Journal of the American Heart Association

ORIGINAL RESEARCH

Ischemic Stroke in Acute Decompensated Heart Failure: From the KCHF Registry

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BACKGROUND: Heart failure (HF) is a known risk factor for ischemic stroke, but data regarding ischemic stroke during hospitalization for acute decompensated HF (ADHF) are limited.

METHODS AND RESULTS: We analyzed the data from a multicenter registry (Kyoto Congestive Heart Failure [KCHF] Registry) that enrolled 4056 consecutive patients with ADHF in Japan (mean age, 78 years; men, 2238 patients [55%]; acute coronary syndrome [ACS], 239 patients [5.9%]). We investigated the incidence and predictors of ischemic stroke during hospitalization for ADHF. During the hospitalization, 63 patients (1.6%) developed ischemic stroke. The median interval from admission to the onset of ischemic stroke was 7 [interquartile range: 2–14] days, and the most common underlying cause was cardioembolism (64%). Men (OR, 1.87; 95%CI, 1.11–3.24), ACS (OR, 2.31; 95%CI, 1.01–4.93), absence of prior HF hospitalization (OR, 2.21; 95%CI, 1.24–4.21), and high B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) levels (above the median) at admission (OR, 3.15; 95%CI, 1.84–5.60) were independently associated with ischemic stroke. In patients without ACS, the independent risk factors for ischemic stroke were fully consistent with those in the main analysis. Higher quartiles of BNP/NT-proBNP levels were significantly associated with higher incidence of ischemic stroke (*P* for trend, <0.001). Patients with ischemic stroke showed higher in-hospital mortality, longer length of hospital stay, and poorer functional status at discharge.

CONCLUSIONS: During hospitalization for ADHF, 1.6% of the patients developed ischemic stroke. Men, ACS, absence of prior HF hospitalization, and high BNP/NT-proBNP levels at admission were independently associated with ischemic stroke.

Key Words: acute heart failure ■ B-type natriuretic peptide ■ ischemic stroke ■ N-terminal pro B-type natriuretic peptide

The presence of heart failure fulfills all of the Virchow's triad for a hypercoagulable state, increasing the propensity to thrombosis,[1] and is considered to be a risk of ischemic stroke. A previous study demonstrated that the risk of ischemic stroke was 2 to 3-fold higher in patients with heart failure.[2] Furthermore, it was reported that decompensation further increased the risk of ischemic stroke. A previous population-based prospective cohort study demonstrated that patients with heart failure had more than 5-fold increased age- and sex-adjusted risk of ischemic stroke in the first month after diagnosis of heart failure as compared with participants without heart failure,[3] which was also supported by another community-based study.[4,5] The increased

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022525

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- During hospitalization for ADHF, 1.6% of patients developed ischemic stroke (median intervals from admission to onset, 7 [interquartile range, 2–14] days), and the most common underlying cause was cardioembolism (64%).
- Independent risk factors for ischemic stroke were men, acute coronary syndrome, absence of prior heart failure hospitalization, and high B-type natriuretic peptide/N-terminal-B-type natriuretic peptide.
- Patients with ischemic stroke showed higher in-hospital mortality and poorer functional status at discharge.

What Are the Clinical Implications?

- Ischemic stroke is a serious complication during hospitalization for acute decompensated heart failure, and its incidence is not rare.
- We should pay more attention to the prevention of ischemic stroke when treating patients with acute decompensated heart failure, and future studies are warranted to explore the optimal therapy to prevent ischemic stroke.

Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
KCHF	Kyoto Congestive Heart Failure
HFpEF	heart failure with preserved LVEF
HFmrEF	heart failure with mildly reduced LVEF
HFrEF	heart failure with reduced LVEF
TOAST	Trial of Org 10172 Acute Stroke Treatment

risk of ischemic stroke in the acute phase of hospitalization for heart failure was also observed in patients with atrial fibrillation.[6] However, there is a paucity of data on the incidence and risk factors of ischemic stroke during hospitalization for acute decompensated heart failure (ADHF). Therefore, we investigated the incidence and risk factors of ischemic stroke during hospitalization for ADHF using data from a large Japanese registry.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. Additional methods can be found in Data S1.

Study Population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicenter cohort study that enrolled consecutive patients who were hospitalized for ADHF for the first time between October 2014 and March 2016 in the 19 participating hospitals in Japan without exclusion (Clinical Trial Registration: NCT02334891 and UMIN000015238). The overall design of the KCHF study has been previously described in detail.[7] We enrolled 4056 consecutive patients with ADHF as defined by the modified Framingham criteria admitted to the participating centers, who received heart failure-specific treatment involving intravenous drugs within 24 hours after hospital presentation.

Ethics

The investigation conformed with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethical committees at Kyoto University Hospital (local identifier: E2311) and each participating hospital. A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating center as the study met the conditions of the Japanese ethical guidelines for medical and health research involving human subjects.[8,9] We disclosed the details of the present study to the public as an opt-out method, and the notice clearly informed patients of their right to refuse enrollment.

Data Collection and Definitions

We collected data on patient demographics, medical history, underlying heart disease, pre-hospital activities, socioeconomic status, signs, symptoms, medications, laboratory tests at hospital presentation, electrocardiogram, echocardiography, and clinical events during the index hospitalization. Heart failure was classified according to left ventricular ejection fraction (LVEF) as heart failure with preserved LVEF (HFpEF: LVEF ≥50%), heart failure with mildly reduced LVEF (HFmrEF: 40% ≤LVEF <50%), and heart failure with reduced LVEF (HFrEF: LVEF <40%). Atrial fibrillation was defined based on prior history and electrocardiograms at admission. B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) was measured at admission at each participating institution using commercially available immunochemical assays. Data values exceeding limits of detection were replaced with the limits of detection. BNP and NT-proBNP data were available in 3590 patients (88.5%) and 698 patients (17.2%), respectively. Since a conversion formula between BNP and NT-proBNP has not been established in patients with ADHF, we divided the patients according to the

median or quartiles of BNP and NT-proBNP levels, and NT-proBNP values were adopted if no BNP values were measured. Antithrombotic therapy was defined as use of intravenous heparin within 24 hours after admission, or prescription of antiplatelet drugs (aspirin, thienopyridines, and cilostazol) and/or oral anticoagulants (vitamin K antagonists and direct oral anticoagulants) at admission.

Ischemic stroke was defined as an episode of sudden onset focal neurologic deficit lasting >24 hours where computed tomography or magnetic resonance imaging showed findings that were consistent with ischemic stroke and relevant to the clinical symptoms. The underlying cause of ischemic stroke was classified into cardioembolism, large-artery atherosclerosis, small-vessel occlusion, stroke of other determined cause, and stroke of undetermined cause according to the Trial of Org 10172 Acute Stroke Treatment (TOAST) classification.[10] Intracranial hemorrhage was defined as subarachnoid hemorrhage, hemorrhagic infarction, cerebral bleeding, and subdural hematoma confirmed by computed tomography or magnetic resonance imaging. Major bleeding was defined as moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification. The definitions of the causes of death and in-hospital adverse events in the KCHF registry were previously reported.[9] The causes of death were adjudicated by a clinical event committee. Death was placed into 1 of 2 categories in the KCHF registry: (1) cardiac death, which includes death related to heart failure and sudden death; and (2) non-cardiac death, which includes death related to stroke, other vascular death, pulmonary disease, sepsis, other infection, gastrointestinal disease, malignancy, renal failure, and other non-cardiovascular death. Sudden death was defined as unexplained death in a previously stable patient. Physical activity at discharge was classified by mobility status based on the definition of the Japanese long-term care insurance system as ambulatory (including those patients using any aid such as stick), use of wheelchair, and bedridden state.

Statistical Analysis

We evaluated the incidence of and the risk factors for ischemic stroke during index hospitalization for ADHF. The categorical variables are presented as numbers and percentages, and were compared using a chi-square test. The continuous variables are expressed as mean±SD or median with interquartile range (IQR). On the basis of their distributions, the continuous variables were compared using Student's *t* test or the Wilcoxon rank sum test. To explore the risk factors of ischemic stroke, we used univariate and multivariable logistic regression models not accounting for the time to events, in order to better visualize the differences in the number of events between groups. Because atrial fibrillation and left ventricular (LV) dysfunction (LVEF <40%) were established risk factors for ischemic stroke in heart failure, we selected these variables and use of intravenous heparin in addition to those variables with significant difference in the univariate analyses as the potential risk factors in the multivariable analysis.

In addition, we sought to investigate the association of BNP/NT-proBNP levels with the risk of ischemic stroke in detail, because high BNP/NT-proBNP was reported to be associated with the incidence of ischemic stroke in patients with chronic heart failure.[11,12] We performed a multivariable logistic regression analysis using the quartiles of BNP or NT-proBNP levels. *P* for trend was calculated by using the quartiles of BNP/NT-proBNP levels as continuous variable. Because BNP data were available for most of the patients, we investigated the association of BNP level with the incidence of ischemic stroke in 3590 patients with BNP data as a sensitivity analysis. The BNP level was entered into the model as a categorical variable according to the quartile of baseline levels or as a log-transformed continuous variable. We also conducted multivariable logistic regression analyses in a population excluding patients with acute coronary syndrome as sensitivity analyses, because acute coronary syndrome without heart failure increases the risk for incidence of ischemic stroke in its acute phase.[13]

We performed subgroup analyses to investigate the effect of high BNP/NT-proBNP levels (above the median of each cohort) for ischemic stroke in the subgroups based on the categories used for the multivariable analysis mentioned above (sex, prior heart failure hospitalization, acute coronary syndrome, LV dysfunction, prevalence of atrial fibrillation, and use of intravenous heparin within 24 hours after admission). Odds ratios of high BNP/NT-proBNP for the incidence of ischemic stroke were estimated in the multivariable logistic regression analysis with adjustment by the 6 variables mentioned above. *P* values for interaction were calculated by logistic regression analysis.

We also compared the incidence of ischemic stroke and bleeding events (major bleeding and intracranial hemorrhage) in patients with and without antithrombotic therapy using a chi-square test. In-hospital death, length of hospital stay, physical activity at discharge, and the rates of the patients who were discharged to home among those who were discharged alive were compared using a chi-square test.

All statistical analyses were conducted by a physician (M.I.) and a statistician (T.M.) using JMP 12.0. All the reported *P* values were 2-tailed, and *P* values <0.05 were considered statistically significant.

RESULTS

Incidence and Risk Factors of Ischemic Stroke During Hospitalization for ADHF

The mean age of the current study population was 77.9±12.0 years and 44.8% were women (Table 1). A total of 1442 patients (36.2%) had a history of prior hospitalization for heart failure, and 239 patients (5.9%) had acute coronary syndrome at hospital admission. HFpEF, HFmrEF, and HFrEF accounted for 43.2%, 18.5%, and 38.4% of the study population, respectively. Atrial fibrillation was seen in 1898 patients (46.8%), and 662 patients (16.3%) had a history of stroke. The median BNP and NT-proBNP levels at admission were 721 (IQR: 398–1308) pg/mL and 5880 (IQR: 2721–13 241) pg/mL, respectively. Antiplatelet drugs and oral anticoagulants were prescribed at admission in 1634 patients (40.3%) and 1280 patients (31.6%), respectively, and intravenous heparin was used within 24 hours after admission in 1113 patients (27.4%).

During hospitalization, 63 patients (1.6%) developed ischemic stroke (Figure 1). The median interval from admission to the onset of ischemic stroke was 7 (IQR: 2–14) days, and 34 patients (54.0%) had ischemic stroke during the first week after hospital admission (Figure 2A). The most common underlying cause of ischemic stroke was cardioembolism (64%), followed by large-artery atherosclerosis (19%) (Figure 2B).

Table 1 and Table S1 shows the baseline characteristics in patients with and without ischemic stroke. Patients with ischemic stroke as compared with those without had a higher prevalence of men, lower prevalence of prior heart failure hospitalization and higher prevalence of acute coronary syndrome (Table 1). Age was comparable between the two groups. BNP and NT-proBNP were measured in 3590 and 698 patients, respectively. Patients with ischemic stroke as compared with those without had higher BNP and NT-proBNP levels. There were no significant between-group differences in the LVEF category (HFpEF/HFmrEF/HFrEF), presence of atrial fibrillation, history of stroke, or prescription of antithrombotic therapy (Table 1). Prescriptions of medications for heart failure were also comparable between the groups, though prescriptions of loop diuretics and renin angiotensin receptor blockers before admission tended to be lower in patients with ischemic stroke (Table S1).

In the univariate logistic regression analysis, men, acute coronary syndrome, absence of prior hospitalization for heart failure, and high BNP/NT-proBNP (above the median) were significantly associated with ischemic stroke (Table 2). In the multivariable analysis, men (OR, 1.87; 95%CI, 1.11–3.24), acute coronary syndrome (OR, 2.31; 95%CI, 1.01–4.73), absence of prior heart failure hospitalization (OR, 2.21; 95%CI, 1.24–4.21), and high BNP/NT-proBNP (OR, 3.15; 95%CI, 1.84–5.60) were independently associated with ischemic stroke (Table 2). In the sensitivity analysis, among 3817 patients—ie, 4056 patients excluding 239 patients (5.9%) with acute coronary syndrome—ischemic stroke occurred in 54 patients (1.4%). The independent risk factors for ischemic stroke in the sensitivity analysis were fully consistent with those in the main analysis (Table S2). When prescription of oral anticoagulants at admission were included in the multivariate analysis, the results were also consistent with those in the main analysis (Table S3).

Effect of the Levels of High BNP/NT-proBNP on Ischemic Stroke

The risk for developing ischemic stroke progressively increased according to the increase in BNP/NT-proBNP levels in both the entire cohort and patients without acute coronary syndrome (Figure 3). Moreover, when we evaluated only those patients in whom BNP values were available, higher BNP levels at admission were also independently associated with higher risk for ischemic stroke both in the entire cohort and in patients without acute coronary syndrome (Figure S1).
In the subgroup analyses based on the variables used in the multivariable analysis, there was no interaction between the subgroup factors and the association of high BNP/NT-proBNP with ischemic stroke (Figure 4).

Incidence of Ischemic Stroke and Bleeding Events in Patients With and Without Antithrombotic Therapy

The incidence of ischemic stroke was not different between patients receiving and those not receiving heparin within 24 hours after hospitalization, while the incidence of major bleeding was significantly higher in patients receiving heparin than in patients not receiving heparin (Table 3). There were no differences in the incidences of ischemic stroke or major bleeding between patients receiving and those not receiving antiplatelet drugs or oral anticoagulants at admission (Table 3).

Clinical Outcomes in Patients With and Without Ischemic Stroke During Hospitalization for ADHF

Patients with ischemic stroke had significantly higher incidence of all-cause death, cardiac death, and non-cardiac death than patients without ischemic stroke (Table 4). Among patients who were discharged alive, the length of hospital stay was significantly longer in those with ischemic stroke than in those without, and the proportions of patients who were ambulatory, and patients who were discharged to home, were lower in patients with ischemic stroke than in those without.

Table 1. Baseline Characteristics of the Entire Cohort and Patients With and Without Ischemic Stroke

Variables	Entire cohort (N=4056)	Ischemic stroke (N=63)	No ischemic stroke (N=3993)	*P* value
Age, y	77.9±12.0	76.8±12.3	78.0±12.0	0.5
Age ≥80 y	2147 (52.9)	31 (49.2)	2116 (53.0)	0.6
Men	2238 (55.2)	44 (69.8)	2194 (55.0)	0.02
BMI, kg/m^2	22.8±4.5	21.8±4.2	22.8±4.5	0.07
BMI ≤22 kg/m^2	1787 (46.7)	30 (51.7)	1757 (46.6)	0.4
Current smoker	476 (12.0)	7 (11.1)	469 (12.0)	0.8
Ambulatory	3149 (78.5)	48 (76.2)	3101 (78.5)	0.7
Prior HF hospitalization	1442 (36.2)	13 (21.0)	1429 (36.5)	0.009
Ischemic cause	1327 (32.7)	30 (47.6)	1297 (32.5)	0.01
ACS	239 (5.9)	9 (14.3)	230 (5.8)	0.01
Non-ACS	1088 (26.8)	21 (33.3)	1067 (26.7)	0.3
HFpEF/HFmrEF/HFrEF	1744/746/1551 (43.2/18.5/38.4)	28/12/23 (44.4/19.0/36.5)	1716/734/1528 (43.1/18.5/38.4)	0.95
Comorbidities				
Hypertension	2909 (71.7)	49 (77.8)	2860 (71.6)	0.3
Dyslipidemia	1549 (38.2)	23 (36.5)	1526 (38.2)	0.8
Diabetes	1510 (37.2)	26 (41.3)	1484 (37.2)	0.5
Prior myocardial infarction	908 (22.4)	12 (19.0)	896 (22.4)	0.5
Prior stroke	662 (16.3)	14 (22.2)	648 (16.2)	0.2
Peripheral artery disease	343 (8.5)	5 (7.9)	338 (8.5)	0.9
AF	1898 (46.8)	29 (46.0)	1869 (46.8)	0.9
Chronic kidney disease	1809 (44.6)	35 (55.6)	1774 (44.4)	0.08
Anemia	2705 (66.8)	36 (57.1)	2669 (67.0)	0.1
Malignancy	585 (14.4)	9 (14.3)	576 (14.4)	0.98
Dementia	770 (19.0)	15 (23.8)	755 (18.9)	0.3
Presentation at emergency room				
Systolic blood pressure, mm Hg	147.2±35.3	153.2±39.8	147.1±35.2	0.2
Diastolic blood pressure, mm Hg	84.5±24.0	91.8±27.9	84.3±23.9	0.04
Pulse rate, bpm	96.0±27.5	104.9±32.1	95.8±27.4	0.03
Body temperature, °C	36.5±0.6	36.5±0.7	36.5±0.6	0.8
AF at emergency room	1457 (35.9)	23 (36.5)	1434 (35.9)	0.9
NYHA III/IV	1589/1948 (39.4/48.3)	24/31 (38.1/49.2)	1565/1917 (39.4/48.3)	0.8
Biomarkers				
BNP, pg/mL (N=3590)	721 [397.75–1307.5]	1301 [634.5–1731.5]	719 [394–1294]	<0.001
NT-proBNP, pg/mL (N=698)	5880 [2720.75–13 241.5]	11 929 [4893–31 741.5]	5809 [2718–12 946.5]	0.06
High BNP/NT-proBNP*	1999 (50.0)	45 (71.4)	1954 (49.6)	<0.001
Serum albumin, mg/dL	3.5±0.5	3.3±0.5	3.5±0.5	0.04
Serum albumin <3 g/dL	567 (14.4)	13 (20.6)	554 (14.3)	0.2
eGFR, mL/min per 1.73 m^2	45.7±23.5	38.8±18.0	45.8±23.5	0.003
eGFR <30 mL/min per 1.73 m^2	1118 (27.6)	22 (34.9)	1096 (27.5)	0.2
Serum Na, mEq/L	139.0±4.3	138.7±3.0	139.0±4.3	0.4
Serum Na <135 mEq/L	519 (12.8)	4 (6.3)	515 (12.9)	0.09
Antithrombotic therapy	2983 (73.5)	46 (73.0)	2937 (73.6)	0.9
Antiplatelet drugs	1634 (40.3)	19 (30.2)	1615 (40.4)	0.09
Oral anticoagulants	1280 (31.6)	18 (28.6)	1262 (31.6)	0.6
Warfarin	872 (21.5)	12 (19.0)	860 (21.5)	0.6
Direct oral anticoagulants	409 (10.1)	6 (9.5)	403 (10.1)	0.9

(*Continued*)

Table 1. Continued

Variables	Entire cohort (N=4056)	Ischemic stroke (N=63)	No ischemic stroke (N=3993)	*P* value
Heparin	1113 (27.4)	23 (36.5)	1090 (27.3)	0.1

Continuous variables are expressed as mean±standard deviation or median [interquartile range] according to the distributions. Categorical variables are presented as numbers (percentages). ACS indicates acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF with reduced EF; HF, heart failure; HFmrEF, HF with mildly-reduced EF; HFrEF, HFpEF, HF with preserved ejection fraction (EF); Na, sodium; NT-proBNP, N-terminal proBNP; and NYHA, New York Heart Association.

*Above the median in the entire cohort.

DISCUSSIONS

The principal findings in the present study were as follows: (1) 1.6% of patients hospitalized for ADHF developed ischemic stroke during hospitalization; (2) men, acute coronary syndrome, absence of prior heart failure hospitalization, and high BNP/NT-proBNP were independently associated with ischemic stroke; (3) the risk for ischemic stroke progressively increased with increasing BNP/NT-proBNP levels at admission; (4) patients who developed ischemic stroke had higher mortality rate and poorer functional status at discharge than those who did not develop ischemic stroke.

Ischemic stroke is a serious complication of heart failure. Regarding chronic heart failure, the Framingham study showed that the risk of ischemic stroke was 2- to 3-fold higher in patients with heart failure than in those without.[2] A recent population-based cohort study also showed that patients with heart failure had 1.5- to 2.1-fold higher risk of ischemic stroke compared to the general population.[5] Decompensation further increases the risk of ischemic stroke through elevated intra-cardiac and venous pressure, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and endothelial dysfunction induced by hypoxia.[14–16] In addition, patients with ADHF are often treated with diuretics after admission, and subsequent dehydration may also cause a hypercoagulable state.[17] Thus, the risk of ischemic stroke is considered to be especially increased in patients with hospitalization for ADHF. However, data on the incidence and predictors of ischemic stroke during hospitalization for ADHF are limited. In our single-center, retrospective study, 2.6% of the patients with hospitalization for ADHF developed ischemic stroke during hospitalization (interval from admission to the onset of stroke: median 10 days [IQR 5–17 days]).[18] In the present study of 4056 patients hospitalized for ADHF, 63 (1.6%) patients developed ischemic stroke during hospitalization. The incidence rate of 1.6% was not extremely high, but could not be ignored. Moreover, those who developed ischemic stroke showed a higher mortality rate and poorer functional status at discharge. These results suggest that

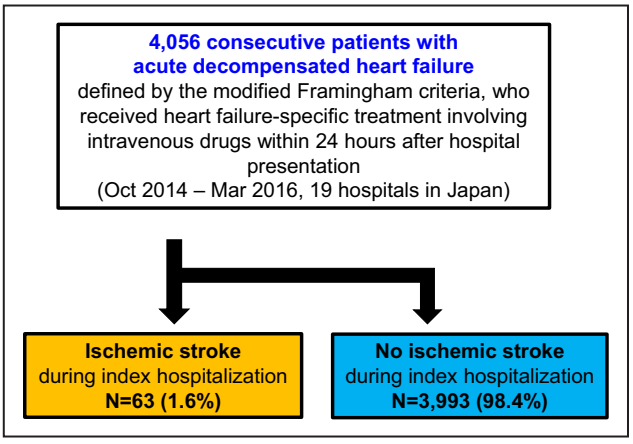

Figure 1. Study flow chart.

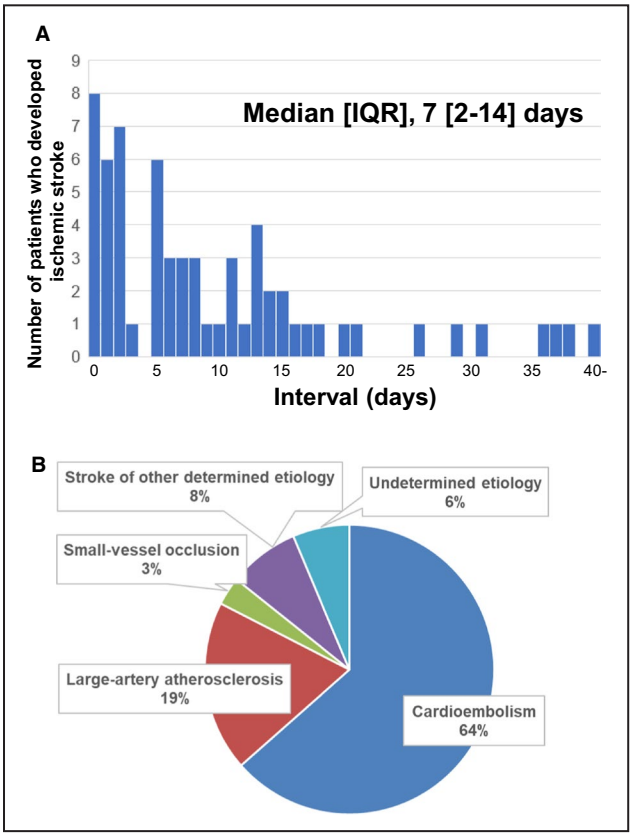

Figure 2. Timing and cause of ischemic stroke during hospitalization for acute decompensated heart failure.
A, Intervals from admission to the onset of ischemic stroke. Intervals were calculated by subtracting the day of admission from the day of onset. **B**, Underlying cause of incident ischemic stroke. IQR indicates interquartile range.

Table 2. Univariate and Multivariable Logistic Regression Analysis for the Risk Factors of Ischemic Stroke

	Univariate analysis			Multivariable analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age ≥80 y	0.86	0.52–1.41	0.6			
Men	1.90	1.10–3.26	0.02	1.87	1.11–3.24	0.02
BMI ≤22 kg/m^2	1.23	0.73–2.06	0.4			
Current smoker	0.92	0.42–2.03	0.8			
Ambulatory	0.88	0.49–1.57	0.7			
Absence of prior HF hospitalization	2.16	1.17–4.00	0.009	2.21	1.24–4.21	0.006
Ischemic cause	1.89	1.15–3.11	0.01			
ACS	2.73	1.33–5.59	0.01	2.31	1.01–4.73	0.045
Non-ACS	0.73	0.43–1.24	0.3			
LV dysfunction (EF<40%)	0.92	0.55–1.55	0.8	0.64	0.37–1.08	0.1
Comorbidities						
Hypertension	1.39	0.76–2.52	0.3			
Dyslipidemia	0.93	0.55–1.56	0.8			
Diabetes	1.19	0.72–1.97	0.5			
Prior myocardial infarction	0.81	0.43–1.53	0.5			
Prior stroke	1.47	0.81–2.69	0.2			
Peripheral artery disease	0.93	0.37–2.34	0.9			
AF	0.97	0.59–1.60	0.9	1.53	0.92–2.56	0.1
Chronic kidney disease	1.56	0.95–2.58	0.08			
Anemia	0.66	0.40–1.09	0.1			
Malignancy	0.99	0.49–2.01	0.98			
Dementia	1.34	0.75–2.41	0.3			
Presentation at emergency room						
Systolic blood pressure <100 mm Hg	0.89	0.32–2.47	0.8			
Diastolic blood pressure >90 mm Hg	1.32	0.80–2.19	0.3			
Pulse rate >100 bpm	1.54	0.93–2.55	0.1			
NYHA class IV	0.96	0.59–1.58	0.9			
Body temperature ≥37.5 °C	0.99	0.35–2.74	0.98			
AF at emergency room	1.03	0.61–1.72	0.9			
Biomarkers						
High BNP/NT-proBNP*	2.54	1.47–4.40	<0.001	3.15	1.84–5.60	<0.0001
Serum albumin <3 g/dL	1.56	0.84–2.89	0.2			
eGFR <30 mL/min per 1.73 m^2	1.41	0.84–2.39	0.2			
Serum Na<135 mEq/L	0.46	0.16–1.26	0.09			
Antithrombotic therapy	0.97	0.56–1.70	0.9			
Antiplatelet drugs	0.64	0.37–1.09	0.09			
Oral anticoagulants	0.87	0.50–1.50	0.6			
Heparin	1.53	0.91–2.57	0.1	1.14	0.66–1.93	0.6

ACS indicates acute coronary syndrome; AF, atrial fibrillation; BNP, B-type natriuretic peptide; CI, confidence interval; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricular; Na, sodium; NT-proBNP, N-terminal proBNP; NYHA, New York Heart Association; and OR, odds ratio.

*Above the median.

we should pay more attention to the prevention of ischemic stroke when we treat patients with ADHF.

The current study shows that men, acute coronary syndrome, absence of prior HF hospitalization, and high BNP/NT-proBNP levels at admission were the risks for ischemic stroke. The incidence of ischemic stroke after acute coronary syndrome has been reported in several studies. Acute coronary syndrome causes cardiac injury, leading to cardiac dysfunction and hypokinesis of cardiac chambers, which in turn may predispose to thrombus formation in cardiac chambers and embolism.[13] Catheter-based coronary reperfusion therapies

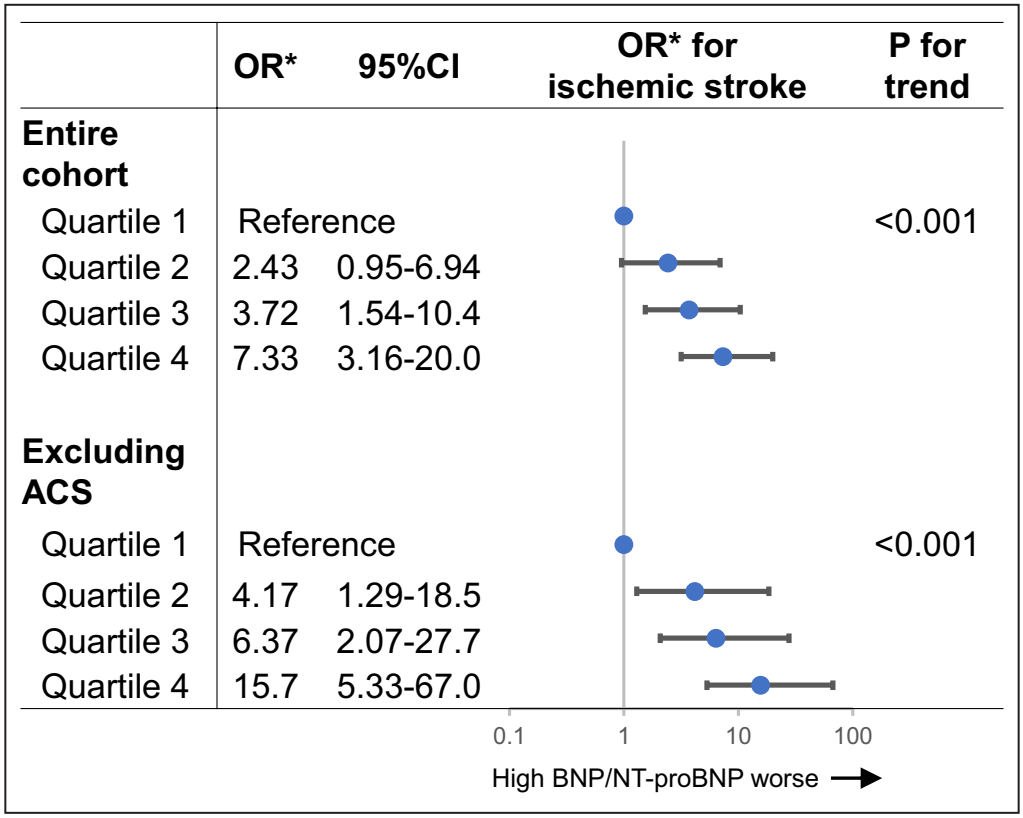

Figure 3. Forest plots for the risk for ischemic stroke according to the quartiles of BNP or NT-proBNP levels.
*ORs were adjusted for sex, ACS, prior HF hospitalization, left ventricular dysfunction (ejection fraction <40%), atrial fibrillation, and use of intravenous heparin within 24 hours after admission. ACS indicates acute coronary syndrome; BNP, B-type natriuretic peptide; CI, confidence interval; NT-proBNP, N-terminal proBNP; OR, odds ratio.

performed in acute coronary syndrome may also have a risk for ischemic stroke. In addition, ischemic stroke and coronary heart disease share common risk factors and have a similar pathophysiology.[19]

High BNP/NT-proBNP was also a risk for ischemic stroke during hospitalization for ADHF. This is the first study demonstrating an association between BNP/NT-proBNP levels and the incidence of ischemic stroke during hospitalization for ADHF. Previous studies reported that NT-proBNP was an independent predictor of ischemic stroke in patients with chronic heart failure without atrial fibrillation,[11] and revealed a significant association of BNP/NT-proBNP levels with the incidence of ischemic stroke in patients with atrial fibrillation.[20,21] An association of BNP/NT-proBNP levels with the incidence of ischemic stroke was also reported in patients with transient ischemic attack[22] and in asymptomatic patients.[23] BNP/NT-proBNP are released from the heart in response to pressure and volume overload, and their plasma levels are elevated in patients with heart failure in proportion to disease severity. High BNP/NT-proBNP levels reflect cardiac congestion, as well as LV systolic and diastolic function.[24] Both severe cardiac congestion and decline in LV function increase thrombogenicity in the heart. Moreover, in patients with these conditions, starting treatment for ADHF is likely to cause greater hemodynamic change, leading to a hypercoagulable state.[25] Thus, elevated BNP/NT-proBNP levels may become a marker of the propensity for ischemic stroke.

Absence of prior heart failure hospitalization (de novo heart failure hospitalization) was also a risk for ischemic stroke in this study. The clinical characteristics of patients with de novo heart failure hospitalization were previously reported,[26] and included higher blood pressure and a lower rate of prescription of heart failure medications at admission, including renin angiotensin inhibitors, beta blockers, and diuretics. Patients with de novo heart failure might be particularly vulnerable,[27] because initiation of heart failure medications after admission may lead to larger changes in hemodynamics. Actually, decrease in body weight and rise in creatinine levels were lager in patients with ischemic stroke (Table S1), suggesting the association of larger hemodynamic changes with ischemic stroke.

The precise mechanism underlying the sex difference in the incidence of ischemic stroke is unclear.

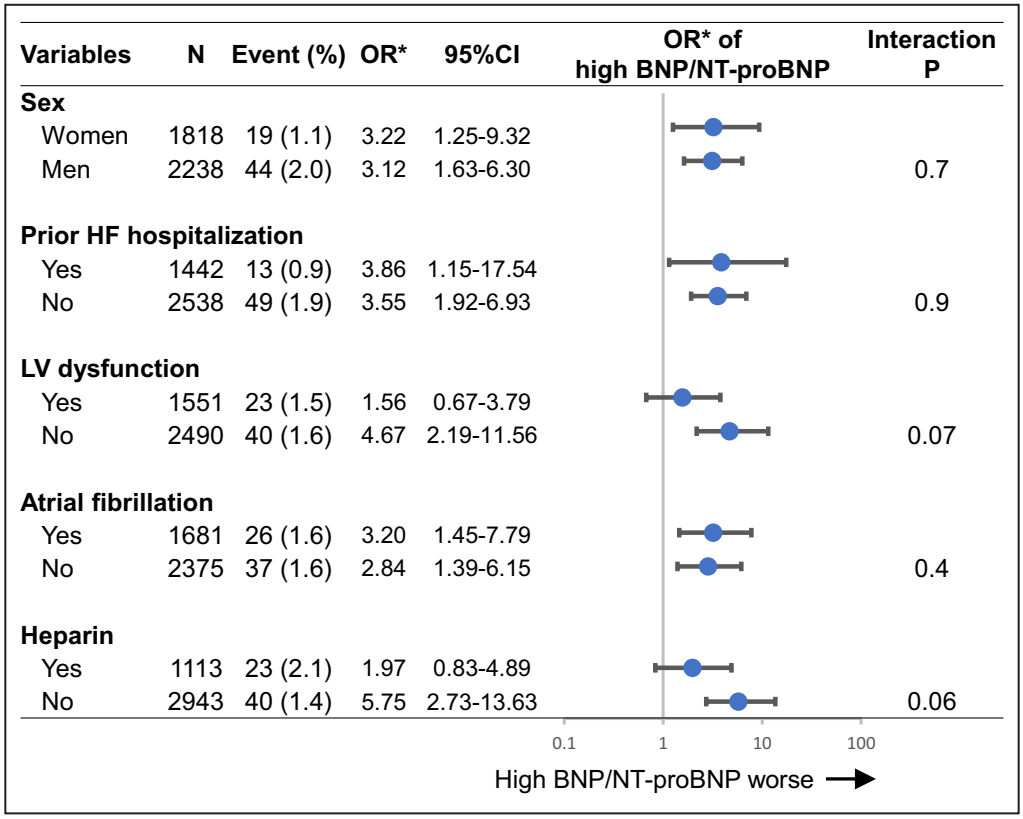

Figure 4. Subgroup analysis for the risk for ischemic stroke according to high BNP/NT-proBNP. High BNP/NT-proBNP was defined as above the median in each cohort. *ORs were adjusted for sex, ACS, prior HF hospitalization, LV dysfunction (ejection fraction <40%), atrial fibrillation, and use of intravenous heparin within 24 hours after admission. ACS indicates acute coronary syndrome, BNP, B-type natriuretic peptide; CI, confidence interval; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal proBNP; and OR, odds ratio.

However, it was reported that women had an overall lower age-adjusted stroke incidence than men, and the difference was suggested to be related to sex steroid hormones, particularly estrogen.[28]

Table 3. The Incidence of Ischemic Stroke and Bleeding Events in Patients With and Without Antithrombotic Therapy

Heparin	(+) (N=1113)	(–) (N=2943)	*P* value
Ischemic stroke	23 (2.1)	40 (1.4)	0.1
Major bleeding	44 (4.0)	48 (1.6)	<0.001
Intracranial hemorrhage	7 (0.6)	8 (0.3)	0.1
Antiplatelet drugs	(+) (N=1634)	(–) (N=2422)	*P* value
Ischemic stroke	19 (1.2)	44 (1.8)	0.09
Major bleeding	46 (2.8)	46 (1.9)	0.06
Intracranial hemorrhage	8 (0.5)	7 (0.3)	0.3
Oral anticoagulants	(+) (N=1280)	(–) (N=2776)	*P* value
Ischemic stroke	18 (1.4)	45 (1.6)	0.6
Major bleeding	28 (2.2)	64 (2.3)	0.8
Intracranial hemorrhage	4 (0.3)	11 (0.4)	0.7

Variables are expressed as numbers (percentages).

Surprisingly, atrial fibrillation was not associated with the incidence of ischemic stroke in this study. Several possible explanations are conceivable. First, as it is well-known that atrial fibrillation is a major risk for cardioembolic stroke, oral anticoagulants were more often prescribed in this group (Table S4, Table S5), which might reduce the incidence of ischemic stroke. Second, patients without atrial fibrillation showed higher prevalence of ACS, de-novo heart failure and high BNP/NT-proBNP (Table S4). These might increase the risks for ischemic stroke in those without atrial fibrillation. Third, the duration of follow-up was very short in this study, which focused on the incidence of ischemic stroke during hospitalization for ADHF. While atrial fibrillation is the risk of ischemic stroke during long-term follow-up, high BNP/NT-proBNP, a marker of pressure and volume overload, might be more strongly associated with ischemic stroke in the acute phase of heart failure. Importantly, it is noteworthy that, even in patients without atrial fibrillation at admission, 1.6% of the patients developed ischemic stroke during hospitalization.

Table 4. In-Hospital Events and Status at Discharge

	Ischemic stroke (N=63)	No ischemic stroke (N=3993)	*P* value
All-cause death	19 (30.2)	252 (6.3)	<0.001
Cardiac death	9 (14.3)	181 (4.5)	0.003
Non-cardiac death	10 (15.9)	71 (1.8)	<0.001
Status at discharge	(N=44)	(N=3741)	
Length of hospital stay (d)	30 [20–44]	16 [11–24]	<0.001
Ambulatory/wheelchair use/bedridden	16/16/11 (37.2/37.2/25.6)	2722/828/127 (74.0/22.5/3.5)	<0.001
Discharged to home	18 (41.9)	3068 (82.6)	<0.001

Continuous variables are expressed as median [interquartile range]. Categorical variables are presented as numbers (percentages).

The optimal therapy to prevent ischemic stroke during hospitalization for ADHF is a topic of debate.[27] Oral anticoagulants are beneficial to prevent ischemic stroke in patients with atrial fibrillation. However, the efficacy of antithrombotic therapy in chronic heart failure patients without atrial fibrillation is controversial,[29,30] and there is no data on the efficacy of antithrombotic therapy in ADHF. Consistent with the BRIDGE trial, in which heparin-bridge therapy failed to prevent incidence of ischemic stroke during the peri-operative periods of non-cardiac surgery in patients with atrial fibrillation, who interrupted their course of oral anticoagulants,[31] intravenous heparin was not associated with reduced incidence of ischemic stroke during hospitalization for ADHF in the current study. However, patients receiving heparin had higher prevalence of de-novo heart failure, high BNP/NT-proBNP, and ACS, and less prescription of oral anti-coagulants (Table S4), which might counteract the efficacy of heparin. Direct oral anti-coagulants have been demonstrated to be beneficial in patient with atrial fibrillation and venous thromboembolisms as alternatives to warfarin and heparin. There is evidence that low dose rivaroxaban started early post-ADHF discharge reduces thromboembolic events, specifically stroke.[32,33] Future studies are warranted to explore the efficacy of heparin or direct oral anticoagulants for preventing ischemic stroke during hospitalization for ADHF.

Limitations

This study has several limitations. First, the results were derived from a prospective observational study; therefore, they only reflect association and not causality. Second, the number of patients with ischemic stroke was limited, which in turn limited the number of covariates, including in the multivariable analysis. Therefore, we cannot rule out the possibility of residual confounding. However, higher BNP/NT-proBNP levels were consistently associated with ischemic stroke in all the subgroups (Figure 4), which might suggest robustness of the association between BNP/NT-proBNP levels and ischemic stroke. Third, BNP/NT-proBNP levels were not analyzed by a unified protocol or kit in a central laboratory, and the difference in natriuretic peptide assays across sites may have introduced some bias. Fourth, the decision regarding the prescription of antithrombotic therapy including intravenous heparin was left to the discretion of the attending physician, which might also have resulted in bias. Fifth, the changes and intensity of antithrombotic therapy, such as APTT, PT-INR, and dose of direct oral anticoagulants, were not taken into consideration. The quality of anticoagulation therapy might affect the incidence of ischemic stroke. Finally, atrial fibrillation was diagnosed based on previous history and electrocardiograms at admission, and new onset atrial fibrillation after hospitalization was not taken into consideration. Despite these limitations, this study clarified the non-negligible incidence of ischemic stroke during hospitalization for ADHF from a large-scale multicenter registry, and could provide new insights on the management of patients with ADHF.

CONCLUSIONS

During hospitalization for ADHF, 1.6% of the patients in the present cohort suffered from ischemic stroke. Men, presence of acute coronary syndrome, de novo heart failure hospitalization, and high BNP/NT-proBNP levels at admission were independently associated with ischemic stroke.

ARTICLE INFORMATION

Received June 10, 2021; accepted September 15, 2021.

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Sources of Funding

This work was supported by the Japan Agency for Medical Research and Development [18059186] (Drs T. Kato, T. Kuwahara, and N. Ozasa).

Disclosures

None.

Supplementary Material

Data S1
Table S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Definitions for the baseline factors

The definitions of the baseline factors in the KCHF registry were as described in the previous report (Ref. 9). Atrial fibrillation (AF) included paroxysmal AF, persistent AF, permanent AF, and atrial flutter. Hypertension was defined as receiving anti-hypertensive drugs or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as treatment with oral hypoglycemic agents and/or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥6.5%, casual blood glucose level ≥200 mg/dl, or fasting blood glucose level ≥126 mg/dl. The presence of COPD was determined clinically by local investigators based on history, clinical presentation, previous examinations, and medications, and recorded as COPD in the case report form at enrollment. Poor medical adherence was judged by the attending physician. Public assistance is one of the social security systems in Japan, as explained elsewhere (http://www.ipss.go.jp/s-info/e/ssj2014/006.html). Underlying heart disease was defined as the most likely cause of structural or functional cardiac disorders among the following: (i) coronary artery disease, (ii) hypertensive heart disease, (iii) cardiomyopathy, (iv) valvular heart disease, (v) other heart diseases. Coronary artery disease was defined as acute coronary syndrome (ACS), old myocardial infarction, or prior PCI/CABG. ACS was defined as the range of myocardial ischemic states that includes ST-elevated myocardial infarction, non-ST elevated myocardial infarction, or unstable angina. Primary cardiomyopathy was classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, and dilated phase of hypertrophic cardiomyopathy. Valvular heart disease was classified as moderate to severe aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation (excluding functional mitral regurgitation), tricuspid regurgitation, and prosthetic valve dysfunction. For valvular heart disease, we chose only a single category, i.e., the category that seemed to be most closely related to acute heart failure. Other heart diseases included other cardiomyopathy, arrhythmia (bradycardia or tachycardia), congenital heart disease, and constrictive pericarditis. Other cardiomyopathy included arrhythmogenic right ventricular dysplasia, takotsubo cardiomyopathy, cardiac sarcoidosis, cardiac amyloidosis, left ventricular noncompaction, drug-induced cardiomyopathy, pacemaker-induced cardiomyopathy, mitochondrial cardiomyopathy, peripartum cardiomyopathy, alcoholic cardiomyopathy, beriberi heart, and others. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 at admission. The eGFR was calculated using the equation for the Japanese population: eGFR = 194 × (serum creatinine$^{-1.094}$) × (age$^{-0.287}$) × 0.739 (for women).

Table S1. Baseline characteristics and clinical course in patients with and without ischemic stroke.

Variables	Ischemic stroke (N=63)	No ischemic stroke (N=3993)	P value
HF medications at admission			
Loop diuretics	24 (38.1)	1952 (48.9)	0.09
Mineral corticoid receptor antagonists	10 (15.9)	723 (18.1)	0.6
Renin angiotensin system inhibitors	23 (36.5)	1827 (45.8)	0.1
Beta blockers	22 (34.9)	1538 (38.5)	0.6
Intravenous treatment during hospitalization			
Furosemide	51 (81.0)	3461 (86.7)	0.2
Vasodilators	41 (65.1)	2204 (55.2)	0.1
Inotropes	14 (22.2)	842 (21.1)	0.8
Clinical course during hospitalization			
Decrease in body weight, kg*	5.0±5.1	3.8±4.3	0.08
Percent changes in body weight, %†	8.4±8.5	6.5±7.0	0.08
Maximum levels of creatinine, mg/dl	2.4±2.0	1.9±1.6	0.02
Maximum increase in creatinine levels, mg/dl‡	0.8±1.2	0.4±0.8	<0.001
Worsening renal function§	20 (46.5)	1287 (34.9)	0.1

* Decrease in body weight from admission to discharge. † Percent change in body weight from admission to discharge. ‡ Maximum increase in creatinine levels from admission. § Worsening renal function was defined as increase in creatinine level ≥ 0.3 mg/dl from baseline. HF=heart failure.

Table S2. Univariate and multivariable logistic regression analysis for the risk factors of ischemic stroke in patients without ACS.

	Univariate analysis			Multivariable analysis		
Variables	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**
Age ≥80 years	0.86	0.50-1.47	0.6			
Men	1.99	1.11-3.58	0.02	1.96	1.13-3.55	0.02
BMI ≤22 kg/m^2	1.41	0.81-2.44	0.2			
Current smoker	0.78	0.31-1.98	0.6			
Ambulatory	0.89	0.47-1.66	0.7			
Absence of prior HF hospitalization	1.87	1.00-3.51	0.04	2.10	1.17-4.03	0.01
Ischemic etiology	1.61	0.93-2.79	0.1			
ACS		N.A.			N.A.	
Non-ACS	1.61	0.93-2.79	0.1			
LV dysfunction (EF<40%)	0.96	0.55-1.68	0.9	0.64	0.36-1.12	0.1
Comorbidities						
Hypertension	1.39	0.73-2.65	0.3			
Dyslipidemia	0.83	0.47-1.47	0.5			
Diabetes	0.95	0.54-1.67	0.9			
Prior myocardial infarction	1.00	0.52-1.91	0.9992			
Prior stroke	1.47	0.77-2.80	0.3			
Peripheral artery disease	0.85	0.31-2.38	0.8			
AF	1.06	0.62-1.81	0.8	1.60	0.93-2.75	0.09
Chronic kidney disease	1.34	0.78-2.29	0.3			
Anemia	0.69	0.40-1.18	0.2			
Malignancy	1.02	0.48-2.18	0.95			
Dementia	1.21	0.63-2.30	0.6			
Presentation at emergency room						
Systolic blood pressure <100 mmHg	0.26	0.04-1.87	0.09			
Diastolic blood pressure >90 mmHg	1.40	0.82-2.41	0.2			
Pulse rate >100 bpm	1.50	0.87-2.60	0.1			
NYHA class IV	1.13	0.66-1.93	0.7			
Body temperature ≥37.5 °C	1.18	0.42-3.30	0.8			
AF at emergency room	1.16	0.67-2.00	0.6			
Biomarkers						
High BNP/NT-proBNP*	3.20	1.71-5.99	<0.001	3.98	2.18-7.72	<0.001
Serum albumin <3 g/dl	1.35	0.68-2.70	0.4			
eGFR <30 ml/min/1.73m^2	1.20	0.67-2.14	0.5			
Serum Na<135 mEq/l	0.40	0.13-1.30	0.08			
Antithrombotic therapy	0.87	0.48-1.56	0.6			
Antiplatelet drugs	0.62	0.35-1.12	0.1			
Oral anticoagulants	1.02	0.58-1.81	0.9			
Heparin	1.25	0.69-2.25	0.5	1.03	0.56-1.83	0.9

*Above the median in patients without ACS. BNP and NT-proBNP were measured in 3,373 and 659 patients, and the median [IQR] values of BNP and NT-proBNP were 721 [404-1,296] pg/ml and 5,784 [2,677-13,308] pg/ml. ACS=acute coronary syndrome, OR=odds ratio, CI=confidence interval, BMI=body mass index, HF=heart failure, LV=left ventricular, EF=ejection fraction, AF=atrial fibrillation, NYHA=New York Heart Association, BNP=B-type natriuretic peptide, NT-proBNP=N-terminal proBNP, ALB=albumin, eGFR=estimated glomerular filtration rate, Na=serum sodium.

Table S3. Multivariable logistic regression analyses for the risk factors of ischemic stroke.

	Entire cohort			Excluding ACS		
Variables	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**
Men	1.87	1.11-3.23	0.02	1.95	1.12-3.53	0.02
Absence of prior HF hospitalization	2.24	1.24-4.29	0.007	2.18	1.19-4.22	0.01
ACS	2.31	1.02-4.73	0.046		N.A.	
LV dysfunction (EF<40%)	0.64	0.37-1.08	0.1	0.64	0.36-1.12	0.1
AF	1.50	0.84-2.64	0.2	1.48	0.80-2.70	0.2
High BNP/NT-proBNP*	3.16	1.84-5.64	<0.001	4.04	2.20-7.87	<0.001
Heparin	1.15	0.66-1.96	0.6	1.07	0.57-1.90	0.8
Oral anticoagulants	1.07	0.55-2.01	0.8	1.21	0.62-2.33	0.6

*Above the median in each cohort. OR=odds ratio, CI=confidence interval, HF=heart failure, ACS=acute coronary syndrome, LV=left ventricular, EF=ejection fraction, AF=atrial fibrillation, BNP=B-type natriuretic peptide, NT-proBNP=N-terminal proBNP.

Table S4. Baseline characteristics in patients with and without AF.

Variables	AF (N=1898)	No AF (N=2158)	P value
Age, years	79.7±10.4	76.4±13.1	<0.001
Age ≥80 years	1103 (58.1)	1044 (48.4)	<0.001
Men	1240 (57.5)	998 (52.6)	0.002
BMI, kg/m^2	22.9±4.4	22.8±4.5	0.4
BMI ≤22 kg/m^2	837 (46.3)	950 (47.0)	0.7
Current smoker	168 (9.1)	308 (14.5)	<0.001
Ambulatory	1454 (77.3)	1695 (79.5)	0.1
Prior HF hospitalization	800 (43.1)	642 (30.2)	<0.001
Ischemic etiology	457 (24.1)	870 (40.3)	<0.001
ACS	41 (2.2)	198 (9.2)	<0.001
Non-ACS	416 (21.9)	672 (31.1)	<0.001
HFpEF/HFmrEF/HFrEF	973/344/574 (51.5/18.2/30.4)	771/402/977 (35.9/18.7/45.4)	<0.001
Comorbidities			
Hypertension	1305 (68.8)	1604 (74.3)	<0.001
Dyslipidemia	662 (34.9)	887 (41.1)	<0.001
Diabetes	619 (32.6)	891 (41.3)	<0.001
Prior myocardial infarction	336 (17.7)	572 (26.5)	<0.001
Prior stroke	355 (18.7)	307 (14.2)	<0.001
Peripheral artery disease	149 (7.9)	194 (9.0)	0.2
Chronic kidney disease	860 (45.3)	949 (44.0)	0.4
Anemia	1271 (67.1)	1434 (66.6)	0.7
Malignancy	271 (14.3)	314 (14.6)	0.8
Dementia	407 (21.4)	363 (16.8)	<0.001
Presentation at emergency room			
Systolic blood pressure, mmHg	140.8±31.5	152.8±37.4	<0.001
Diastolic blood pressure, mmHg	83.5±22.9	85.3±24.8	0.02
Pulse rate, bpm	99.5±31.0	92.9±23.7	<0.001
Body temperature, °C	36.5±0.6	36.5±0.7	0.7
AF at emergency room	1457 (76.8)	0 (0.0)	<0.001
NYHA III/IV	854/780 (45.1/41.2)	735/1168 (34.3/54.5)	<0.001
Biomarkers			
BNP, pg/ml (N=3,590)	580 [339-981]	884 [475-1598]	<0.001
NT-proBNP, pg/ml (N=698)	4498 [2384-9645]	7354 [3764-16294]	<0.001
High BNP/NT-proBNP*	729 (39.0)	1270 (59.5)	<0.001
Serum albumin, mg/dl	3.5±0.5	3.5±0.5	0.004
Serum albumin <3 g/dl	232 (12.7)	335 (15.9)	0.004
eGFR, ml/min/1.73m^2	45.6±22.1	45.7±24.6	0.9
eGFR <30 ml/min/1.73m^2	491 (25.9)	627 (29.1)	0.02
Serum Na, mEq/l	139.1±4.3	139.0±4.3	0.4
Serum Na <135 mEq/l	240 (12.7)	279 (13.0)	0.8
Antithrombotic therapy	1580 (83.2)	1403 (65.0)	<0.001
Antiplatelet drugs	695 (36.6)	939 (43.5)	<0.001
Oral anticoagulants	1098 (57.9)	182 (8.4)	<0.001
Warfarin	707 (37.2)	165 (7.6)	<0.001
Direct oral anticoagulants	392 (20.7)	17 (0.8)	<0.001
Heparin	421 (22.2)	692 (32.1)	<0.001

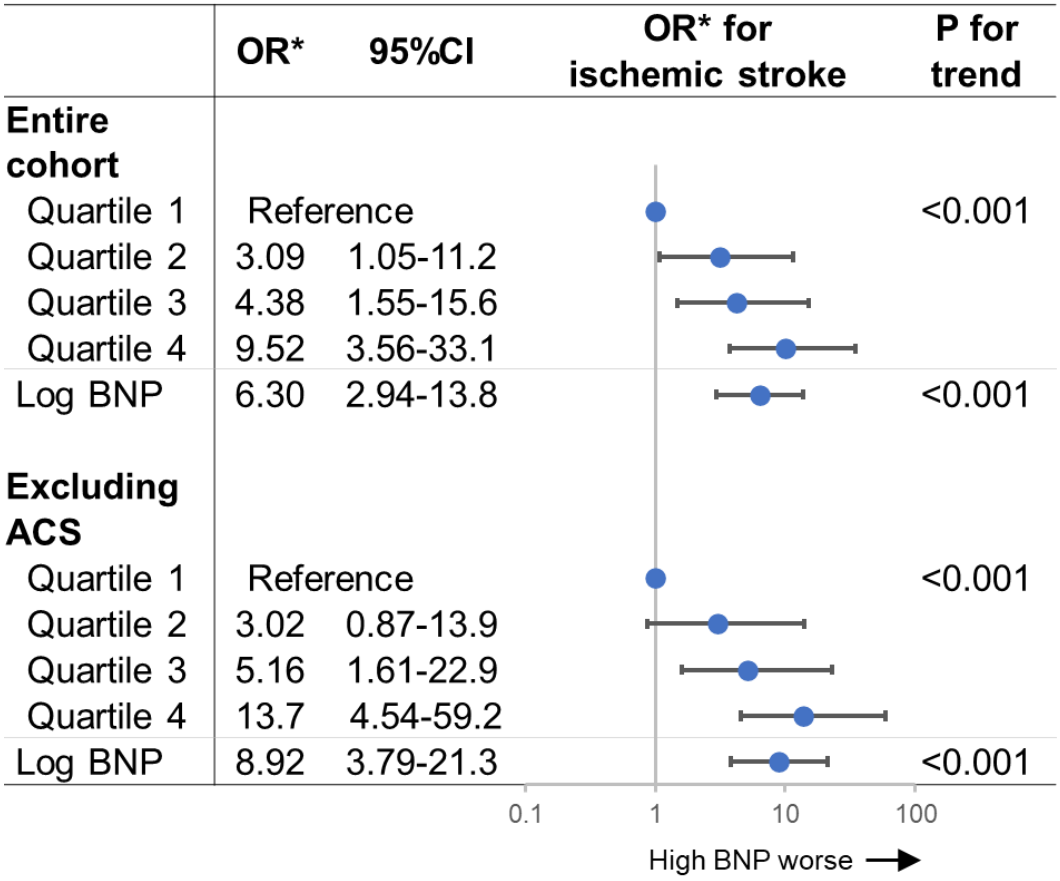
*Above the median in the entire cohort. AF=atrial fibrillation, OR=odds ratio, CI=confidence interval, BMI=body mass index, HF=heart failure, ACS=acute coronary syndrome, LV=left ventricular, EF=ejection fraction, NYHA=New York Heart Association, BNP=B-type natriuretic peptide, NT-proBNP=N-terminal proBNP, eGFR=estimated glomerular filtration rate, Na=serum sodium.

Table S5. Baseline characteristic in patient with and without heparin, and those with and without OAC.

Variables	Heparin (+) (N=1,113)	Heparin (-) (N=2,943)	P value	OAC (+) (N=1,280)	OAC (-) (N=2,776)	P value
Age, years	77.1±12.6	78.3±11.8	0.004	78.7±10.3	77.6±12.7	0.008
Age ≥80 years	562 (50.5)	1585 (53.9)	0.06	693 (54.1)	1454 (52.4)	0.3
Men	625 (56.2)	1613 (54.8)	0.4	710 (55.5)	1528 (55.0)	0.8
BMI, kg/m^2	23.0±4.5	22.7±4.5	0.08	23.0±4.6	22.8±4.4	0.2
BMI ≤22 kg/m^2	460 (44.7)	1327 (47.4)	0.1	555 (45.2)	1232 (47.4)	0.2
Current smoker	137 (12.6)	339 (11.7)	0.4	107 (8.6)	369 (13.5)	<0.001
Ambulatory	868 (78.3)	2281 (78.5)	0.9	1014 (80.0)	2135 (77.7)	0.1
Prior HF hospitalization	298 (26.9)	1144 (39.8)	<0.001	666 (53.2)	776 (28.4)	<0.001
Ischemic etiology	471 (42.3)	856 (29.1)	<0.001	333 (26.0)	994 (35.8)	<0.001
ACS	148 (13.3)	91 (3.1)	<0.001	25 (2.0)	214 (7.7)	<0.001
Non-ACS	323 (29.0)	765 (26.0)	0.053	308 (24.1)	780 (28.1)	0.007
HFpEF/HFmrEF/HFrEF	417/228/467 (37.5/20.5/42.0)	1327/518/1084 (45.3/17.7/37.0)	<0.001	664/209/403 (52.0/16.4/31.6)	1080/537/1148 (39.1/19.4/41.5)	<0.001
Comorbidities						
Hypertension	829 (74.5)	2080 (70.7)	0.02	860 (67.2)	2049 (73.8)	<0.001
Dyslipidemia	457 (41.1)	1092 (37.1)	0.02	491 (38.4)	1058 (38.1)	0.9
Diabetes	472 (42.4)	1038 (35.3)	<0.001	444 (34.7)	1066 (38.4)	0.02
Prior myocardial infarction	273 (24.5)	635 (21.6)	0.046	271 (21.2)	637 (22.9)	0.2
Prior stroke	173 (15.5)	489 (16.6)	0.4	280 (21.9)	382 (13.8)	<0.001
Peripheral artery disease	95 (8.5)	248 (8.4)	0.9	112 (8.8)	231 (8.3)	0.6
AF	421 (37.8)	1477 (50.2)	<0.001	1055 (82.4)	626 (22.6)	<0.001
Chronic kidney disease	536 (48.2)	1273 (43.3)	0.005	639 (49.9)	1170 (42.1)	<0.001
Anemia	697 (62.7)	2008 (68.4)	<0.001	893 (69.8)	1812 (65.4)	0.005
Malignancy	155 (13.9)	430 (14.6)	0.6	185 (14.5)	400 (14.4)	0.97
Dementia	231 (20.8)	539 (18.3)	0.08	227 (17.7)	543 (19.6)	0.2
Presentation at emergency room						
Systolic blood pressure, mmHg	145.8±34.9	147.7±35.4	0.1	138.2±31	151.3±36.3	<0.001
Diastolic blood pressure, mmHg	84.7±24.3	84.4±23.8	0.7	79.9±21.1	86.5±24.9	<0.001
Pulse rate, bpm	98.8±27.2	94.9±27.6	<0.001	92.9±27.7	97.4±27.3	<0.001
Body temperature, °C	36.6±0.7	36.5±0.6	<0.001	36.5±0.6	36.5±0.7	0.3
AF at emergency room	337 (30.3)	1120 (38.1)	<0.001	825 (64.5)	632 (22.8)	<0.001
NYHA III/IV	388/592 (35.0/53.5)	1201/1356 (41.0/46.3)	<0.001	593/510 (46.4/39.9)	996/1438 (36.1/52.1)	<0.001
Biomarkers						
BNP, pg/ml (N=3,590)	758 [433-1425]	705 [383-1262]	0.003	565 [313-949]	809 [454-1479]	<0.001
NT-proBNP, pg/ml (N=698)	6571 [3077-11873]	5680 [2624-13324]	0.5	4292 [2251-8518]	6754 [3221-15878]	<0.001
High BNP/NT-proBNP*	585 (53.2)	1414 (48.7)	0.01	476 (37.7)	1523 (55.6)	<0.001
Serum albumin, mg/dl	3.4±0.5	3.5±0.5	0.1	3.5±0.5	3.4±0.5	<0.001
Serum albumin <3 g/dl	155 (14.0)	412 (14.5)	0.7	136 (11.0)	431 (16.0)	<0.001
eGFR, ml/min/1.73m^2	47.8±25.7	44.9±22.5	0.6	43.4±20.6	46.7±24.6	<0.001
eGFR <30 ml/min/1.73m^2	282 (25.4)	836 (28.5)	0.047	372 (29.1)	746 (26.9)	0.2
Serum Na, mEq/l	138.9±4.6	139.1±4.2	0.4	139.1±4.2	139±4.4	0.9
Serum Na <135 mEq/l	147 (13.2)	372 (12.7)	0.6	160 (12.5)	359 (13.0)	0.7
Antithrombotic therapy	1113 (100)	1870 (63.5)	<0.001	1280 (100)	1703 (61.4)	<0.001
Antiplatelet drugs	465 (41.8)	1169 (39.7)	0.2	481 (37.6)	1153 (41.5)	0.02
OAC	165 (14.8)	1115 (37.9)	<0.001			
Warfarin	119 (10.7)	753 (25.6)	<0.001	872 (68.0)	0 (0.0)	<0.001
Direct oral anticoagulants	46 (4.1)	363 (12.3)	<0.001	409 (32.0)	0 (0.0)	<0.001
Heparin				165 (12.9)	948 (34.1)	<0.001

*Above the median in the entire cohort. OAC=oral anticoagulants, AF=atrial fibrillation, OR=odds ratio, CI=confidence interval, BMI=body mass index, HF=heart failure, ACS=acute coronary syndrome, LV=left ventricular, EF=ejection fraction, NYHA=New York Heart Association, BNP=B-type natriuretic peptide, NT-proBNP=N-terminal proBNP, eGFR=estimated glomerular filtration rate, Na=serum sodium.

Figure S1. Forrest plots for the risk for ischemic stroke according to the quartiles of BNP levels and log-transformed BNP levels in patients with data on BNP.



*ORs were adjusted for sex, ACS, prior heart failure hospitalization, left ventricular dysfunction (ejection fraction <40%), atrial fibrillation, and use of intravenous heparin within 24 hours after admission.

OR=odds ratio, CI=confidence interval, ACS=acute coronary syndrome, BNP=B-type natriuretic peptide.