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ORIGINAL RESEARCH ARTICLE

Stroke and systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type

Jae-Sun Uhm[1*†], Jun Kim[2†], Hee Tae Yu[1], Tae-Hoon Kim[1], So-Ryoung Lee[3], Myung-Jin Cha[3], Eue-Keun Choi[3], Jung Myung Lee[4], Jin-Bae Kim[4], Junbeom Park[5], Jin-Kyu Park[6], Ki-Woon Kang[7], Jaemin Shim[8], Hyung Wook Park[9], Young Soo Lee[10], Chang-Soo Kim[11], Ji Eun Mun[12], Nak-Hoon Son[12] and Boyoung Joung[1*]

[1]*Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul, 03722, South Korea;* [2]*Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea;* [3]*Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea;* [4]*Division of Cardiology, Kyung Hee University Hospital, Seoul, South Korea;* [5]*Department of Cardiology, College of Medicine, Ewha Woman's University, Seoul, South Korea;* [6]*Division of Cardiology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea;* [7]*Division of Cardiology, Eulji University Hospital, Daejeon, South Korea;* [8]*Arrhythmia Center, Korea University Medical Center Anam Hospital, Seoul, South Korea;* [9]*Department of Cardiovascular Medicine, The Heart Center of Chonnam National University Hospital, Gwangju, South Korea;* [10]*Department of Cardiology, College of Medicine, Catholic University of Daegu, Daegu, South Korea;* [11]*Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea; and* [12]*Data Science Team, Center for Digital Health, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, South Korea*

Abstract

Aims This study aimed to elucidate the risk for stroke and systemic embolism (SE) in patients with atrial fibrillation and heart failure (HF) according to HF type.

Methods and results A total of 10 780 patients with atrial fibrillation were enrolled in a multicentre prospective registry and divided according to HF type: no-HF, HF with preserved ejection fraction (EF) (HFpEF), HF with mid-range EF (HFmrEF), and HF with reduced EF (HFrEF). Each group included 237 age-matched and sex-matched patients (age, 69.0 ± 10.3 years; men, 69.6%). The baseline characteristics, cumulative incidence, and hazard ratios for stroke/SE and major bleeding were compared across the groups. Patients with HF accounted for 10.3% of the total population; HFpEF, HFmrEF, and HFrEF represented 43.7%, 23.6%, and 32.7% of the patients with HF, respectively. The CHA_2DS_2-VASc score was significantly higher in the HFpEF, HFmrEF, and HFrEF groups than in the no-HF group. The annual stroke/SE incidence rates were 2.8%, 0.7%, 1.1%, and 0.9% in the HFpEF, HFmrEF, HFrEF, and no-HF groups, respectively. The cumulative incidence of stroke/SE was significantly highest in the HFpEF group at 22.8 ± 10.0 months (P = 0.020). The stroke/SE risk was higher in the HFpEF group than in the HFmrEF and HFrEF groups (hazard ratio, 3.192; 95% confidence interval, 1.039–9.810; P = 0.043). E/e' value was an independent risk factor for stroke/SE. There were no significant differences in the incidence of major bleeding across the groups.

Conclusions The stroke/SE risk was the highest in the HFpEF group and comparable between the HFmrEF and HFrEF groups.

Keywords Atrial fibrillation; Bleeding; Ejection fraction; Heart failure; Stroke; Systemic embolism

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**Correspondence to: Boyoung Joung, Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul 03722, South Korea. Tel: +82-2-2228-8460; Fax: +82-2-2227-7732. Email: cby6908@yuhs.ac*
Jae-Sun Uhm, Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul 03722, South Korea. Tel: +82-2-2228-8443; Fax: +82-2-2227-7732. Email: jason@yuhs.ac

†These authors contributed equally to this work as the first authors.

Introduction

Atrial fibrillation (AF) is the most commonly observed type of sustained arrhythmia. The risk for stroke and systemic embolism (SE) increases according to the CHA_2DS_2-VASc score in patients with AF.[1] AF and heart failure (HF) often coexist and share common risk factors. The prevalence of AF is increased in patients with HF and vice versa.[2,3] In addition, HF is among

the risk factors for stroke and SE in patients with AF.[1] Previously, HF was classified into HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF), according to the left ventricular (LV) ejection fraction (LVEF).[4] Recently, the guidelines for management of HF by the European Society of Cardiology recommended a new category—HF with mid-range ejection fraction (HFmrEF) for patients with HF and an LVEF of 40–50%.[5] There exists controversy surrounding the risk for stroke and SE in patients with AF with HFpEF and HFrEF. In addition, there is a lack of clarity on the risk for stroke and SE in patients with AF and HFmrEF. Accordingly, the present study aimed to elucidate the risk for stroke and SE in patients with AF and HF according to the HF type.

Methods

Study population

This was a prospective, multicentre cohort study. The study design was approved by the institutional review board (number: 4-2016-0105) and registered at www.clinicaltrial.gov (NCT02786095). The investigation conforms with the principles outlined in the *Declaration of Helsinki*. Patients aged ≥18 years with nonvalvular AF have been enrolled in a multicentre, prospective, outpatient-based registry—CODE-AF (COmparison study of Drugs for symptom control and complication prEvention of AF) in 18 tertiary centres in the Republic of Korea since June 2016.[6] Patients with valvular AF (AF with moderate-to-severe mitral stenosis and a mechanical valve), with transient AF due to reversible causes, with a life expectancy <1 year, who were pregnant or breastfeeding, and who required long-term anticoagulant use for conditions other than AF were excluded.

Data collection

Detailed data on the patients' medical history, including their symptoms, past history, and medication history were obtained. The results of laboratory tests [haemoglobin, creatinine, and N-terminal pro-B-type natriuretic peptide (NT-proBNP)], electrocardiography, and echocardiography [LVEF, E/e', left atrial (LA) diameter, and LA volume index (LV volume/body surface area)] were collected. The CHA_2DS_2-VASc score was used for the assessment of stroke and SE risk. This score was defined as a sum of 1 for HF, 1 for hypertension, 2 for age ≥ 75 years, 1 for diabetes, 2 for prior stroke or transient ischaemic attack (TIA), 1 for vascular disease, 1 for age 60–74 years, and 1 for female sex. The HAS-BLED score was used for the assessment of bleeding risk. It was defined as 1 for uncontrolled hypertension, 1 for abnormal kidney or liver function, 1 for prior stroke, 1 for bleeding tendency or predisposition, 1 for labile international normalized ratio, 1 for age > 65 years, and 1 for usage of concomitant drugs predisposing an individual to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs) or alcohol intake (≥8 drinks/week). After enrolment, each patient was scheduled to be followed up every 6 months, either through the outpatient clinic or by a telephone interview. Data obtained from June 2016 to January 2020 were analysed in the present study.

Data analyses

The patients were divided into four groups according to their HF type: no-HF, HFpEF, HFmrEF, and HFrEF. HF was defined as a condition in which the heart is unable to pump enough blood to meet the body's oxygen requirement. HFpEF was defined as the presence of symptoms or signs related to HF, an LVEF ≥ 50%, elevated level of natriuretic peptides (NT-proBNP > 125 pg/mL), and relevant structural heart disease (LV hypertrophy or LA enlargement) or diastolic dysfunction. HFmrEF was defined as the presence of symptoms or signs related to HF, LVEF of 40–49%, an elevated level of natriuretic peptides (NT-proBNP > 125 pg/mL), and relevant structural heart disease (LV hypertrophy or LA enlargement) or diastolic dysfunction. HFrEF was defined as the presence of symptoms or signs related to HF and an LVEF < 40%.[5] After the patients with intermediate or high risk (CHA_2DS_2-VASc score ≥ 1 in men and CHA_2DS_2-VASc score ≥ 2 in women) who did not take oral anticoagulant were excluded, age-matched and sex-matched patients were included in the four groups. The endpoints were stroke/SE and major bleeding. Stroke/SE included stroke, TIA, and embolic events in any area or organ. Diagnosis of stroke and TIA was made based on brain magnetic resonance imaging by neurologists. Diagnosis of embolism of the other area or organ was made based on computed tomography. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a decrease in the haemoglobin level by 2 g/dL or more or leading to the requirement of transfusion of two or more units of red blood cells, based on International Society on Thrombosis and Haemostasis criteria.[7] Data on the baseline characteristics, cumulative incidence of stroke/SE and major bleeding, and risk for stroke/SE and major bleeding were compared across the four groups. Echocardiographic parameters (LVEF, E/e', LA diameter, and LA volume index) were analysed for the elucidation of the independent risk factors for stroke/SE in the patients with HF.

Statistical analyses

Continuous data are expressed as mean ± standard deviation, whereas categorical data are presented as numbers (%). Data matching was conducted for the adjustment of differences in the patients' age and sex using a multi-group propensity

score matching method.[8] The patients underwent 1:1:1:1 matching according to age group (by 5 years) and sex and were then included in each group. We compared the baseline characteristics of the patients across the four groups using a one-way analysis of variance with Bonferroni's test for post hoc analyses of the continuous data and a χ^2 test for the categorical data. The Kaplan–Meier method was used to analyse the cumulative incidence of stroke/SE and major bleeding across the four groups. Cox regression analyses were used to compare the hazard ratios for stroke/SE and major bleeding across the four groups and elucidate the independent echocardiographic risk factors for stroke/SE. The results of the Cox regression analyses are expressed as hazard ratios and 95% confidence intervals. A *P*-value < 0.05 for a two-sided test was considered statistically significant. Data were analysed using Statistical Package for the Social Sciences Version 25.0 (IBM Corporation, Armonk, NY, USA) and R software Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 10 780 patients (age, 66.8 ± 11.1 years; male, 64.7%) with nonvalvular AF were included in this registry. *Table 1* shows the baseline characteristics of the total population of the patients in each group. Overall, 10.3% of the patients had HF. Those with HFpEF, HFmrEF, and HFrEF comprised 43.7%, 23.6%, and 32.7% of the total HF population, respectively.

A total of 948 age-matched and sex-matched patients (age, 69.0 ± 10.3 years; men, 69.6%) were included in the analyses; 237 were assigned to each group. *Table 2* shows the baseline characteristics of the age-matched and sex-matched patients in each group. The matching variables (age and sex) were well balanced across the groups. Paroxysmal AF was significantly more frequently reported in the no-HF group than in the HFpEF, HFmrEF, and HFrEF groups. The CHA_2DS_2-VASc score was significantly higher in the HFpEF, HFmrEF, and HFrEF groups than in the no-HF group. There were no significant differences in the CHA_2DS_2-VASc score across the HFpEF, HFmrEF, and HFrEF groups. There were no significant differences in the HAS-BLED score across the four groups. Vascular disease and prior myocardial infarction were significantly more frequently reported in the HFmrEF and HFrEF groups than in the no-HF and HFpEF groups. There were no significant differences in the frequency of hypertension, uncontrolled (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg even with antihypertensive agents) hypertension, diabetes, stroke history, chronic kidney disease, end-stage renal disease, and creatinine level across the four groups. The NT-proBNP level was significantly higher in the HF groups than in the no-HF group, while the E/e' value was significantly higher in the HFrEF group than in the no-HF, HFpEF, and HFmrEF groups. The LA volume index was significantly higher in the HFpEF and HFrEF groups than in the no-HF group. There were no significant differences in the LA volume index across the HFpEF, HFmrEF, and HFrEF groups. There were no significant differences in the administration rates of antiplatelet agents across the four groups. Usage of antiarrhythmic drugs was significantly lower in the HFrEF group than in the other groups. Usage of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers was significantly higher in the HF groups than in the no-HF group. Usage of mineralocorticoid receptor antagonist was significantly higher in the HFmrEF and HFrEF groups than in the no-HF

Table 1 Baseline characteristics of the total population

	No-HF (*n* = 9666)	HFpEF (*n* = 487)	HFmrEF (*n* = 263)	HFrEF (*n* = 364)	*P*-value
Age (years)	$66.6 \pm 11.0_a$	$70.2 \pm 11.1_b$	$68.6 \pm 11.2_{b,c}$	$66.9 \pm 11.6_{a,c}$	<0.001
Male	$6274\ (64.9)_a$	$260\ (53.4)_b$	$178\ (67.7)_c$	$260\ (71.4)_d$	<0.001
Paroxysmal AF	$6417\ (66.4)_a$	$222\ (45.6)_b$	$106\ (40.3)_c$	$185\ (50.8)_d$	<0.001
CHA_2DS_2-VASc score	$2.5 \pm 1.6_a$	$4.0 \pm 1.7_b$	$3.8 \pm 1.8_b$	$3.7 \pm 1.7_b$	<0.001
Hypertension	$6286\ (65.0)_a$	$358\ (73.5)_b$	$159\ (60.5)_c$	$237\ (65.1)_d$	0.001
Diabetes	$2363\ (24.4)_a$	$127\ (26.1)_{a,b}$	$76\ (28.9)_{b,c}$	$114\ (31.3)_c$	0.009
Stroke history	$1473\ (15.2)_a$	$81\ (16.6)_{a,b}$	$53\ (20.2)_{b,c}$	$80\ (22.0)_c$	0.001
Vascular disease	$548\ (5.7)_a$	$38\ (7.8)_b$	$35\ (13.3)_c$	$55\ (15.1)_c$	<0.001
HAS-BLED score	$1.8 \pm 1.1_a$	$2.2 \pm 1.2_b$	$1.9 \pm 1.2_{a,c}$	$2.0 \pm 1.2_c$	<0.001
LVEF (%)	$62.5 \pm 7.0_a$	$60.0 \pm 6.0_b$	$43.9 \pm 2.6_c$	$31.4 \pm 6.1_d$	<0.001
LA diameter (mm)	$43.2 \pm 8.1_a$	$47.1 \pm 8.4_b$	$46.8 \pm 8.2_b$	$47.7 \pm 9.3_b$	<0.001
LA volume index (mL/m^2)	$26.7 \pm 15.6_a$	$36.6 \pm 24.3_b$	$34.3 \pm 17.7_b$	$37.0 \pm 19.6_b$	<0.001
OAC	$7616\ (78.8)_a$	$436\ (89.5)_b$	$246\ (93.5)_c$	$334\ (91.8)_c$	<0.001

AF, atrial fibrillation; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant.
Values are presented as mean ± standard deviation for continuous variables or as number (%) for categorical variables.
The same subscript letters indicate non-significant differences and the different subscript letters indicate significant differences across the groups based on Bonferroni multiple comparison tests.

Table 2 Baseline characteristics of the age-matched and sex-matched patients

	No-HF (n = 237)	HFpEF (n = 237)	HFmrEF (n = 237)	HFrEF (n = 237)	P-value
Age (years)	69.0 ± 10.3	69.0 ± 10.2	69.0 ± 10.4	69.1 ± 10.4	>0.999
Male	69.6	69.6	69.6	69.6	1.000
BMI (kg/m^2)	24.7 ± 3.3$_{a,b}$	24.9 ± 3.6$_a$	24.4 ± 3.3$_{a,b}$	24.1 ± 3.2$_b$	0.024
Paroxysmal AF	62.9$_a$	45.1$_b$	38.1$_b$	46.8$_b$	<0.001
CHA_2DS_2-VASc score	2.7 ± 1.6$_a$	3.7 ± 1.7$_b$	3.8 ± 1.8$_b$	3.9 ± 1.7$_b$	<0.001
Hypertension	65.8	69.6	59.1	65.8	0.110
Diabetes	27.0	26.6	28.7	31.6	0.605
Stroke history	15.6	19.0	20.7	23.2	0.206
Vascular disease	6.3$_a$	6.8$_a$	11.8$_b$	13.5$_b$	0.014
HAS-BLED score	1.9 ± 1.0	2.1 ± 1.2	1.9 ± 1.2	2.0 ± 1.2	0.053
Uncontrolled hypertension	17.7	16.9	12.7	19.0	0.276
Myocardial infarction	1.7$_a$	3.4$_a$	6.8$_b$	9.3$_b$	0.001
Chronic kidney disease	8.5	13.5	13.5	14.9	0.175
End-stage renal disease	0.4	1.7	1.7	1.7	0.543
Haemoglobin (g/dL)	13.9 ± 1.8	13.6 ± 2.5	13.8 ± 2.0	13.8 ± 2.1	0.434
Creatinine (mg/dL)	1.0 ± 0.8	1.1 ± 0.6	1.1 ± 0.8	1.1 ± 1.0	0.290
NT-proBNP (pg/mL)	16.0 ± 39.5$_a$	856.9 ± 673.1$_b$	2519.6 ± 2534.1$_{b,c}$	4046.2 ± 3971.6$_c$	<0.001
LVEF (%)	62.3 ± 6.9$_a$	59.7 ± 5.6$_b$	43.9 ± 2.6$_c$	31.6 ± 6.3$_d$	<0.001
E/e'	11.9 ± 6.0$_a$	12.4 ± 6.1$_a$	12.9 ± 6.2$_a$	16.2 ± 8.5$_b$	<0.001
LA diameter (mm)	43.7 ± 8.1$_a$	47.0 ± 8.3$_b$	46.7 ± 8.1$_b$	48.1 ± 9.9$_b$	<0.001
LA volume index (mL/m^2)	48.6 ± 25.3$_a$	63.2 ± 46.0$_b$	58.3 ± 27.2$_{a,b}$	65.5 ± 32.3$_b$	<0.001
Antiplatelet agent	21.5	15.6	16.0	17.3	0.312
OAC + antiplatelet agent	21.5	15.6	16.0	17.3	0.312
Antiarrhythmic drugs	42.2$_a$	46.4$_a$	37.1$_a$	29.1$_b$	0.001
ACE-I or ARB	37.1$_a$	60.8$_b$	63.3$_{b,c}$	70.0$_c$	<0.001
Beta-blockers	46.0$_a$	60.3$_b$	66.7$_b$	75.1$_c$	<0.001
MR antagonist	1.3$_a$	3.4$_a$	6.3$_b$	7.6$_b$	0.004
FU duration (months)	23.5 ± 9.5	23.5 ± 10.3	21.9 ± 9.8	22.3 ± 10.1	0.214

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; FU, follow-up; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OAC, oral anticoagulant.
Values are presented as mean ± standard deviation for continuous variables or as number (%) for categorical variables.
The same subscript letters indicate non-significant differences and the different subscript letters indicate significant differences across the groups based on Bonferroni multiple comparison tests.

and HFpEF groups. The patients were followed up for 22.8 ± 10.0 months.

Stroke/systemic embolism and major bleeding

The annual stroke/SE incidence was 2.8% in the HFpEF group, 0.7% in the HFmrEF group, 1.1% in the HFrEF group, and 0.9% in the no-HF group. The cumulative incidence of stroke/SE was significantly higher in the HFpEF group than in the no-HF (P = 0.025) and HFmrEF (P = 0.015) groups (*Figure 1*). There were no significant differences in the cumulative incidence of stroke/SE across the HFpEF and HFrEF groups (P = 0.068). There were no significant differences in the cumulative incidence of stroke/SE across the HFmrEF, HFrEF, and no-HF groups. The risk for stroke/SE was significantly higher in the HFpEF group than in the no-HF group, after adjustment for the hypertension, diabetes, stroke/TIA history, and vascular disease (*Table 3*). There were no significant differences in the risk for stroke/SE between the HFmrEF and no-HF groups and between the HFrEF and no-HF groups. Stroke occurred in eight, two, three, and four patients in the HFpEF, HFmrEF, HFrEF, and no-HF groups, respectively. TIA occurred in three and one patient in the HFpEF and HFrEF groups. Renal infarction occurred in two, one, and one patient in the HFpEF, HFmrEF, and HFrEF groups, respectively.

The annual major bleeding incidence was 0.7% in the HFpEF group, 0% in the HFmrEF group, 0.2% in the HFrEF group, and 0.2% in the no-HF group. There were no significant differences in the cumulative incidence of major bleeding across the four groups (*Figure 1*). The risk for major bleeding was not increased in the HFpEF, HFmrEF, and HFrEF groups, compared with that in the no-HF group, after adjustment for the HAS-BLED score (*Table 4*).

Echocardiographic parameters as risk factors for stroke/systemic embolism in patients with heart failure

Elevated E/e' value was an independent risk factor for stroke/SE after adjustment for hypertension, diabetes, stroke/TIA history, vascular disease, and HF type (*Table 5*). However,

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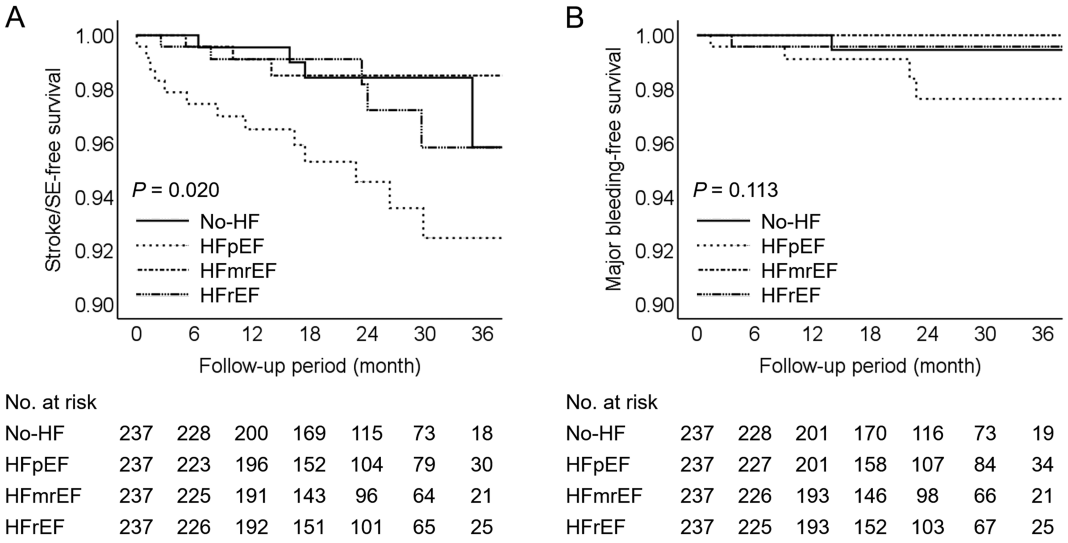
Figure 1 Cumulative incidence of stroke/systemic embolism (A) and major bleeding (B) according to heart failure type. HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SE, systemic embolism.



No. at risk

No-HF	237	228	200	169	115	73	18
HFpEF	237	223	196	152	104	79	30
HFmrEF	237	225	191	143	96	64	21
HFrEF	237	226	192	151	101	65	25

No. at risk

No-HF	237	228	201	170	116	73	19
HFpEF	237	227	201	158	107	84	34
HFmrEF	237	226	193	146	98	66	21
HFrEF	237	225	193	152	103	67	25

Table 3 Incidence and risk of stroke/systemic embolism according to heart failure type

Group	Annual incidence	Univariable		Multivariable	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)[a]	*P*-value
No-HF	0.9	1.000 (reference)		1.000 (reference)	
HFpEF	2.8	3.348 (1.091–10.273)	0.035	3.192 (1.039–9.810)	0.043
HFmrEF	0.7	0.806 (0.180–3.605)	0.778	0.806 (0.179–3.616)	0.778
HFrEF	1.1	1.322 (0.355–4.923)	0.678	1.261 (0.336–4.724)	0.731

CI, confidence interval; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Hazard ratio and 95% confidence interval that were compared with no-HF and adjusted for hypertension, diabetes, stroke/transient ischaemic attack history, and vascular disease.

Table 4 Risk for major bleeding according to heart failure type

Group	Annual incidence	Univariable		Multivariable	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)[a]	*P*-value
No-HF	0.2	1.000 (reference)		1.000 (reference)	
HFpEF	0.7	4.198 (0.469–37.569)	0.200	4.118 (0.459–36.954)	0.206
HFmrEF	0	—	—	—	—
HFrEF	0.2	1.071 (0.067–17.130)	0.961	1.224 (0.076–19.621)	0.887

CI, confidence interval; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Hazard ratio and 95% confidence interval that were compared with no-HF and adjusted for uncontrolled hypertension, abnormal liver/kidney function, stroke history, bleeding tendency, labile international normalized ratio, and concomitant drugs predisposing to bleeding or alcohol intake.

Table 5 Risk associated with echocardiographic parameters for stroke/systemic embolism

	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)[a]	*P*-value
LVEF (%)	1.006 (0.968–1.045)	0.764	1.003 (0.967–1.041)	0.874
E/e'	1.056 (1.017–1.095)	0.004	1.070 (1.022–1.120)	0.004
LA diameter	1.078 (1.003–1.158)	0.040	1.064 (0.985–1.150)	0.114
LA volume index	0.995 (0.974–1.016)	0.614	0.998 (0.977–1.020)	0.856

CI, confidence interval; LA, left atrium; LVEF, left ventricular ejection fraction.
[a]Hazard ratio and 95% confidence interval that were adjusted for hypertension, diabetes, stroke/transient ischaemic attack history, vascular disease, and heart failure type.

LVEF, LA diameter, and LA volume index were not significantly associated with stroke/SE.

Discussion

Main findings

The main findings of the present study are as follows: (i) the cumulative incidence and risk of stroke/SE were significantly higher in the HFpEF group than in the other HF groups; (ii) the cumulative incidence and risk of stroke/SE were comparable between the HFmrEF and HFrEF groups; (iii) there were no significant differences in terms of major bleeding across the groups; and (iv) high E/e' value was an independent risk factor for stroke/SE.

Stroke/systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type

The results of previous studies pertaining to the risk for stroke/SE in patients with AF and HF, according to HF type, are inconsistent. In these previous studies, HF was grouped into HFpEF and HFrEF. Moreover, the cut-off LVEF values used for the classification of patients into the HFpEF and HFrEF groups differed across the studies, between 40% and 50%; this indicates that HFmrEF was classified as HFpEF at a cut-off of 40% whereas HFmrEF was classified as HFrEF at a cut-off of 50%. The subgroup analyses of the ARISTOTLE trial demonstrated that the risk for stroke/SE in patients with an LVEF $\leq$ 40% was comparable with that observed in patients with HF and an LVEF $>$ 40%.[9] The ORBIT-AF study revealed that the risk for stroke was similar between patients with HFpEF and HFrEF (LVEF $\leq$ 40%).[10] Medical insurance data obtained from the USA showed that the risk for ischaemic stroke was comparable between people with HFpEF and HFrEF, based on the International Classification of Disease, 9th revision code.[11] Retrospective single-centre data from Japan demonstrated the absence of significant differences in the SE rate between patients with HFpEF and HFrEF (LVEF $<$ 50%).[12] In contrast, Korean prospective AF registry data (CODE-AF study) revealed that the risk for stroke/SE was higher in patients with HFpEF than in patients with HFrEF (LVEF $<$ 50%).[13]

In only few studies focusing on the risk for stroke/SE in patients with AF and HF, HF was grouped into HFpEF, HFmrEF, and HFrEF. Consistent with the present study, the Swedish HF registry showed that the composite incidence of stroke or TIA or death was higher in patients with HFpEF and lower in HFmrEF than in the other HF types.[14] In contrast, the European AF registry (PREFER in AF-HF substudy) revealed that the risk of thromboembolic events was the highest in the HFrEF group, followed by the HFmrEF and HFpEF groups.[15]

Epidemiological studies have reported a close relationship between AF and HFpEF.[16] Although it is not clear why the risk for stroke/SE was the highest in the HFpEF group in the present study, the following explanation may be plausible. High E/e' value was identified as an independent risk factor for stroke/SE. The risk for stroke/SE was not associated with LVEF. These findings suggest that LV diastolic dysfunction contributes to the risk for stroke/SE rather than LV systolic dysfunction in patients with AF and HF. LV diastolic dysfunction may contribute to stroke/SE via the following mechanism: blood flow from the LA to LV is hindered under conditions of LV diastolic dysfunction. Impairment of the blood flow to the LV results in blood stasis in the LA, which leads to predisposition to thrombus formation, subsequently resulting in an increase in the risk for stroke/SE. Therefore, the use of anticoagulation therapy is imperative in patients with AF and HFpEF or LV diastolic dysfunction. However, this explanation is not sufficient, as patients with HFrEF, HFmrEF, and HFpEF also have diastolic dysfunction. High prevalence of hypertension and high warfarin administration rate in the HFpEF group might partly contribute to the risk for stroke/SE.

Major bleeding in patients with atrial fibrillation and heart failure

The findings of previous studies and the present study are consistent as the risk for major bleeding in patients with AF

and HF was comparable across the HF types. The subgroup analyses of the ARISTOTLE trial showed that the risk for major bleeding was not different between patients with an LVEF $\leq$ 40% and patients with HF and an LVEF $>$ 40%.[9] Apixaban use reduced the risk for bleeding, compared with warfarin.[9] The medical insurance data from the USA revealed that the risk for bleeding was comparable between patients with HFpEF and HFrEF.[11] The CODE-AF study data demonstrated that the risk for major bleeding was not different between HFpEF and HFrEF (LVEF $<$ 50%).[13] The European AF registry (PREFER in AF-HF substudy) revealed that the level of bleeding risk was not different across the HFrEF, HFmrEF, and HFpEF groups.[15] In summary, these findings suggest that the risk for major bleeding is not associated with HF type.

Limitations

First, follow-up echocardiography data were not available. Therefore, reversible LV dysfunction was not detected. Second, the follow-up duration was relatively short. Third, the types of oral anticoagulants [warfarin and non-vitamin K antagonist oral anticoagulants (NOACs)] used were not consistent in the study population. Generally, the bleeding risk associated with warfarin is higher than that related to NOAC use. Therefore, the proportion of people who were taking warfarin and NOACs may have affected the incidence of major bleeding. Fourth, data on international normalized ratio in the patients who were taking warfarin were not available. Fifth, data on the indications of antiplatelet agents in the patients who were taking antiplatelet agents were not available. Sixth, data on dosage of the drugs that the patients were taking during the study period were not available. Seventh, data on stroke subtypes were not available.

Conclusions

In patients with AF and HF, the risk for stroke/SE was the highest in association with HFpEF among the three HF types. The risk for stroke/SE was comparable between HFmrEF and HFrEF. LV diastolic dysfunction may contribute to the risk for stroke/SE.

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Conflict of interest

None declared.

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