembolism

The present study indicated that age advance, low BW, history of stroke or SE, CKD, LA enlargement, and the absence of OAC were significantly associated with thromboembolic event in the entire cohort. In contrast, the majority of the components of CHA_2DS_2-VASc score, which are commonly listed as determinants for any ischemic stroke in patients with AF, were not found to be significant determinants for thromboembolism, and this result also applied to the age-categorized subgroups. The guideline from AHA/ACC/HRS, which is currently used worldwide, recommend antithrombotic therapy for AF management based on the thromboembolic risk according to the CHA_2DS_2-VASc score; however, there are no other variables to date that are advocated for risk assessment [23,24]. On the other hand, the Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF), an ongoing prospective non-interventional study in order to prevent stroke in patients with newly diagnosed AF, demonstrated that one of the novel variables, CKD, is significantly associated with thromboembolic risk in addition to the components of CHA_2DS_2-VASc score [19]. A recent meta-analysis [25] found that low BW was associated with an increased thromboembolism risk in Asian patient with AF, which was also consistent with the present study.

Furthermore, LA enlargement was described as an independent determinant of thromboembolism from both in Asian and Western AF population [26,27]. These results indicate that other novel variables, in addition to the components of CHA_2DS_2-VASc score, should be considered for the risk assessment of thromboembolism in Japanese patients with AF, with older age, leaner and smaller physical features, which are consequently more likely to have several comorbidities compared with other Western countries. Indeed, the score assignment which specifically stratified the patients with AF using the determinants of thromboembolism in our present study indicated that the cumulative incidence of thromboembolism increased progressively with higher HRs depending on the score. In line with our present study, one recent study proposed a novel risk scoring system as the HELT-E_2S_2 score, which assigns 1 point for hypertension (H), age 75–84 years (E), Body Mass Index < 18.5 kg/m^2 (L), and type of AF (persistent/permanent) (T), and 2 points for age ≥ 85 years (EE) and history of stroke (S) [28]. This may predict the risk of thromboembolism more effectively than globally recognized $CHADS_2$ and CHA_2DS_2-VASc scores for Japanese patients with non-valvular AF.

With regard to the multivariable analysis in the age ≤ 64 year subgroup, pre-existing HF and hypertension were significantly associated with lower incidence of thromboembolism. The interpretation of this result which contradicts the common fact in clinical practice is unclear, and may be due to the small number of events in this subgroup.

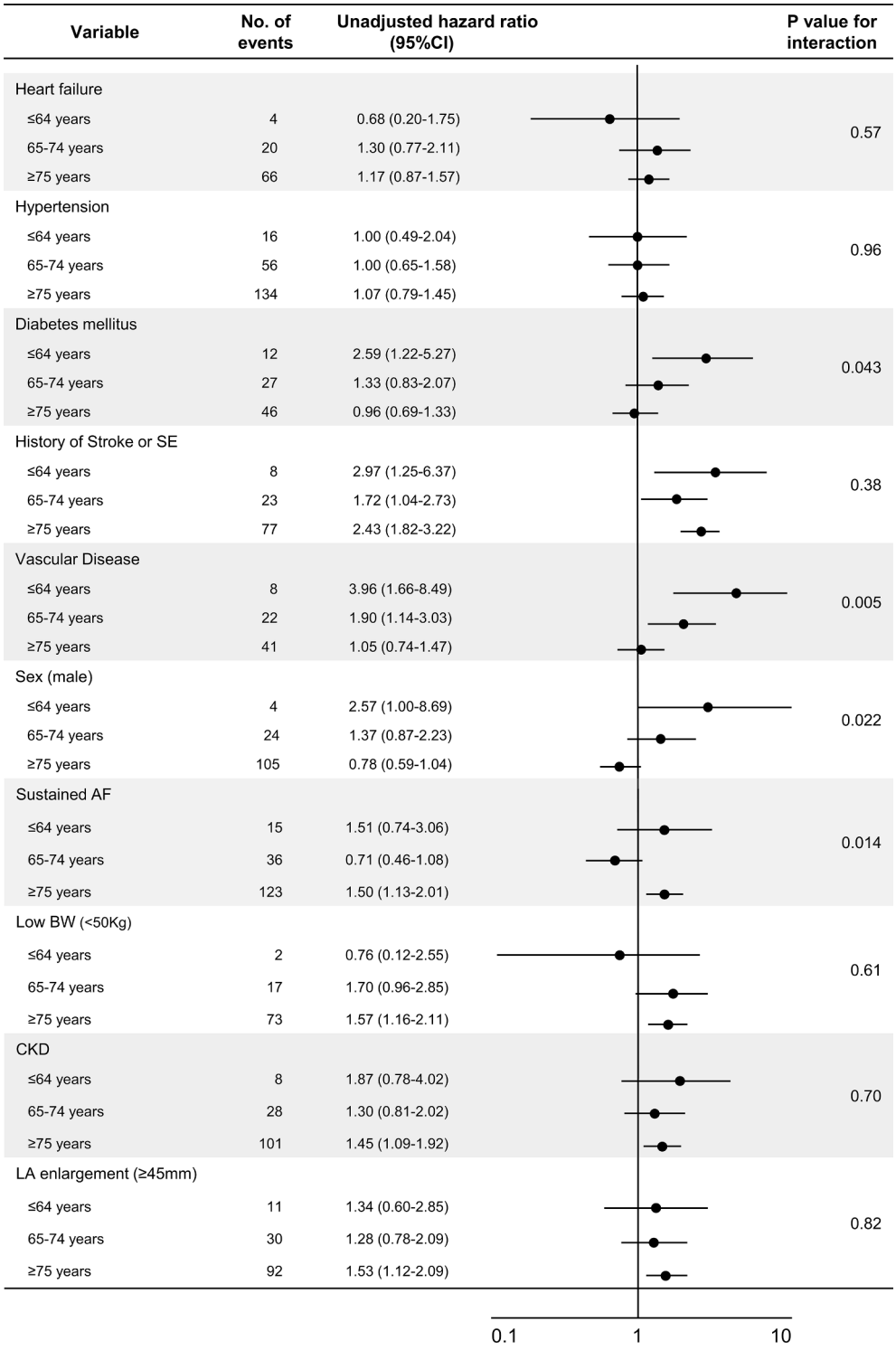

Fig. 3. Impact of major variables on the incidence of thromboembolism between age subgroups. AF indicates atrial fibrillation; BW, body weight; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; LA, left atrium; and SE, systemic embolism.

4.2. Age subgroup analysis

In the present study, the impact of specific variables (diabetes mellitus, vascular disease, sex male, and sustained AF) on the incidence of thromboembolism significantly varied depending on the patient's age. Whereas other variables, including the components of CHA_2DS_2-VASc score (i.e., preexisting heart failure, hypertension, and history of stroke or SE), did not indicate significant interaction leading to the thromboembolic event among different age subgroups. Thus, prognostic impacts of clinical backgrounds on the thromboembolism in patients with AF specifically differed depending on the patient's age. This difference may be partly due to the higher prevalence of other cardiovascular (CV) and non-CV co-morbidities, in accordance with age advance. Previous studies demonstrated that the large-artery atherosclerosis subtype is one of the highly relevant prognosticators in younger patients with regard to the endpoint of thromboembolic events [29,30]. As diabetes mellitus, and male aged $\geq$ 45 years (i.e., younger generations) are well known as risk factors of atherosclerotic progression [31], these variables may

cause a greater impact on the incidence of thromboembolism, especially in the younger subgroup. In addition, one report had demonstrated that the inflammatory cell infiltration, which is also known as a risk factor of atherosclerotic progression, significantly increased from patients with sinus rhythm to paroxysmal AF and sustained AF (i.e. paroxysmal AF vs. sinus rhythm; $P < 0.001$, sustained AF vs. paroxysmal AF; $P = 0.003$) [32]. Thus, the variable may also cause a greater impact on the incidence of thromboembolism in the younger subgroup with sustained AF. The most possible explanation is that several CV and/or non-CV comorbidities, including the specific variables described above, may interact with each other, consequently causing the differential (relatively small or large due to the individual variables) impact on the incidence of thromboembolism, depending on age subgroup. Further studies, including more detailed and stratified analyses, using the pooled data will be of great interest.

5. Study limitations

The present study has some limitations. First, the results were derived from a prospective observational study; therefore, they only reflect association and not causality due to the limitations inherent to the design, such as selection bias and unmeasured confounders, even with adjustments for clinically relevant factors using multivariable analyses. Second, the present study was conducted in an urban district in Japan, and the results cannot be easily extrapolated to rural areas or countries. The lack of external validation and calibration regarding the novel risk score assignment in the present study should be acknowledged. Third, the currently used clinical AF classifications may poorly reflect the AF temporal persistence, as demonstrated in a recent study about patients with cardiac implantable devices [33]. This issue may affect the result of the clinical determinants of thromboembolism, though an accurate classification of AF types may be difficult in routine clinical practice. Forth, the number of thromboembolic events especially in younger age subgroup ($\leq$64 years) was small, providing difficulties in drawing firm conclusions. Finally, the present study was based on cross-sectional analyses with clinical details at the time of enrollment. Thus, longitudinal changes in clinical backgrounds and treatments including OAC prescription were not taken into consideration during the follow-up period.

Regardless of these limitations, our present study demonstrated the specific variables that indicated significant relevant interactions on the thromboembolism along with the clinical determinants among different age subgroups from a large community-based cohort study, which provides important insights into the optimal AF antithrombotic management depending on the patient's age.

6. Conclusions

The clinical determinants and the impact of baseline characteristics on thromboembolism in Japanese patients with AF varied depending on individual age; thus, close attention to the variables, including CV or non-CV comorbidities other than those in $CHADS_2$ or CHA_2DS_2-VASc scores, is needed.

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Declaration of Competing Interest

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