

Incidence and predictors of ischemic stroke during hospitalization for congestive heart failure

Short title: Heart failure and ischemic stroke

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Abstract

Background: Heart failure (HF) increases the risk of ischemic stroke. Data regarding the incidence and predictors of ischemic stroke during hospitalization for HF are limited.

Methods: The study population of this retrospective cohort study consisted of patients with congestive HF, consecutively admitted to our center from October 2010 to April 2014. We excluded patients complicated with acute myocardial infarction, infective endocarditis, and takotsubo cardiomyopathy. We also excluded those with dialysis or mechanical circulatory support. We investigated the incidence of ischemic stroke during hospitalization for HF. Thereafter, we divided the patients without oral anticoagulants at admission into two groups: patients with ischemic stroke and those without it, and explored the predictors of ischemic stroke.

Results: A total of 558 patients (287 without atrial fibrillation (AF), 271 with AF) were enrolled. The mean age was 76.8 ± 12.3 years, and 244 patients (44%) were female. The mean left-ventricular ejection fraction was 47.4%. Oral anticoagulants were prescribed in 147 patients (8 without AF, 139 with AF). During hospitalization (median length 18 days), symptomatic ischemic stroke (excluding catheter-related) occurred in 15 patients (2.7% of the total, 8 without AF, 7 with AF). Predictors significantly associated with increased risk of ischemic stroke in patients without oral anticoagulants were as follows; short-term increases in blood urea nitrogen after admission (at day3; odds ratio (per 1 md/dl): 1.06, 95% confidence interval (CI): 1.01-1.11, $p=0.02$, and at day7; odds ratio: 1.03, 95%

CI: 1.00-1.07, $p=0.03$, respectively), and previous stroke (odds ratio; 3.33, 95% CI: 1.01-11.00, $p=0.04$).

Conclusions: The incidence of ischemic stroke during hospitalization for HF was high, even in patients without AF. Previous stroke and short-term increases in blood urea nitrogen was significantly associated with the incidence of ischemic stroke.

Key words: Heart failure, ischemic stroke, predictors, hospitalization

1 **Introduction**

2 Heart failure (HF) is a common and serious disorder with high mortality and morbidity, with an
3 increasing incidence in the elderly (1). Atrial fibrillation (AF) is common in patients with HF, and it
4 increases the risk of ischemic stroke (2). However, HF per se is an important risk factor for ischemic
5 stroke (3). Oral anticoagulants (OAC) were proven to be effective for stroke prevention in AF
6 patients (4), but there is no generally accepted consensus on OAC treatment for HF patients without
7 AF (5, 6).

8 Data from a cohort study indicated that the risk of ischemic stroke is 2 to 3 times higher for patients
9 with HF than for those without it. The estimated stroke risk in patients with HF was reported to be
10 1.3–3.9 per 100 patient-years (7). Notably, recent reports demonstrated that stroke risk is highest
11 within 1 month after the diagnosis of HF (3, 8, 9). Although the initiation of HF treatment has been
12 considered to be a risk factor for stroke (10), the underlying mechanism of the increased risk of
13 ischemic stroke after the diagnosis of HF have remained unknown.

14 It was reported that between 6.5% and 15.0% of all strokes occur in patients already in hospital,
15 many of whom are there for the treatment of cardiac disorders (11). However, the incidence of
16 ischemic stroke during hospitalization for HF has not been investigated. Thus, we retrospectively
17 investigated consecutive patients who were hospitalized for HF and investigated the incidence and
18 predictors of ischemic stroke.

1 **Methods**

2 **Study design and study population**

3 This is an observational, single-center, retrospective cohort study. The study population consisted
 4 of patients with congestive HF, consecutively admitted to Kyoto Medical Center from October 2010
 5 to April 2014. We included patients who were prescribed or added diuretics during the
 6 hospitalization for HF. The diagnosis of HF was confirmed based on the Framingham definition of
 7 HF (12) by two or more cardiologists at a conference at the cardiology department of the hospital.
 8 We excluded patients complicated with the diagnosis of acute myocardial infarction, infective
 9 endocarditis, and takotsubo cardiomyopathy. We also excluded patients with dialysis, and those with
 10 mechanical circulatory support (intra-aortic balloon pump or extracorporeal membrane
 11 oxygenation). Patients' characteristics, co-morbidities, medications, and outcomes were obtained
 12 through the electronic medical records. The study protocol was approved by the institutional review
 13 boards. Informed consent was waived because the study was conducted in a historical cohort fashion
 14 without any intervention and individual identifying information was not used, according to the
 15 ethical guidelines for epidemiological research issued by the Ministry of Education, Culture, Sport,
 16 Science and Technology and the Ministry of Health, Labor and Welfare, Japan. The investigations
 17 were in accordance with the Declaration of Helsinki.

18 **Outcomes**

The primary endpoint in this analysis was ischemic stroke during hospitalization for HF. Other endpoints were hemorrhagic stroke, systemic embolism, all-cause death during hospitalization for HF, 30-day mortality rate, and all-cause death during the follow-up period.

Stroke ascertainment and definitions

We identified stroke cases by screening the medical records, and two independent neurologists reviewed the cases and confirmed the diagnoses of stroke. Stroke was defined as the acute onset of a focal neurologic deficit, with computed tomography or magnetic resonance imaging documentation.

The underlying ischemic stroke etiology was classified into cardioembolism, large-artery atherosclerosis, small-vessel occlusion, stroke of other determined etiology, and undetermined etiology according to the Trial of Org 10172 Acute Stroke Treatment (TOAST) classification (13).

We did not include strokes found only on brain imaging without correlated clinical symptoms, and catheter-related strokes. The stroke was considered to be catheter-related if it occurred during or within 24 hours of the cardiac catheterization (14).

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Additional definitions

Systemic embolism was defined as abrupt vascular insufficiency in any peripheral area associated with clinical evidence of arterial occlusion. Co-morbidities such as AF, hypertension, diabetes mellitus, dyslipidemia, history of HF, and history of stroke were defined as clinical documentation of

disease at admission for HF. The severity of HF was assessed by the New York Heart Association (NYHA) functional classes. Echocardiography was obtained within 2 weeks of admission. Left ventricular ejection fraction (EF) was calculated by the Teichholz method. Reduced EF was defined as less than 40%. Local asynergy was defined as any resting local wall motion abnormalities. OAC was defined as warfarin, dabigatran, rivaroxaban, or apixaban. Antiplatelet therapy was defined as the use of aspirin, thienopyridine, or cilostazol. The administration of unfractionated heparin (UFH) was defined as starting UFH on the day of admission. The decision of whether a patient should be treated with antithrombotic drugs was based on the judgment of the attending cardiologist. Data of medications were collected at the time of admission.

Data of body weight were collected at the time of admission, at day 3 (if data were not available, we used data at days 2-5), and at day 7 (if not available, at days 6-10). The laboratory data of hemoglobin, hematocrit, blood urea nitrogen (BUN), and creatinine were also collected at the time of admission, at day 3, and at day 7.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (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 or Wilcoxon rank-sum test on the basis

1 of the distribution. Data were analyzed as crude, stratified by the presence of AF, and by the
2 presence of OAC prescription. The Kaplan-Meier method was used to estimate the cumulative
3 incidences of clinical events, and the curves were compared using log-rank test. Thereafter, we
4 analyzed the patients without OAC at admission, in order to explore the predictors of ischemic
5 stroke. We used JMP software version 10 (SAS Institute, Cary, NC) to perform all of these analyses.
6 Two-sided P values less than 0.05 were considered statistically significant.

7

Results

A total of 558 consecutive HF patients were enrolled from October 2010 to April 2014. Median length of hospitalization was 18 days (IQR 12 days to 27 days). Median observation period was 393 days (IQR 134 days to 778 days).

Baseline characteristics and co-morbidities in the entire cohort, stratified by the presence of AF, and by the prescription of OAC are shown in Table 1. The mean age was 76.8 ± 12.3 years. A total of 244 patients (44%) were female. In addition, 421 patients (75%) had NYHA III-IV symptoms. The mean left-ventricular EF was $47.4 \pm 16.6\%$. A total of 271 patients (49%) had AF (paroxysmal: 14%, persistent: 6%, and permanent: 29%). The median CHADS₂ score was 3 (IQR 2 to 3.5) in patients with AF. Patients with AF were older and had a higher prevalence of prior stroke. UFH was administered in 97 patients (17% in the entire cohort, 14% in patients without AF, and 21% in patients with AF). OAC was prescribed to 8 (3%) patients without AF and to 139 (51%) patients with it. Patients with OAC had higher prevalence of AF, history of HF, and prior stroke.

The major clinical endpoints during hospitalization for HF were as follows (Table 2): ischemic stroke in 15 (2.7%), hemorrhagic stroke in 1 (0.2%), systemic embolism in 1 (0.2%), and all-cause death in 29 (5.2%). 30-day mortality rate was 3.9% (22/558 patients). All stroke cases are shown in

Table 3. None of 15 patients with ischemic stroke was prescribed OAC, whereas 4 patients with ischemic stroke were prescribed antiplatelet drugs. A total of 5 patients with ischemic stroke were

given UFH, but activated partial thromboplastin time was not prolonged in 4 patients. Ischemic stroke in 6 of 7 AF patients were caused by cardioembolism, 1 by undermined etiology. Meanwhile, in patients without AF, 2 cases were caused by cardioembolism, 6 by undetermined etiology.

The intervals from the admission of HF to the onset of ischemic stroke are shown in Figure 1-A.

The median interval was 10 days (IQR 5 days to 17 days). Most of ischemic stroke events occurred at around 1-2 weeks after admission for HF. The Kaplan-Meier curves for all-cause death during the follow-up period are shown in Figure 1-B. Patients complicated with ischemic stroke during hospitalization for HF showed worse prognosis than those without it (hazard ratio: 3.14, 95% confidence interval (CI): 1.22-6.60).

To explore the predictors of ischemic stroke, we analyzed the patients without OAC at admission (Table 4). We investigated the impact of baseline characteristics, co-morbidities, and changes of clinical parameters after admission on the incidence of ischemic stroke. History of stroke was significantly associated with a higher incidence of ischemic stroke (odds ratio: 3.33, 95% CI: 1.01-11.00).

We also explored the impact of decongestion markers, such as changes of body weight, and laboratory data (BUN, creatinine, hemoglobin, and hematocrit) on the incidence of ischemic stroke (Table 5). Short-term increases in BUN after admission were associated with increased risk of ischemic stroke (at day3; odds ratio (per 1 md/dl): 1.06, 95% CI: 1.01-1.11, $p=0.02$, and at day7;

1 odds ratio: 1.03, 95% CI: 1.00-1.07, $p=0.03$, respectively). Similarly, those in creatinine were also
2 associated with increased risk of ischemic stroke (at day 3; odds ratio (per 1 md/dl): 4.24, 95% CI:
3 1.45-11.71, $p=0.01$). Other decongestion markers such as in-hospital weight loss and hematocrit
4 change after admission were not associated with increased risk of ischemic stroke. We did not
5 perform the multivariate analysis because of the small number of ischemic stroke events.

6

Discussion

Incidence of ischemic stroke in patients with HF

HF is an important risk factor for ischemic stroke. The mechanisms leading to increased ischemic stroke in HF may be related to Virchow's triad (15, 16). First, HF can cause blood flow abnormalities due to the dilatation of cardiac chambers, reduced myocardial contractility, and increased intracardiac and central venous pressure. Second, blood constituent abnormalities can result from platelet and thrombin activation, as a consequence of activation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system. Third, HF can also cause vessel wall abnormalities due to inflammation, endothelial dysfunction, and neurohormonal activation.

Underlying mechanism and predictors of ischemic stroke during hospitalization for HF

Interestingly, recent reports demonstrated that stroke risk is highest within 1 month after the diagnosis of HF (3, 8, 9). The present study showed that the incidence of ischemic stroke was 2.7% (15/558 patients) during hospitalization for HF (median length: 18 days), which was considerably high compared with previous reports (1.3-3.9 events per 100 patient-years). Our study population was not so different from Japanese large registry of hospitalized HF patients, such as ATTEND Registry (17), and JCARE-CARD Registry (18). Why do ischemic stroke events of HF patients predominantly occur during the hospitalization period? Here, we hypothesized and investigated the following mechanisms of increased risk of ischemic stroke during hospitalization for HF. First, the

deterioration of HF may increase the blood viscosity and endothelial dysfunction through hypoxia and activation of the sympathetic nervous system (19, 20). Second, reduced EF or dilated cardiac chamber may cause blood stasis (21). Third, dehydration after the initiation of diuretics may promote hemoconcentration and hypercoagulation (22-26). Severity of HF, such as NYHA functional classes or the presence of hypoxia at admission did not differ between patients with ischemic stroke and those without it. Echocardiographic parameters such as left ventricular EF were not statistically different between the two groups, even if we used another cut off value (EF less than 50%) or analyzed EF as a continuous variable. However, these results could be due to lack of power considering the small number of the incidence of ischemic stroke (N=15). Markers of dehydration, such as weight loss, and markers of hemoconcentration, such as hemoglobin or hematocrit, also did not differ between the two groups. Meanwhile, short-term increases in BUN at day 3 or at day 7, and those in creatinine at day 3 were associated with higher incidence of ischemic stroke. Although high serum creatinine was reportedly a risk factor for cerebrovascular events (27), the significance of the acute increase in creatinine or BUN as a risk factor for stroke in HF patients is unknown, and these issues should be clarified in future studies.

OAC in patients during hospitalization for HF

In our study, none of patients with OAC was complicated with ischemic stroke, regardless of the presence of AF. By contrast, 4 patients with antiplatelet therapy, and 5 patients with UFH (given in

sub-therapeutic dose in 4 patients) were complicated with ischemic stroke. Moreover, our study showed that the etiology of ischemic stroke during hospitalization for HF was mainly cardioembolism. Although there was no significant difference in composite endpoint of death and stroke between warfarin and aspirin in patients with HF, warfarin treatment was associated with reduced risk of ischemic stroke (6). Recent case report demonstrated that novel oral anticoagulant was effective treatment for intracardiac thrombus (28, 29). Given our small sample size, we cannot draw a definite conclusion, but anticoagulation therapy may reduce the risk of ischemic stroke during hospitalization for HF. Further studies are needed to test this hypothesis.

Study limitation

First, this study was a single-center retrospective cohort study, so it was subjected to various biases inherent in such data. Second, antithrombotic prescription was based on the judgment of the attending cardiologist, which may have resulted in selection bias. In fact, anticoagulation was not prescribed to 29% of AF patients with CHADS₂ score ≥ 2 points in our study. However, anticoagulation is reportedly underused in daily practice, because physicians often concern about the bleeding complications (30). Third, stroke predictors in our study were based on only univariate analysis, so it was uncertain whether they were actually independent predictors. The number of patients with ischemic stroke was relatively small, so might be insufficient to perform the multivariate analysis and investigate the mechanisms or associated risk factors precisely. Fourth, we

could not investigate the etiology of HF or the existence of cardiogenic shock precisely because of the retrospective fashion, so we could not analyzed the impact of these factors.

Conclusions

The incidence of ischemic stroke during hospitalization for HF was high, even in patients without AF. Previous stroke and short-term increases in BUN was significantly associated with the incidence of ischemic stroke. Considering its frequency and poor prognosis, further studies are necessary to investigate the mechanism and risk factors of ischemic stroke during hospitalization for HF.

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Disclosures

The authors declare that there is no conflict of interest.

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1 **Figure legends**

2 Figure 1.

3 A. The intervals from the admission of HF to the onset of ischemic stroke.

4 B. The Kaplan-Meier curves for all-cause death during follow-up of patients with stroke and those
5 without it.

6 HF: heart failure, IQR: interquartile range.

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Table 1. Patients' characteristics in the entire cohort, stratified by the presence of AF, and by the OAC prescription

	Total N=558	Without AF N=287	With AF N=271	P value	Without OAC N=411	With OAC N=147	P value
Age (years)	76.8 ± 12.3	75.8 ± 13.7	77.9 ± 10.6	0.04	76.6 ± 13.5	77.4 ± 8.4	0.47
Sex (female, %)	244 (44%)	123 (43%)	121 (45%)	0.67	183 (45%)	61 (42%)	0.52
Height (cm)	156.6 ± 10.6	156.1 ± 10.7	157.1 ± 10.5	0.28	156.3 ± 10.8	157.3 ± 10.2	0.33
Body weight (kg)	57.8 ± 15.8	57.1 ± 15.4	58.6 ± 16.1	0.25	57.6 ± 16.2	58.5 ± 14.5	0.54
SBP (mmHg)	140.7 ± 32.9	146.8 ± 34.0	134.2 ± 30.4	<0.01	144.6 ± 33.2	129.8 ± 29.6	<0.01
DBP (mmHg)	79.8 ± 21.9	79.7 ± 22.6	80.0 ± 21.2	0.87	80.8 ± 22.2	77.1 ± 20.8	0.08
Heart rate (beats/min)	93.3 ± 26.1	89.2 ± 22.1	97.6 ± 29.1	<0.01	93.2 ± 25.6	93.7 ± 27.6	0.81
Hypoxia at admission	252 (45%)	149 (52%)	103 (38%)	<0.01	201 (49%)	51 (35%)	<0.01
NYHA class III/IV	421 (75%)	223 (78%)	198 (73%)	0.20	314 (76%)	107 (73%)	0.38
LVEF (%)	47.4 ± 16.6	45.5 ± 17.5	49.4 ± 15.3	<0.01	47.0 ± 16.9	48.6 ± 15.5	0.30
<Co-morbidities>							
Atrial fibrillation	271 (49%)	0 (0%)	271 (100%)	<0.01	132 (32%)	139 (95%)	<0.01
History of heart failure	181 (32%)	84 (29%)	97 (36%)	0.10	120 (29%)	61 (42%)	<0.01
Myocardial infarction	93 (17%)	53 (18%)	40 (15%)	0.24	65 (16%)	28 (19%)	0.37
Valvular heart disease	117 (21%)	54 (19%)	63 (23%)	0.20	75 (18%)	42 (29%)	0.01
Cardiomyopathy	28 (5%)	18 (6%)	10 (4%)	0.16	18 (4%)	10 (7%)	0.25
History of stroke	74 (13%)	27 (9%)	47 (17%)	<0.01	43 (10%)	31 (21%)	<0.01
Hypertension	395 (71%)	199 (69%)	196 (72%)	0.44	289 (70%)	106 (72%)	0.68
Diabetes mellitus	182 (33%)	107 (37%)	75 (28%)	0.02	137 (33%)	45 (31%)	0.55
Dyslipidemia	194 (35%)	105 (37%)	89 (33%)	0.35	139 (34%)	55 (37%)	0.43
Chronic kidney disease	247 (44%)	125 (44%)	122 (45%)	0.73	180 (44%)	67 (46%)	0.71
<Laboratory data>							
BUN (mg/dl)	23 (17, 32)	23 (17, 33)	22 (16, 32)	0.41	23 (17, 33)	22 (17, 31)	0.93
Creatinine (mg/dl)	1.0 (0.8, 1.3)	1.0 (0.8, 1.5)	1.0 (0.8, 1.3)	0.16	1.0 (0.8, 1.4)	1.0 (0.8, 1.3)	0.82
Hemoglobin (g/dl)	11.5 (9.9, 13.2)	11.2 (9.7, 13.1)	11.7 (10.3, 13.2)	0.04	11.4 (9.9, 13.2)	11.6 (10.3, 13.2)	0.20
Hematocrit (%)	35.2 (30.9, 40.2)	34.7 (29.9, 40.2)	36.3 (31.9, 40.3)	0.04	35.1 (30.4, 40.4)	35.8 (32.2, 39.9)	0.25
NT-pro BNP (pg/ml)	3254 (1609, 7419)	3560 (1780, 10157)	2948 (1435, 6348)	0.06	3402 (1716, 8285)	2885 (1478, 6307)	0.20
<Medications>							
Administration of UFH	97 (17%)	39 (14%)	58 (21%)	0.01	83 (20%)	14 (10%)	<0.01
Oral anticoagulant	147 (26%)	8 (3%)	139 (51%)	<0.01	0 (0%)	147 (100%)	<0.01
Warfarin	129 (23%)	7 (3%)	122 (45%)	<0.01	0 (0%)	129 (88%)	<0.01
NOAC	18 (3%)	1 (1%)	17 (6%)	<0.01	0 (0%)	18 (12%)	<0.01
Antiplatelet therapy	158 (28%)	94 (33%)	64 (24%)	0.02	124 (30%)	34 (23%)	0.10
Aspirin	145 (26%)	88 (31%)	57 (21%)	0.01	113 (27%)	32 (22%)	0.17
Thienopyridine	46 (8%)	30 (10%)	16 (6%)	0.05	39 (9%)	7 (5%)	0.07
Cilostazol	1 (0.2%)	0 (0%)	1 (0.4%)	0.49	0 (0%)	1 (0.7%)	0.26

Categorical data are presented as number (%). Continuous data are presented as mean ± standard deviation or median and interquartile range (25%, 75%). AF, atrial fibrillation; OAC, oral anticoagulants; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; UFH, unfractionated heparin; NOAC, novel oral anticoagulant.

Table 2. Patients with events during hospitalization for HF

	Total N=558	Without AF N=287	With AF N=271	P value	Without OAC N=411	With OAC N=147	P value
Ischemic stroke	15 (2.7%)	8 (2.8%)	7 (2.6%)	0.88	15 (3.7%)	0 (0.0%)	0.01
Hemorrhagic stroke	1 (0.2%)	0 (0.0%)	1 (0.4%)	0.49	1 (0.2%)	0 (0.0%)	1.00
Systemic embolism	1 (0.2%)	0 (0.0%)	1 (0.4%)	0.49	1 (0.2%)	0 (0.0%)	1.00
All-cause death	29 (5.2%)	11 (3.8%)	18 (7.0%)	0.14	25 (6.1%)	4 (2.7%)	0.13

Data are presented as number (%). HF, heart failure; AF, atrial fibrillation; OAC, oral anticoagulant.

Table 3. Stroke cases in our cohort

Pt	Sex	Age	HF etiology	NYHA	LVEF	Rhythm	CHADS2	APT	UFH	aPTT	Onset date	Stroke etiology	mRS
1	male	77	DCM	III	29	PM			-		7	cardioembolism	2
2	female	85	severe AS	IV	28	sinus			-		17	cardioembolism	5
3	female	82	CAD	II	41	sinus			-		10	undetermined	4
4	male	74	DCM	IV	56	sinus		+	+ not prolonged		18	undetermined	6
5	male	89	DCM	IV	44	sinus			-		12	undetermined	5
6	male	70	DCM	III	23	sinus			-		6	undetermined	1
7	male	69	HHD	IV	36	sinus			+ not prolonged		20	undetermined	2
8	male	89	CAD	II	47	sinus		+	-		16	undetermined	3
9	female	90	severe AS	III	48	AF	2		-		5	cardioembolism	5
10	male	78	CAD	III	45	AF	4	+	+ not prolonged		4	cardioembolism	2
11	female	89	HHD	IV	73	AF	4		+ not prolonged		3	cardioembolism	3
12	male	82	CAD	III	36	AF	4	+	+ prolonged		31	cardioembolism	6
13	male	77	severe MR	III	29	AF	4		-		7	cardioembolism	5
14	female	88	severe AS	IV	49	AF	3		-		13	cardioembolism	3
15	female	91	HHD	IV	73	AF	3		-		4	undetermined	4

Pt, patient; HF, heart failure; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; APT, antiplatelet therapy; UFH, unfractionated heparin; aPTT, activated partial thromboplastin time; mRS, modified Rankin Scale; DCM, dilated cardiomyopathy; AS, aortic stenosis; CAD, coronary artery disease; HHD, hypertensive heart disease; MR, mitral regurgitation; PM, pacemaker; AF, atrial fibrillation.

aPTT was defined to be prolonged if it was over 1.5 times normal value.

Table 4. Univariate analysis of predictors of ischemic stroke in patients without OAC (N=411): baseline characteristics at admission

Variable	Odds ratio	95% CI	P Value
<Baseline characteristics>			
Age (per 1 years)	1.04	0.99 - 1.10	0.08
Advanced age (≥ 75 years)	2.21	0.61 - 7.96	0.21
Male sex	1.21	0.42 - 3.47	0.72
Antiplatelet therapy	0.84	0.26 - 2.68	0.76
<Severity of HF>			
Hypoxemia at admission	1.58	0.55 - 4.52	0.39
NYHA class III/IV	2.05	0.45 - 9.25	0.34
Reduced EF (<40%)	1.23	0.43 - 3.53	0.70
Dilated LVDd (>55 mm)	2.06	0.73 - 5.81	0.16
Local asynergy	1.52	0.54 - 4.29	0.42
<Co-morbidities>			
Atrial fibrillation	1.90	0.67 - 5.35	0.22
History of stroke	3.33	1.01 - 11.00	0.04
History of heart failure	1.65	0.57 - 4.74	0.35
Prior myocardial infarction	2.00	0.62 - 6.48	0.24
Hypertension	0.84	0.28 - 2.51	0.75
Diabetes mellitus	2.37	0.84 - 6.67	0.09

OAC, oral anticoagulant; CI, confidence interval; HF, heart failure; NYHA, New York Heart Association functional class; EF, ejection fraction; LVDd, left ventricular end-diastolic diameter.

Table 5. Univariate analysis of predictors of ischemic stroke in patients without OAC (N=411): changes of clinical parameters.

	Odds ratio	95% CI	P Value
< At day 3 >			
Change of body weight			
Δ body weight loss (per 1 kg)	0.99	0.81 - 1.23	0.95
Changes of laboratory data			
Δ BUN (per 1 mg/dl)	1.06	1.01 - 1.11	0.02
Δ Cre (per 1 mg/dl)	4.24	1.45 - 11.71	0.01
Δ Hemoglobin (per 1 g/dl)	0.87	0.53 - 1.42	0.59
Δ Hematocrit (per 1%)	0.96	0.83 - 1.12	0.60
< At day 7 >			
Change of body weight			
Δ body weight loss (per 1 kg)	0.97	0.81 - 1.14	0.73
Changes of laboratory data			
Δ BUN (per 1 mg/dl)	1.03	1.00 - 1.07	0.03
Δ Cre (per 1 mg/dl)	1.15	0.32 - 2.40	0.79
Δ Hemoglobin (per 1 g/dl)	1.15	0.71 - 1.81	0.57
Δ Hematocrit (per 1%)	1.04	0.91 - 1.19	0.58

OAC, oral anticoagulants; CI, confidence interval; BUN, blood urea nitrogen; Cre, creatinine.

Figure 1

