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

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Abstract

Aims This study aimed to elucidate the risk for stroke and systemic embolism (SE) in patients with atrial fibrillation and heart failure (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 CHA2DS2-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 higher in the HFpEF group than in the HFmrEF and HFrEF groups (hazard ratio, 3.192; 95% confidence interval, 1.039–10.810; 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, 1.039–10.810; 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

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 CHA2DS2-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 HF according to the HF type. 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 \(\geq 18\) 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\(_2\)DS\(_2\)-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 \(\geq 75\) 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 drugs or nonsteroidal anti-inflammatory drugs) or alcohol intake (\(\geq 8\) 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 \(\geq 50\%\), 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\(_2\)DS\(_2\)-VASc score \(\geq 1\) in men and CHA\(_2\)DS\(_2\)-VASc score \(\geq 2\) 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. 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 $\chi^2$ 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, HFrEF, 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 HFrEF, HFrEF, and HFrEF groups. The CHA2DS2-VASc score was significantly higher in the HFpEF, HFrEF, and HFrEF groups than in the no-HF group. There were no significant differences in the CHA2DS2-VASc score across the HFrEF, HFrEF, 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 HFrEF 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 ≥ 140 mmHg or diastolic blood pressure ≥ 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 HFrEF 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, HFrEF, 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 HFrEF and HFrEF groups than in the no-HF.

Table 1 Baseline characteristics of the total population

|                      | No-HF (n = 9666) | HFpEF (n = 487) | HFrEF (n = 263) | HFrEF (n = 364) | P-value |
|----------------------|-----------------|----------------|----------------|----------------|---------|
| Age (years)          | 66.6 ± 11.0, a  | 70.2 ± 11.1, b | 68.6 ± 11.2, b,c| 66.9 ± 11.6, a,c| <0.001  |
| Male                 | 6274 (64.9), a  | 260 (53.4), b  | 106 (40.3), b  | 185 (50.8), a  | <0.001  |
| Paroxysmal AF        | 6417 (66.4), a  | 222 (45.6), b | 106 (40.3), b  | 334 (91.8), c  | <0.001  |
| CHA2DS2-VASc score   | 2.5 ± 1.6, a    | 1.0 ± 1.7, b   | 3.8 ± 1.9, b   | 3.7 ± 1.7, b   | <0.001  |
| Hypertension         | 6286 (65.0), a  | 159 (60.5), b  | 237 (65.1), b  | 114 (31.3), c  | 0.009   |
| Diabetes             | 2363 (24.4), a  | 127 (26.1), ab | 76 (28.9), b   | 82 (22.0), c   | 0.001   |
| Stroke history       | 1473 (15.2), a  | 81 (16.6), ab  | 53 (20.2), b   | 56 (15.1), b   | 0.001   |
| Vascular disease     | 548 (5.7), a    | 38 (7.8), b    | 35 (13.3), c   | 55 (15.1), b   | <0.001  |
| HAS-BLED score       | 1.5 ± 1.1, a    | 2.2 ± 1.2, b   | 1.9 ± 1.2, a,c| 2.0 ± 1.2, a,c | <0.001  |
| LVEF (%)             | 62.5 ± 7.0, a   | 50.0 ± 6.0, b  | 43.9 ± 2.6, a  | 31.4 ± 6.1, a  | <0.001  |
| LA diameter (mm)     | 43.2 ± 8.1, a   | 47.1 ± 8.4, b  | 46.8 ± 8.2, b  | 47.2 ± 9.3, a  | <0.001  |
| LA volume index (mL/m²)| 26.7 ± 15.6, a| 36.6 ± 24.3, b| 34.3 ± 17.7, b| 37.0 ± 19.6, b| <0.001  |
| OAC                  | 7616 (78.8), a  | 436 (89.5), c  | 246 (93.5), c  | 334 (91.8), c  | <0.001  |

AF, atrial fibrillation; HF, heart failure; HFrEF, 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.
and HFrEF 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 HFrEF group, 0.7% in the HFrEF 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 HFrEF group than in the no-HF (P = 0.025) and HFrEF (P = 0.015) groups (Figure 1). There were no significant differences in the cumulative incidence of stroke/SE across the HFrEF and HFrEF groups (P = 0.068). There were no significant differences in the cumulative incidence of stroke/SE across the HFrEF, HFrEF, and no-HF groups. The risk for stroke/SE was significantly higher in the HFrEF 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 HFrEF and no-HF groups and between the HFrEF and no-HF groups. Stroke occurred in eight, two, three, and four patients in the HFrEF, HFrEF, HFrEF, and no-HF groups, respectively. TIA occurred in three and one patient in the HFrEF and HFrEF groups. Renal infarction occurred in two, one, and one patient in the HFrEF, HFrEF, and HFrEF groups, respectively.

The annual major bleeding incidence was 0.7% in the HFrEF group, 0% 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 HFrEF, HFrEF, 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,
Table 3 Incidence and risk of stroke/systemic embolism according to heart failure type

| Group     | Annual incidence | Hazard ratio (95% CI) | Univariable P-value | Hazard ratio (95% CI) a | Multivariable P-value |
|-----------|------------------|-----------------------|---------------------|-------------------------|-----------------------|
| No-HF     | 0.9              | 1.000 (reference)     | 1.000 (reference)   | 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.

aHazard 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 | Hazard ratio (95% CI) | Univariable P-value | Hazard ratio (95% CI) a | Multivariable P-value |
|-----------|------------------|-----------------------|---------------------|-------------------------|-----------------------|
| No-HF     | 0.2              | 1.000 (reference)     | 1.000 (reference)   | 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    | 0.3              |                       |                     |                         |                       |
| 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.

aHazard 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.
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 HFrEF and HFpEF. 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 HFrEF at a cut-off of 40% whereas HFmrEF was classified as HFpEF 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 ≤ 40% was comparable with that observed in patients with HF and an LVEF > 40%. The ORBIT-AF study revealed that the risk for stroke was similar between patients with HFpEF and HFrEF (LVEF ≤ 40%). 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%).

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. 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. Epidemiological studies have reported a close relationship between AF and HFpEF. 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 HFrEF 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
Conclusions

In patients with AF and HF, the risk for stroke/SE was the highest in association with HFrEF 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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