Incidence and Risk Factors of Stroke or Systemic Embolism in Patients With Atrial Fibrillation and Heart Failure

— The Fushimi AF Registry —

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Background: Heart failure (HF) is a heterogeneous syndrome, but the effect of the type and severity of HF on the incidence of stroke or systemic embolism (SE) in atrial fibrillation (AF) patients is unclear.

Methods and Results: The Fushimi AF Registry is a community-based prospective survey of AF patients in Fushimi-ku, Kyoto, Japan. Follow-up data were available for 3,749 patients. We defined pre-existing HF as having one of the following: prior hospitalization for HF, presence of HF symptoms (NYHA ≥2), or reduced ejection fraction (<40%). At baseline, 1,008 (26.9%) patients had pre-existing HF. On multivariate analysis, the incidence of stroke/SE was not associated with pre-existing HF (hazard ratio (HR), 1.24; 95% confidence interval (CI), 0.92–1.64) or each criterion for the definition of pre-existing HF, but was associated with high B-type natriuretic peptide (BNP) or N-terminal proBNP levels (above the median of the pre-existing HF group) at baseline (HR, 1.65; 95% CI, 1.06–2.53). Stroke/SE was markedly increased in the initial 30-day period following hospital admission for HF (HR, 12.0; 95% CI, 4.59–31.98).

Conclusions: The effect of HF on the incidence of stroke/SE may depend on the stage or severity of HF in patients with AF. The incidence of stroke/SE was markedly increased in the 30 days after admission for HF, but compensated ‘stable’ HF did not appear to confer an independent risk.

Key Words: Atrial fibrillation; Decompensated heart failure; Heart failure; Stroke

Heart failure (HF) is an important comorbidity, along with stroke or systemic embolism (SE), in patients with atrial fibrillation (AF). AF and HF are part of a vicious cycle, and concomitant HF leads to higher mortality in AF subjects.1 The presence of HF fulfills all of Virchow’s triad of characteristics of a hypercoagulable state, increasing the propensity to thrombosis.2 Indeed, HF especially where moderate-severe left ventricular (LV) dysfunction is present, is a risk for stroke/SE even in patients with sinus rhythm.3–6 HF is also a significant risk for stroke/SE among patient with AF, and is included in the currently used stroke risk stratification schemes in AF patients, such as the CHADS2 and CHA2DS2-VASc scores.7,8

However, there are variations in the definition of HF (congestion, prior history of hospitalization, New York Heart Association (NYHA) class, and ejection fraction (EF)), and controversy exists regarding the effect of HF on the incidence of stroke in AF patients.9–12 The risk of stroke may vary according to the type or severity of HF.13 The objective of this study was to examine the incidence and risk factors of stroke/SE in patients with AF and HF using data from the Fushimi AF Registry, a community-based prospective survey of AF patients.

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Methods

Study Cohort
The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all AF patients who visited participating medical institutions in Fushimi-ku, Kyoto, Japan. The detailed study design, patient enrollment, the definition of the measurements, and baseline clinical characteristics of the Fushimi AF Registry have been described (UMIN Clinical Trials Registry: UMIN000005834). The inclusion criterion for the registry is documentation of AF on 12-lead ECG or by Holter monitoring at any time. There were no exclusion criteria. The enrollment of patients started in March 2011. A total of 4,441 patients were enrolled by the end of November 2015. Of 4,182 patients who were enrolled in the year before (by the end of November 2014), follow-up data (collected every year until death) were available for 3,749 patients (follow-up rate: 89.6%). The median follow-up period was 1,099 [interquartile range (IQR): 533–1,470] days. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

Definition of HF
The definition of pre-existing HF used in this study was having one of the following at enrollment: (1) history of hospitalization for HF prior to enrollment, (2) symptomatic HF (NYHA ≥2), in association with heart disease, or (3) LV dysfunction (EF ≤40%). History of hospitalization for HF was assessed by review of medical records. NYHA class was assessed by each attending physician on the basis of their interpretation of the patient’s reported symptoms, medical history, and results from clinical tests on cardiac structure and function. Echocardiographic data were available for 2,713 patients. We classified the patients with EF ≤40% as HF with reduced EF (HFrEF), and others as HF with preserved EF (HFrpEF). B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) was measured at each participating institution using commercially available immunochemical assays.

A total of 338 patients (9.0% of whole cohort) required hospital admission for HF during follow-up. Admission for HF was determined by the attending physician based on history, clinical presentation (symptoms and physical examination), response to HF therapy, chest radiography, echocardiography, cardiac catheterization findings, and in-hospital course. We defined HF-admission(+) as patients with admission for HF, and HF-admission(−) as those without admission for HF.

Study Endpoints
The primary endpoint in this analysis was the incidence of stroke/SE during the follow-up period. Other clinical endpoints included the incidence of all-cause death, cardiovascular (CV) death, transient ischemic attack (TIA), and hospital admission for HF 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, and the diagnosis of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organ. TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Statistical Analysis
Continuous variables are expressed as the mean±standard deviation (SD), or median and IQR. Categorical variables are presented as numbers and percentages. We compared categorical variables using the chi-square test when appropriate; otherwise, we used Fisher’s exact test. We compared continuous variables using Student’s t-test on the basis of the distribution. The Kaplan-Meier method was used to estimate the cumulative incidences of clinical events. We carried out multivariate analysis using a Cox proportional hazards model. The covariates chosen to be included in model 1 were components of the CHA2DS2-VASc risk score (congestive HF, hypertension, age ≥75 years, age 65–74 years, diabetes mellitus, history of stroke/SE, vascular disease defined as having prior myocardial infarction or peripheral artery disease, and female sex) and prescription of oral anticoagulants (OAC). OAC included warfarin, dabigatran, rivaroxaban, apixaban and edoxaban. We used each criterion of pre-existing HF (history of hospitalization for HF, NYHA ≥2, or LV dysfunction) in model 2.

To examine whether compensated HF increased the risk of stroke/SE, we calculated the incidence of stroke/SE before and after admission for HF (Be-HF-admission and Af-HF-admission, respectively). To describe the incidence of stroke/SE in Af-HF-admission, the date of admission for HF was used as the index date. To describe that in Be-HF-admission and in the HF-admission(−) groups, the date of enrollment was used as the index date. Furthermore, we calculated the incidence rates of stroke/SE by dividing the number of observed cases by the number of persons at risk in each 30-day period from enrollment to admission for HF, after admission for HF, and in the HF-admission(−) group, respectively.

To reduce the effect of potential confounding in this observational study, we used propensity score matching to perform rigorous adjustment for the differences in the baseline characteristics. The covariates entered into the propensity score were OAC prescription at baseline, the components of the CHA2DS2-VASc risk score, and clinically relevant factors (sustained (persistent or permanent) AF, chronic kidney disease (CKD), and LV dysfunction). After propensity score generation, the HF-admission(+) and HF-admission(−) groups underwent 1:1 nearest neighbor matching of the logit of the propensity score with a caliper width of 0.20. The incidences of stroke/SE were compared between the Af-HF-admission and HF-admission(−) groups after matching.

Data analysis was performed with JMP version 12 (SAS Institute, Cary, NC, USA). A 2-sided P-value <0.05 was considered significant. Confidence intervals (CI) were 95%.

Results

Patients’ Baseline Characteristics
At baseline, 1,008 (26.9% of total) patients had pre-existing HF (pre-existing HF(+) group). Table 1 shows the baseline characteristics of patients with and without pre-existing HF (pre-existing HF(−) group; n=2,741, 73.1%). The pre-existing HF(+) group was older, included more females, and was more likely to have sustained types of AF than the pre-existing HF(−) group. The prevalences of hyperten-
During the follow-up, 154 (2.1/100 person-years) of the pre-existing HF(−) group and 71 (2.9/100 person-years) of the pre-existing HF(+) group developed stroke/SE. In the Kaplan-Meier analysis, the pre-existing HF(+) group had higher unadjusted rates of stroke/SE (HR, 1.40; 95% CI, 1.05–1.85; P=0.02 by log-rank test) (Figure 1A), as well as higher incidences of all-cause death and composite of all-
In the pre-existing HF(+) group, BNP and NT-proBNP data were available for 182 (18.1%) and 486 (48.2%) patients, and the median BNP and NT-proBNP levels were 169.4 [87.7–307.7] pg/mL and 1,457 [758–2,870] pg/mL, respectively. We divided the pre-existing HF(+) group into 2 groups based on the median BNP and NT-proBNP levels of the pre-existing HF(+) group. High BNP/NT-proBNP (above the median) was associated with increased stroke/SE (Figure 2D). In the Cox proportional hazard analysis, high BNP/NT-proBNP was an independent predictor of stroke/SE in HF (HR, 1.65; 95% CI, 1.06–2.53). The incidence of ischemic stroke/SE was also associated with High BNP/NT-proBNP, but not with the presence of history of hospitalization for HF, NYHA class, or EF (Figure S1).

Factors Associated With the Incidence of Stroke/SE in Patients With AF and HF

We further examined the factors associated with increased risk of stroke/SE in patients with AF and HF. We divided the pre-existing HF(+) group into 2 groups based on the presence of a history of hospitalization for HF, NYHA class, and EF at baseline. None of these factors was associated with the incidence of stroke/SE (Table 2, model 2).

BNP and NT-proBNP data were available for 517 patients (13.8%) and 1,064 patients (28.4%), respectively. The median [IQR] of BNP and NT-proBNP of the entire cohort was 83.8 [36.0–174.6] pg/mL and 492 [155–1,006] pg/mL, respectively. In the pre-existing HF(+) group, BNP and NT-proBNP data were available for 182 (18.1%) and 486 (48.2%) patients, and the median BNP and NT-proBNP levels were 169.4 [87.7–307.7] pg/mL and 1,457 [758–2,870] pg/mL, respectively. We divided the pre-existing HF(+) group into 2 groups based on the median BNP and NT-proBNP levels of the pre-existing HF(+) group. High BNP/NT-proBNP (above the median) was associated with increased stroke/SE (Figure 2D). In the Cox proportional hazard analysis, high BNP/NT-proBNP was an independent predictor of stroke/SE in HF (HR, 1.65; 95% CI, 1.06–2.53). The incidence of ischemic stroke/SE was also associated with High BNP/NT-proBNP, but not with the presence of history of hospitalization for HF, NYHA class, or EF (Figure S1).

Relationship Between Hospitalization for HF and Incidence of Stroke/SE

In our cohort, 338 patients (9.0% of total cohort) were admitted to hospital for HF after enrollment. Table 1 shows the baseline characteristics of the patients with hospital admission for HF (HF-admission(+): n=338) and those without (HF-admission(−): n=3,411). The HF-admission(+) group was older and had more comorbidities, including pre-existing HF, than the HF-admission(−) group. The
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Table 2. Multivariate Cox Proportional Hazard Analysis for Stroke/SE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2.42 (1.56–3.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>65≤Age&lt;75</td>
<td>1.24 (0.76–2.09)</td>
<td>0.4</td>
</tr>
<tr>
<td>Female</td>
<td>0.91 (0.69–1.19)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14 (0.86–1.52)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.13 (0.83–1.51)</td>
<td>0.4</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>1.81 (1.36–2.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>1.09 (0.71–1.61)</td>
<td>0.7</td>
</tr>
<tr>
<td>OAC</td>
<td>0.99 (0.75–1.30)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pre-existing HF</td>
<td>1.24 (0.92–1.65)</td>
<td>0.2</td>
</tr>
<tr>
<td>Prior hospitalization for HF</td>
<td>–</td>
<td>1.29 (0.89–1.82)</td>
</tr>
<tr>
<td>NYHA ≥2</td>
<td>–</td>
<td>1.10 (0.76–1.56)</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>–</td>
<td>0.80 (0.36–1.53)</td>
</tr>
</tbody>
</table>

The covariates included in model 1 were components of the CHA2DS2-VASc risk score (congestive heart failure, hypertension, age ≥75 years, age 65–74 years, diabetes mellitus, history of stroke/SE, vascular disease, and female sex) and prescription of OAC, and we used each criterion of pre-existing HF (history of hospitalization for HF, NYHA ≥2, or LV dysfunction) in model 2. *Vascular disease was defined as having prior myocardial infarction or peripheral artery disease. HR, hazard ratio; NYHA, New York Heart Association; SE, systemic embolism. Other abbreviations as in Table 1.

Figure 2. Incidence of stroke/SE in patients with pre-existing HF. The pre-existing HF(+) group was divided into 2 subgroups based on the presence of prior hospitalization for HF (A), NYHA class (B), EF at baseline (C) and BNP/NT-proBNP levels (D). BNP, B-type natriuretic peptide; EF, ejection fraction; NYHA, New York Heart Association. Other abbreviations as in Figure 1.
prevalence of prior stroke/SE was comparable between the groups. Mean CHADS2 and CHA2DS2-VASc scores were higher in the HF-admission(+) group, and prescription of OAC was higher in the HF-admission(+) group. EF was lower in the HF-admission(+) group, and BNP and NT-proBNP levels were higher in the HF-admission(+) group.

In the HF-admission(+) group, 13 patients (2.4/100 person-year) developed stroke/SE before admission for HF (10 ischemic strokes, 3 hemorrhagic strokes), and 37 patients (6.8/100 person-years) developed stroke/SE after admission for HF (28 ischemic strokes, 8 hemorrhagic strokes, 1 SE). Stroke/SE occurred in 189 patients in the HF-admission(−) group (2.3/100 person-years) (144 ischemic strokes, 40 hemorrhagic strokes, 5 SEs). The incidence of stroke/SE in the HF-admission(+) group after admission (AF-HF-admission) was significantly higher than that in the HF-admission(−) group (HR, 3.94; 95% CI, 2.42–6.17), whereas risk in the HF-admission(+) group before admission (Be-HF-admission) was not significantly different from the HF-admission(−) group (HR, 1.21; 95% CI, 0.65–2.04) (Figure 3A). Incidence rates of stroke/SE in each 30-day period in these 3 groups are plotted in Figure 3B, showing the very high incidence of stroke/SE in the initial 30-day period following admission for HF (HR, 12.0; 95% CI, 4.59–31.98). We confirmed similar results for ischemic stroke/SE (Figure S2).

Because of the significant imbalance in baseline covariates between the HF-admission(+) and HF-admission(−) group, we carried out subgroup analysis of the patients with and without pre-existing HF, and propensity score matching (baseline characteristics of propensity score-matched pairs were shown in Table S1). The incidence of stroke/SE after HF admission were also higher both in patients with (HR, 3.31; 95% CI, 1.97–5.41) and without pre-existing HF (HR, 3.75; 95% CI, 2.01–6.41) (Figure 4), and in 337 propensity score-matched pairs (HR, 2.86; 95% CI, 1.39–6.29) (Figure S3).

Discussion

In this cohort study, we showed that approximately 25% of AF patients had concomitant pre-existing HF. Patients with pre-existing HF had significantly higher unadjusted rates of death and stroke/SE. Although neither pre-existing HF nor each criterion for the definition of pre-existing HF (history of hospitalization for HF, symptomatic HF, and LV dysfunction) was independently associated with stroke/SE in the multivariate analysis, the incidence of stroke/SE was high early after admission for HF or in patients with high BNP/NT-proBNP level, which indicated that the risk for stroke/SE in patients with AF is not constant, but dependent on the stage or severity of HF.

Effect of HF on Stroke/SE in Patients With AF

There is controversy regarding the effect of HF on stroke/SE in patients with AF. Clinically defined HF (history of hospitalization for HF or presence of HF symptoms) was an independent predictor for stroke/SE in the SPAF I trial and in a prospective cohort study of 1,066 patients from 3 clinical trials. In contrast, HF was not an independent predictor of stroke in a pooled analysis of 5 randomized trials or in an analysis of 2,012 patients from the SPAF I–III trials. The effect of HF defined by LV dysfunction is also controversial. In a prospective study of 312 older patients with...
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chronic AF, the presence of LV dysfunction, but not a history of congestive HF, was an independent predictor of stroke.\textsuperscript{17} Of note, LV dysfunction was not an independent risk for stroke/SE in the Loire Valley Atrial Fibrillation Project,\textsuperscript{18} ARISTOTLE trial\textsuperscript{19} or ACTIVE trial.\textsuperscript{20} In the ACTIVE trial, for example, the degree of symptom severity assessed by NYHA class did not influence the risk of stroke/SE.\textsuperscript{20} In the Stroke in AF Working group analysis, HF did not emerge as an independent stroke risk factor.\textsuperscript{21} Indeed, HF is a syndrome comprising a wide variety of pathogenesis, type, stage and severity, which may partly explain these conflicting results. In addition, patients with pre-existing HF had higher mortality, which might be a competing risk for stroke/SE. In our analysis, pre-existing HF was independently associated with a composite outcome of stroke/SE or all-cause death, but not with stroke/SE alone, suggesting the possibility that the risk of stroke/SE in patients with pre-existing HF might be underestimated.

Variation in the Risk of Stroke/SE in Patients With AF and HF, According to Stage or Severity of HF

In this study, we defined pre-existing HF as having one of the following: history of hospitalization for HF, symptomatic HF, or LV dysfunction. Pre-existing HF was not an independent predictor of stroke/SE, and none of these factors was associated with the incidence of stroke/SE. However, a higher level of BNP/NT-proBNP was associated with the incidence of stroke/SE. Notably, patients requiring admission for HF showed a markedly increased risk of stroke/SE, especially within 30 days after admission for HF. Even in patients with sinus rhythm, admission for HF was a risk for stroke/SE and the risk was higher early after admission.\textsuperscript{22,23} In a single-center, retrospective study, we recently reported an increased incidence of ischemic stroke during hospitalization for HF irrespective of the presence of AF [interval from HF hospitalization to the onset of stroke: median 10 days (IQR 5–17 days)].\textsuperscript{24} HF increases the risk of thrombosis,\textsuperscript{22,25} and decompensated HF requiring admission further increases the risk through elevated intracardiac and venous pressure, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and endothelial dysfunction induced by hypoxia.\textsuperscript{26–28} Decompensation begins days to weeks prior to hospitalization, and the associated increased risk is likely from the outset of decompensation before the actual admission. However, patients are often treated with diuretics after admission, and the subsequent dehydration induced by diuretics may also cause a hypercoagulable state,\textsuperscript{29} which further increases the risk. Patients with AF had a risk of stroke/SE even if they did not have HF, but HF admission might further exacerbate the risk of stroke/SE in patients with AF. Previous studies have also reported that high BNP and NT-proBNP levels were risk factors for stroke/SE in patients with AF,\textsuperscript{30–32} supporting the hypothesis that decompensated HF increases the risk for thromboembolism.

Study Limitations

This study has several limitations. First, it was a prospective observational study, so only associations are shown, not causality. We cannot rule out the possibility of unmeasured or residual confounding. Second, follow-up data were missing for approximately 10% of the patients, and echocardiographic data were not available for all subjects, which may result in a selection bias. BNP/NT-proBNP data were available for 66% of the patients with pre-existing HF, which may also result in a selection bias. Therefore, we performed sensitivity analysis comparing patients with and without BNP/NT-proBNP data. Despite that, there are some differences in baseline characteristics between the 2 groups (Table S2); the overall results were consistent as shown in Figure S4 and Figure S5. Third, data on medical therapy, including OAC, were collected only at the time of enrollment into the study, and therefore we were unable to clarify the relationship between changes in medical therapy and clinical events. Fourth, there were few stroke/SE events in the HFrEF group, providing little power for these comparisons. Fifth, the decision on hospital admission for HF depended on the discretion of the attending physician.

Figure 4. Incidence of stroke/SE before (Be-HF-admission: green line) and after admission for HF (Af-HF-admission: red line), and that in patients without admission for HF (HF-admission(−): blue line), among patients without pre-existing HF (A) and those with pre-existing HF (B). Abbreviations as in Figure 1.
which might result in bias. Sixth, this study involved AF patients recruited from a small region of Japan, and so the study results may not be generalizable to the overall population. Despite these limitations, given the paucity of data from Asian AF populations (including Japan), our study demonstrated the clinical characteristics and outcomes in a large community cohort of patients with AF and HF in clinical practice.

Conclusions

The effect of HF on the incidence of stroke/SE may depend on the stage or severity of HF in patients with AF. The incidence of stroke/SE was markedly increased in the 30 days after admission for HF, but compensated ‘stable’ HF did not appear to confer an independent risk.

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Conflict of Interest

M. Akao has served as a consultant for Bayer/Jansen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microline and Daichi-Sankyo. Professor Lip has served as a consultant for Bayer and all authors report no relationships relevant to the contents of this paper.

References

Supplementary Files

Appendix S1

Figure S1. Incidence of ischemic stroke/systemic embolism (SE) in patients with pre-existing heart failure (HF).

Figure S2. (A) Incidence of ischemic stroke/SE in patients with admission for HF (HF-admission(+)) and those without admission for HF (HF-admission(−)).

Figure S3. Kaplan-Meier curves for the incidence of (A) stroke/SE and (B) ischemic stroke/SE in the propensity score-matched cohort.

Figure S4. Incidence of stroke/SE in patients with pre-existing HF between patients with (Left) and without BNP/NT-proBNP data (Right).

Figure S5. (A) Incidence of stroke/SE after admission for HF (Af-HF-admission: red line), before HF admission (Be-HF-admission: green line), and in patients without admission for HF (HF-admission(−): blue line) among patients with BNP/NT-proBNP data.

Table S1. Baseline characteristics of propensity score-matched cohort

Table S2. Baseline characteristics of pre-existing HF patients with and without BNP/NT-proBNP data

Please find supplementary file(s):