

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, glycosylated hemoglobin level $\geq 6.5\%$, 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 m² at admission. The eGFR was calculated using the equation for the Japanese population: $eGFR = 194 \times (\text{serum creatinine}^{-1.094}) \times (\text{age}^{-0.287}) \times 0.739$ (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 \geq 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.

Variables	Univariate analysis			Multivariable analysis		
	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.

Variables	Entire cohort			Excluding ACS		
	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.

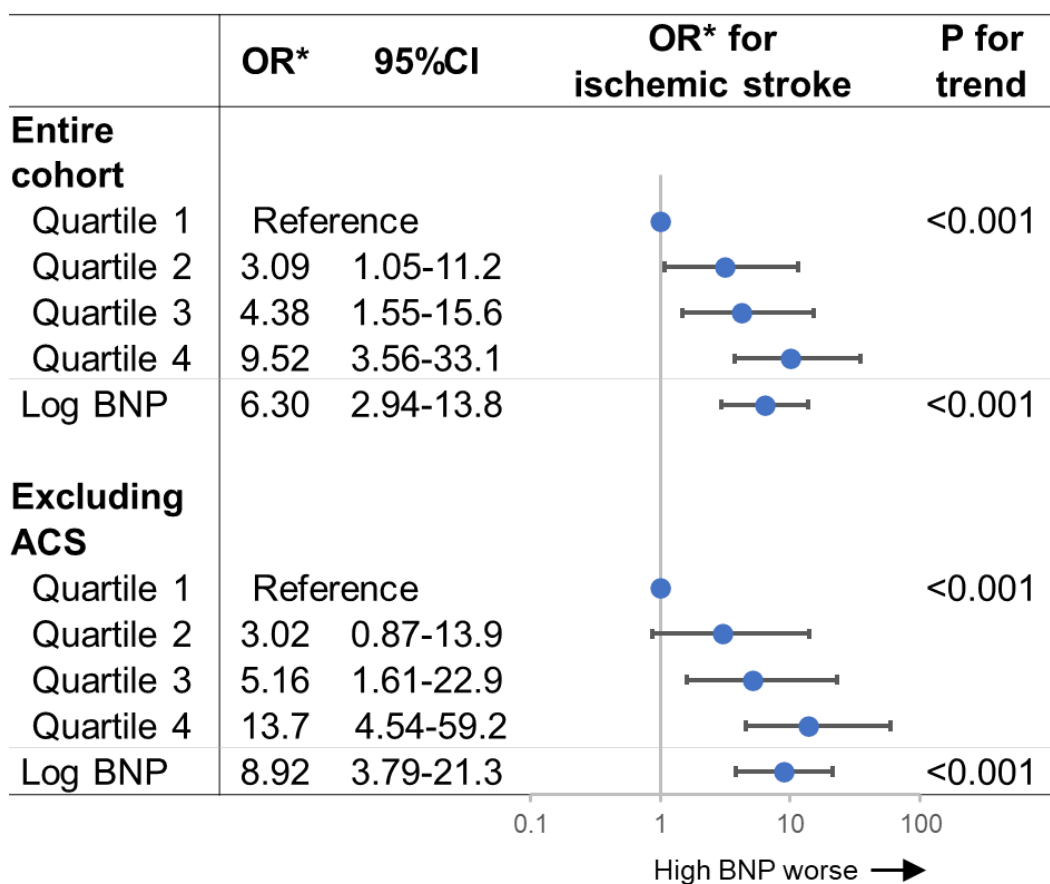
Table S5. Baseline characteristic in patient with and without heparin, and those with and without OAC.

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						
Antiplatelet drugs	1113 (100)	1870 (63.5)	<0.001	1280 (100)	1703 (61.4)	<0.001
OAC	465 (41.8)	1169 (39.7)	0.2	481 (37.6)	1153 (41.5)	0.02
Warfarin	165 (14.8)	1115 (37.9)	<0.001	872 (68.0)	0 (0.0)	<0.001
Direct oral anticoagulants	119 (10.7)	753 (25.6)	<0.001	409 (32.0)	0 (0.0)	<0.001
Heparin	46 (4.1)	363 (12.3)	<0.001	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.