Elevated Plasma D-Dimer Level Is Associated With Short-Term Risk of Ischemic Stroke in Patients With Acute Heart Failure

Yasuhiro Hamatani, MD; Toshiyuki Nagai, MD, PhD; Michikazu Nakai, PhD; Kunihiro Nishimura, MD, PhD; Yasuyuki Honda, MD; Hiroki Nakano, MD; Satoshi Honda, MD, PhD; Naotsugu Iwakami, MD, MPH; Yasuo Sugano, MD, PhD; Yasuhide Asaumi, MD, PhD; Takeshi Aiba, MD, PhD; Teruo Noguchi, MD, PhD; Kengo Kusano, MD, PhD; Kazunori Toyoda, MD, PhD; Satoshi Yasuda, MD, PhD; Hiroyuki Yokoyama, MD, PhD; Hisao Ogawa, MD, PhD; Toshihisa Anzai, MD, PhD; on behalf of the NaDEF Investigators

Background and Purpose—The incidence of heart failure increases the subsequent risk of ischemic stroke, and its risk could be higher in the short-term period after an acute heart failure (AHF) event. However, its determinants remain to be clarified. Plasma D-dimer level reflects fibrin turnover and exhibits unique properties as a biomarker of thrombosis. The aim of this study is to investigate whether D-dimer level is a determinant of short-term incidence of ischemic stroke in patients with AHF.

Methods—We examined 721 consecutive hospitalized AHF patients with plasma D-dimer level on admission from our prospective registry between January 2013 and May 2016. The study end points were incidence of ischemic stroke during hospitalization and at 30 days after admission.

Results—Of the total participants (mean age, 76 years; male, 60%; atrial fibrillation, 54%; mean left ventricular ejection fraction, 38%), in-hospital ischemic stroke occurred in 18 patients (2.5%) during a median hospitalization period of 21 days, and 30-day ischemic stroke occurred in 16 patients (2.2%). Higher D-dimer level on admission was an independent determinant of subsequent risk of in-hospital ischemic stroke even after adjustment by CHA_2DS_2-VASc score (odds ratio, 2.29; 95% confidence interval, 1.46–3.60; $P<0.001$) or major confounders, including age, atrial fibrillation, and antithrombotic therapy (odds ratio, 2.31; 95% confidence interval, 1.43–3.74; $P<0.001$). Subgroup analyses showed consistent findings in patients without atrial fibrillation (odds ratio, 2.46; 95% confidence interval, 1.39–4.54; $P=0.002$) and those without antithrombotic therapy (odds ratio, 2.79; 95% confidence interval, 1.53–5.57; $P<0.001$). Similar results were obtained for 30-day ischemic stroke as an alternative outcome.

Conclusions—Elevated plasma D-dimer level on admission was significantly associated with increased incidence of ischemic stroke shortly after admission for AHF, suggesting a predictive role of D-dimer for short-term ischemic stroke events in patients with AHF.

Clinical Trial Registration—URL: https://www.umin.ac.jp/ctr/index.htm. Unique identifier: UMIN000017024.

(*Stroke*. 2018;49:1737-1740. DOI: 10.1161/STROKEAHA.118.021899.)

Key Words: brain ischemia ■ fibrin ■ heart failure ■ humans ■ incidence ■ stroke

Ischemic stroke is a devastating morbidity in patients with heart failure (HF) and is expected to rise with increasing age and comorbid conditions in the HF population. The risk of ischemic stroke is 2 to 3× higher in patients with HF than in those without.[1] Notably, its risk could be markedly increased in the short-term period after an acute HF (AHF) event[1–4]; however, little is known about the determinants of ischemic stroke shortly after hospitalization for AHF.

D-dimer—a marker of fibrin turnover—exhibits unique properties as a biological marker of hemostatic abnormalities and thrombosis.[5] Elevated D-dimer level is reportedly a determinant of the incidence of ischemic stroke not only in

Received February 4, 2018; final revision received April 24, 2018; accepted May 11, 2018.

From the Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Japan (T. Nagai, T. Anzai); and Department of Cardiovascular Medicine (Y. Hamatani, Y. Honda, H.N., S.H., N.I., Y.S., Y.A., T. Aiba, T. Noguchi, K.K., S.Y., H.Y., H.O.), Department of Statistics and Data Analysis, Center for Cerebral and Cardiovascular Disease Information (M.N., K.N.), and Department of Cerebrovascular Medicine (K.T.), National Cerebral and Cardiovascular Center, Osaka, Japan.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.118.021899/-/DC1.

Correspondence to Toshiyuki Nagai, MD, PhD, Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Kita-15 Nishi-7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan. E-mail tnagai@huhp.hokudai.ac.jp

the general population[6] but also in patients with atrial fibrillation (AF).[7] Nevertheless, the association between D-dimer level and incidence of ischemic stroke in patients with AHF has not been investigated.

Accordingly, the aim of this study was to investigate whether D-dimer level could be a significant determinant of incidence of ischemic stroke shortly after admission for AHF.

Methods

Study Design

Data from the National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry, obtained between January 2013 and May 2016, were retrospectively analyzed. Details of the National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry have been described previously.[8] Briefly, the National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry is a single-center, observational, prospective cohort that includes all patients requiring hospitalization with a diagnosis of AHF according to the Framingham criteria. The authors declare that all supporting data are available within the article and its online-only Data Supplement. In this study, because patient information was anonymized and deidentified before analyses, written informed consent was not obtained from each patient. However, we publicized the study by posting a summary of the protocol on the website of our center; the notice clearly informed patients of their right to refuse enrollment. The study protocol of this registry has been approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M22-025) and registered under the Japanese University Hospital Medical Information Network Clinical Trials Registration (UMIN000017024).

Study Population

From the 850 patients enrolled in the National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry, those without measurement of D-dimer level on admission were excluded. Finally, 721 patients were examined.

D-Dimer Measurement

Plasma D-dimer level was measured using the reagent hexamate D-dimer (Medical and Biological Laboratories, Co, Ltd, Nagoya, Japan) on a STA-R EVOLUTION automated coagulation analyzer (Diagnostica Stago, Asnières, France). D-dimer level was reported as D-dimer concentration, and the reference limit of normal was <1.0 μg/mL.

Definitions

The study end points were incidence of ischemic stroke during hospitalization (in-hospital ischemic stroke) and within 30 days after the indexed admission (30-day ischemic stroke). Ischemic stroke was confirmed using computed tomography or magnetic resonance imaging by at least 2 expert neurologists. Patients with AF were defined as those with either AF confirmed on their baseline ECG or a history of AF.[9] Antithrombotic therapy was defined as oral anticoagulants and aspirin.

Statistical Analyses

Results are presented as mean±SD or as median and interquartile range according to their distribution. Differences between groups were analyzed by unpaired Student *t* test or Mann-Whitney *U* test for continuous variables and by χ^2 test or Fisher exact test for dichotomous variables. The optimal cutoff value of D-dimer level for events was determined by receiver operating characteristic curve analysis. To evaluate the influence of D-dimer level on ischemic stroke, we developed the various multivariable logistic regression models. As a sensitivity analysis, we conducted competing-risks regression models on ischemic stroke considering death as a competing risk according to the method of Fine and Gray. Plasma D-dimer level was transformed to a log-scale, for calculating odds ratio (OR) and its interaction. All tests were 2 tailed, and a value of $P<0.05$ was considered statistically significant. All analyses were performed with JMP, version 10 (SAS Institute, Cary, NC), and Stata 15 (Stata Corporation, College Station, TX).

Results

Baseline Characteristics in Patients With and Without Short-Term Ischemic Stroke Events

Of 721 patients (mean age, 76 years; male, 60%; AF, 54%; and mean left ventricular ejection fraction, 38%), median D-dimer level on admission was 2.1 (interquartile range, 1.1–4.2) μg/mL, and median hospitalization period was 21 (interquartile range, 14–28) days. Ischemic stroke occurred in 18 patients (2.5%) during hospitalization and in 16 patients (2.2%) within 30 days after admission. The incidence of in-hospital ischemic stroke was 34.3 per 100 person-years, whereas that of postdischarge ischemic stroke was 1.9 per 100 person-years. Patients with in-hospital ischemic stroke had significantly higher D-dimer and high-sensitivity troponin T levels and lower prevalence of aspirin and loop diuretic use on admission. Patients with 30-day ischemic stroke had similar characteristics except for the prevalence of aspirin use. Other variables were comparable between the groups (Table I in the online-only Data Supplement).

Plasma D-Dimer Level and Risk of Short-Term Ischemic Stroke

Based on receiver operating characteristic curve analysis, C index was 0.68 (95% confidence interval [CI], 0.54–0.79) for in-hospital ischemic stroke and 0.65 (95% CI, 0.50–0.77) for 30-day ischemic stroke (Figure I in the online-only Data Supplement). The optimal cutoff values for the development of in-hospital and 30-day ischemic stroke events were both 3.5 μg/mL. Importantly, neither in-hospital nor 30-day ischemic stroke events were observed in patients with D-dimer level less than the reference limit of normal (<1.0 μg/mL). This cutoff value of 1.0 μg/mL had a sensitivity of 100%, achieving a negative predictive value of 100%.

Multivariable logistic regression analyses confirmed that elevated D-dimer level was an independent determinant of in-hospital and 30-day ischemic stroke (Table; Table II in the online-only Data Supplement). D-dimer level both as a continuous variable and as a categorical variable was independently associated with increased risk of short-term ischemic stroke. After taking into account the competing risk of death, the increased risk of short-term ischemic stroke by elevated D-dimer level still remained significant (Table III in the online-only Data Supplement).

Subgroup analyses showed that D-dimer level was significantly associated with short-term ischemic stroke events in patients without AF (OR, 2.46; 95% CI, 1.39–4.54; $P=0.002$ for in-hospital ischemic stroke; and OR, 2.20; 95% CI, 1.16–4.15; $P=0.017$ for 30-day ischemic stroke) and those without antithrombotic therapy (OR, 2.79; 95% CI, 1.53–5.57; $P<0.001$ for in-hospital ischemic stroke; and OR, 2.45; 95% CI, 1.30–4.91; $P=0.007$ for 30-day ischemic stroke; Figure).

Table. Logistic Regression Analyses for the Impact of D-Dimer Level on Short-Term Ischemic Stroke Events

	Model 1*		Model 2†		Model 3‡		Model 4§	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
In-hospital ischemic stroke								
D-dimer, log	2.18 (1.40–3.40)	<0.001	2.31 (1.43–3.74)	<0.001	2.29 (1.46–3.60)	<0.001	2.18 (1.35–3.59)	0.002
D-dimer ≥3.5 μg/mL (according to ROC curve analysis)	3.52 (1.37–9.68)	0.009	3.55 (1.33–10.12)	0.011	3.76 (1.45–10.44)	0.007	3.99 (1.45–11.97)	0.007
30-d ischemic stroke								
D-dimer, log	1.98 (1.24–3.13)	0.005	2.18 (1.31–3.59)	0.003	2.04 (1.27–3.25)	0.004	2.01 (1.24–3.26)	0.005
D-dimer ≥3.5 μg/mL (according to ROC curve analysis)	2.85 (1.05–8.08)	0.040	3.10 (1.10–9.13)	0.033	2.97 (1.09–8.48)	0.034	3.41 (1.20–10.38)	0.021

CI indicates confidence interval; OR, odds ratio; and ROC, receiver operating characteristics.

*Unadjusted.

†Adjusted for major confounders: age, atrial fibrillation, and antithrombotic therapy (oral anticoagulant and aspirin).

‡Adjusted for CHA_2DS_2-VASc score.

§Adjusted for clinical variables, which were associated with ischemic stroke events in univariable analysis and were as follows: use of loop diuretic, use of aspirin and high-sensitivity troponin T for in-hospital ischemic stroke, and use of loop diuretic and high-sensitivity troponin T for 30-day ischemic stroke.

Discussion

In the present study, higher D-dimer level on admission was a significant independent determinant of short-term ischemic stroke in patients with AHF.

D-dimer is a soluble fibrin degradation product and is generated when the cross-linked fibrin network undergoes plasmin-mediated degradation. Based on the underlying mechanisms, D-dimer level reflects increases in blood coagulation and degradation of fibrin and could be a marker of thrombosis.[5]

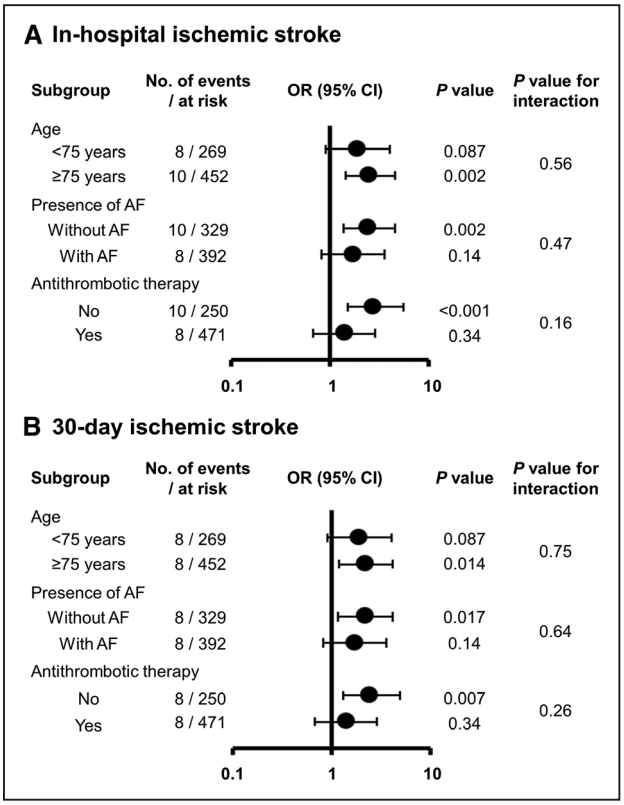

Figure. Impact of D-dimer level on ischemic stroke events, according to major subgroups. **A**, In-hospital ischemic stroke, (**B**) 30-day ischemic stroke. AF indicates atrial fibrillation; CI, confidence interval; and OR, odds ratio.

It is noteworthy that HF per se is an important risk factor for thromboembolism, through the fulfillment of the Virchow triad for thrombogenesis.[9] With regard to AHF, higher intracardiac pressure and reduced ventricular contraction induce further blood flow stasis.[10] Moreover, the coagulation system and endothelial function are more severely impaired in patients with AHF than in those with chronic HF.[11] Indeed, a previous study has suggested that the risk of stroke substantially increases after hospitalization for AHF.[12] Despite the absolute number of ischemic stroke events in our study being relatively low, it should be emphasized that our study end point was set as events within a short-term period (in-hospital [median length was 21 days] and within 30 days) after indexed AHF admission. Our study revealed that the risk of thromboembolism was the highest in the short-term period after AHF events, similar to previous reports.[1–4] Accordingly, risk stratification for short-term ischemic stroke events is strongly warranted for the management of hospitalized patients with AHF. Our findings indicated that D-dimer level on admission could be a useful surrogate marker for stratifying the subsequent risk of ischemic stroke shortly after hospitalization for AHF. Moreover, D-dimer level on admission demonstrated high negative predictive value for ischemic stroke events, indicating that a normal D-dimer level might be informative to exclude short-term subsequent risk of ischemic stroke after AHF.

Antithrombotic therapy for patients with HF without AF is challenging. Current guidelines do not recommend routine antithrombotic therapy for patients with HF without AF (class III, level of evidence B)[13] because clinical trials have shown no overall beneficial effects of antithrombotic therapy in these patients. To date, limited progress has been made in ameliorating the thromboembolic risk in patients with HF. The ongoing COMMANDER-HF trial (Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart

Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) examines the efficacy of rivaroxaban in reducing the risk of death, stroke, and myocardial infarction in patients with a recent exacerbation of HF with reduced ejection fraction and coexisting coronary artery disease without AF.[14] This trial might shed light on the use of antithrombotic therapy in patients with HF, and our study suggested that the inclusion of biomarkers, such as D-dimer level, may be useful to identify patients with HF with high thromboembolic risk who are suitable for antithrombotic therapy.

Limitations

This study has several limitations. First, this was a single-center study with a relatively small sample size, thereby limiting the ability to generalize our findings. The number of ischemic stroke events was small; therefore, the number of covariates entered in the multivariable regression model was limited, resulting in a decrease in the statistical power of the study. Moreover, this study was analyzed retrospectively. Thus, our study is hypothesis-generating research, and further studies are warranted to test this hypothesis. Second, the indication for antithrombotic therapy was decided by each primary physician, which may have resulted in selection bias. Third, D-dimer level is associated with the development of AF in patients with HF[15]; however, we did not have data on newly developed AF during follow-up period. Furthermore, D-dimer level is increased in a variety of conditions, making the results less applicable; although elevated D-dimer level was independently associated with short-term ischemic stroke events even after adjustment for confounders (Table; Figure; Table II in the online-only Data Supplement).

Conclusions

Elevated plasma D-dimer level on admission was significantly associated with increased risk of ischemic stroke shortly after admission for AHF, suggesting the potential role of D-dimer as a predictive marker for short-term ischemic stroke events in patients with AHF. Measurement of D-dimer level is widely available in most hospitals and might be useful for risk stratification of thromboembolism in patients with AHF.

Acknowledgments

We are grateful for the contributions of all the investigators, clinical research coordinators, and data managers involved in the National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry.

Sources of Funding

The National Cerebral and Cardiovascular Center Acute Decompensated Heart Failure registry was supported by a grant from the Japan Cardiovascular Research Foundation (24-4-2, Dr Anzai) and a Grant-in-Aid for Young Scientists (Japan Society for the Promotion of Science KAKENHI, 15K19402, Dr Nagai).

Disclosures

Dr Nagai is supported by grants from the Daiichi Sankyo Foundation of Life Science and the Mochida Memorial Foundation for Medical and Pharmaceutical Research. The other authors report no conflicts.

References

1. Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, et al. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. *Stroke*. 2017;48:1161–1168. doi: 10.1161/STROKEAHA.116.016022.
2. Lip GY, Rasmussen LH, Skjoth F, Overvad K, Larsen TB. Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *BMJ Open*. 2012;2:e000975. doi: 10.1136/bmjopen-2012-000975.
3. Alberts VP, Bos MJ, Koudstaal P, Hofman A, Witteman JC, Stricker B, et al. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol*. 2010;25:807–812. doi: 10.1007/s10654-010-9520-y.
4. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006;152:102–109. doi: 10.1016/j.ahj.2005.10.018.
5. Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. *J Am Coll Cardiol*. 2017;70:2411–2420. doi: 10.1016/j.jacc.2017.09.024.
6. Folsom AR, Gottesman RF, Appiah D, Shahar E, Mosley TH. Plasma d-Dimer and incident ischemic stroke and coronary heart disease: the Atherosclerosis Risk in Communities Study. *Stroke*. 2016;47:18–23. doi: 10.1161/STROKEAHA.115.011035.
7. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *J Am Coll Cardiol*. 2010;55:2225–2231. doi: 10.1016/j.jacc.2009.12.049.
8. Nagai T, Nishimura K, Honma T, Higashiyama A, Sugano Y, Nakai M, et al; NaDEF Investigators. Prognostic significance of endogenous erythropoietin in long-term outcome of patients with acute decompensated heart failure. *Eur J Heart Fail*. 2016;18:803–813. doi: 10.1002/ejhf.537.
9. Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, et al; Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA); GISSI-Heart Failure (GISSI-HF) Committees and Investigators. Risk of stroke in chronic heart failure patients without atrial fibrillation: analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials. *Circulation*. 2015;131:1486–1494; discussion 1494. doi: 10.1161/CIRCULATIONAHA.114.013760.
10. Aispuru GR, Clavier MM, Cardone AJ, Gilberto DO, Barousse AP. Thrombotic biomarkers and left ventricle characteristics as short-term predictors of thrombotic events in patients hospitalized for acute decompensated heart failure. *Eur J Intern Med*. 2012;23:545–551. doi: 10.1016/j.ejim.2012.04.002.
11. Chung I, Choudhury A, Lip GY. Platelet activation in acute, decompensated congestive heart failure. *Thromb Res*. 2007;120:709–713. doi: 10.1016/j.thromres.2007.01.003.
12. Hamatani Y, Iguchi M, Nakamura M, Ohtani R, Yamashita Y, Takagi D, et al. Incidence and predictors of ischemic stroke during hospitalization for congestive heart failure. *Heart Vessels*. 2016;31:1154–1161. doi: 10.1007/s00380-015-0719-4.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807.
14. Zannad F, Greenberg B, Cleland JG, Gheorghiade M, van Veldhuisen DJ, Mehra MR, et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail*. 2015;17:735–742. doi: 10.1002/ejhf.266.
15. Zorlu A, Akkaya E, Altay H, Bektasoglu G, Turkdogan KA, Sincer I, et al. The relationship between D-dimer level and the development of atrial fibrillation in patients with systolic heart failure. *J Thromb Thrombolysis*. 2012;33:343–348. doi: 10.1007/s11239-011-0656-8.

Stroke
Journal of the American Heart Association

Elevated Plasma D-Dimer Level Is Associated With Short-Term Risk of Ischemic Stroke in Patients With Acute Heart Failure

Yasuhiro Hamatani, Toshiyuki Nagai, Michikazu Nakai, Kunihiro Nishimura, Yasuyuki Honda, Hiroki Nakano, Satoshi Honda, Naotsugu Iwakami, Yasuo Sugano, Yasuhide Asaumi, Takeshi Aiba, Teruo Noguchi, Kengo Kusano, Kazunori Toyoda, Satoshi Yasuda, Hiroyuki Yokoyama, Hisao Ogawa and Toshihisa Anzai
on behalf of the NaDEF Investigators

Stroke. 2018;49:1737-1740; originally published online June 7, 2018;
doi: 10.1161/STROKEAHA.118.021899
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Supplemental Table I. Baseline Characteristics in Patients With and Without Short-term Ischemic Stroke Events

Variable	Total (n = 721)	In-hospital		*P* value	Within 30 days		*P* value
		Events (n = 18)	No events (n = 703)		Events (n = 16)	No events (n = 705)	
Age (years)	76 ± 12	74 ± 13	76 ± 12	0.54	73 ± 14	76 ± 12	0.36
Age ≥75 years	452 (63%)	10 (56%)	442 (63%)	0.52	8 (50%)	444 (63%)	0.29
Male sex	436 (60%)	10 (56%)	426 (61%)	0.67	8 (50%)	428 (61%)	0.39
NYHA class III/IV	590 (90%)	14 (88%)	576 (90%)	0.66	12 (86%)	578 (90%)	0.64
Systolic BP (mmHg)	140 ± 32	145 ± 32	140 ± 32	0.50	149 ± 32	140 ± 32	0.26
Heart rate (beats/min)	92 ± 28	97 ± 31	92 ± 28	0.46	99 ± 33	92 ± 28	0.33
SpO2 (%)	94 ± 6	96 ± 4	94 ± 6	0.19	95 ± 4	94 ± 6	0.33
LVEF (%)	38 ± 17	44 ± 17	37 ± 17	0.12	44 ± 17	37 ± 17	0.12
Left atrial diameter (mm)	46 ± 10	44 ± 11	46 ± 9	0.57	45 ± 11	46 ± 10	0.83
Etiology							
ICM	213 (30%)	6 (33%)	207 (29%)	0.65	4 (25%)	209 (30%)	0.60
NICM	232 (32%)	6 (33%)	226 (32%)		6 (38%)	226 (32%)	
Valvular	160 (22%)	5 (28%)	155 (22%)		5 (31%)	155 (22%)	
Others	116 (16%)	1 (6%)	115 (16%)		1 (6%)	115 (16%)	
Oral medications							
ACE-I/ARB	369 (51%)	7 (39%)	362 (52%)	0.28	7 (44%)	362 (52%)	0.53
Beta-blocker	365 (51%)	7 (39%)	358 (51%)	0.31	7 (44%)	358 (51%)	0.57
MRA	168 (23%)	3 (17%)	165 (24%)	0.78	3 (19%)	165 (23%)	1.00
Loop diuretic	368 (51%)	3 (17%)	365 (52%)	0.003	3 (19%)	365 (52%)	0.010
Oral anticoagulant	311 (33%)	6 (33%)	305 (43%)	0.40	6 (38%)	305 (43%)	0.65
Warfarin	266 (37%)	5 (28%)	261 (37%)	0.41	5 (31%)	261 (37%)	0.63
DOAC	45 (6%)	1 (6%)	44 (6%)	1.00	1 (6%)	44 (6%)	1.00
Aspirin	259 (36%)	2 (11%)	257 (37%)	0.026	2 (13%)	257 (37%)	0.063
Co-morbid conditions							
AF	392 (54%)	8 (44%)	384 (55%)	0.39	8 (50%)	384 (54%)	0.72
History of HF	310 (43%)	7 (39%)	303 (43%)	0.72	6 (38%)	304 (43%)	0.65
Stroke/TIA	180 (25%)	4 (22%)	176 (25%)	1.00	4 (25%)	176 (25%)	1.00
ACS	37 (5%)	3 (17%)	34 (5%)	0.06	1 (6%)	36 (5%)	0.57
OMI	178 (25%)	3 (17%)	175 (25%)	0.58	3 (19%)	175 (25%)	0.77
ASO	71 (10%)	2 (11%)	69 (10%)	0.70	2 (13%)	69 (10%)	0.67
Hypertension	539 (75%)	11 (61%)	528 (75%)	0.17	10 (63%)	529 (75%)	0.25
Dyslipidemia	383 (53%)	7 (39%)	376 (53%)	0.22	6 (38%)	377 (53%)	0.21
Diabetes mellitus	274 (38%)	8 (44%)	266 (38%)	0.57	8 (50%)	266 (38%)	0.32
Smoking history	395 (56%)	9 (50%)	386 (56%)	0.64	7 (44%)	388 (56%)	0.34
COPD	30 (4%)	0 (0%)	30 (4%)	1.00	0 (0%)	30 (4%)	1.00
Chronic kidney disease	368 (51%)	7 (39%)	361 (52%)	0.29	7 (44%)	361 (51%)	0.54
Liver cirrhosis	6 (1%)	0 (0%)	6 (1%)	1.00	0 (0%)	6 (1%)	1.00
History of VTE	8 (1%)	0 (0%)	8 (1%)	1.00	0 (0%)	8 (1%)	1.00
Active infection	124 (21%)	4 (29%)	120 (21%)	0.51	4 (31%)	120 (21%)	0.49
Malignancy	108 (15%)	4 (22%)	104 (15%)	0.33	3 (19%)	105 (15%)	0.72

History of cardiac surgery	168 (23%)	2 (11%)	166 (24%)	0.27	2 (13%)	166 (24%)	0.38
$CHADS_2$ score	3.25 ± 1.31	3.06 ± 1.55	3.26 ± 1.31	0.51	3.13 ± 1.63	3.26 ± 1.31	0.68
CHA_2DS_2-VASc score	4.81 ± 1.66	4.56 ± 1.92	4.82 ± 1.65	0.51	4.69 ± 1.99	4.81 ± 1.65	0.76
Laboratory data							
BNP (pg/ml)	635 (337, 1217)	572 (348, 1092)	643 (336, 1219)	0.93	492 (345, 1004)	646 (336, 1222)	0.57
hs TnT (ng/ml)	0.04 (0.02, 0.08)	0.09 (0.04, 1.53)	0.04 (0.02, 0.08)	0.004	0.07 (0.03, 0.21)	0.04 (0.02, 0.08)	0.032
Sodium (mEq/L)	139 ± 4	138 ± 4	139 ± 4	0.18	138 ± 4	139 ± 4	0.21
eGFR (ml/min/1.73m^2)	62.8 ± 30.6	61.8 ± 28.8	62.8 ± 30.7	0.89	64.0 ± 29.3	62.8 ± 30.7	0.87
Hemoglobin (g/dl)	11.9 ± 2.2	12.2 ± 1.8	11.9 ± 2.2	0.56	12.2 ± 1.9	11.9 ± 2.2	0.54
Total bilirubin (mg/dl)	0.7 (0.5, 1.1)	0.7 (0.4, 1.2)	0.7 (0.5, 1.1)	0.72	0.7 (0.4, 1.2)	0.7 (0.5, 1.1)	0.51
Albumin (mg/dl)	3.7 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	0.12	3.6 ± 0.4	3.7 ± 0.4	0.23
Fibrinogen (mg/dl)	364 ± 105	380 ± 145	363 ± 103	0.57	362 ± 134	363 ± 104	0.97
TAT (ng/ml)	2.4 (1.4, 4.9)	4.0 (1.9, 15.2)	2.4 (1.4, 4.9)	0.081	3.3 (1.7, 13.0)	2.4 (1.4, 4.9)	0.25
D-dimer (μg/ml)	2.1 (1.1, 4.1)	3.9 (1.9, 11.2)	2.0 (1.1, 4.1)	0.009	3.7 (1.8, 9.9)	2.1 (1.1, 4.2)	0.045
D-dimer ≥1.0 μg/ml (above normal limit)	586 (81%)	18 (100%)	568 (81%)	0.033	16 (100%)	570 (81%)	0.053

Continuous variables are presented as mean ± standard deviation if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).
ACE-I indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome, AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASO, arteriosclerosis obliterans; BNP, B-type natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HF, heart failure; hs TnT, high-sensitive troponin T; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NICM, non-ischemic cardiomyopathy; NYHA, New York Heart Association; OMI, old myocardial infarction; TAT, thrombin-antithrombin complex; TIA, transient ischemic attack; VTE, venous thromboembolism.

Supplemental Table II. Multivariable Logistic Regression Analysis, Adjusted by Major Confounders

	Model 1*		Model 2†		Model 3‡		Model 4§		Model 5||	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
In-hospital Ischemic Stroke										
D-dimer, log	2.18 (1.41-3.40)	<0.001	2.31 (1.42-3.80)	0.001	2.14 (1.37-3.37)	<0.001	2.19 (1.41-3.42)	<0.001	2.14 (1.37-3.36)	0.001
D-dimer ≥3.5 μg/ml (according to ROC curve analysis)	3.51 (1.36-9.65)	0.009	4.03 (1.37-13.28)	0.014	3.47 (1.35-9.56)	0.010	3.56 (1.38-9.81)	0.009	3.39 (1.31-9.36)	0.012
30-day Ischemic Stroke										
D-dimer, log	1.98 (1.24-3.14)	0.005	2.26 (1.36-3.76)	0.002	1.97 (1.23-3.16)	0.006	1.99 (1.24-3.15)	0.005	1.98 (1.23-3.13)	0.005
D-dimer ≥3.5 μg/ml (according to ROC curve analysis)	2.84 (1.05-8.05)	0.041	3.55 (1.17-11.90)	0.026	2.83 (1.04-8.03)	0.042	2.88 (1.06-8.17)	0.038	2.85 (1.05-8.06)	0.041

*Adjusted for history of venous thromboembolism; †Adjusted for active infection on admission; ‡Adjusted for history of malignancy; §Adjusted for history of cardiac surgery (valve replacement and/or coronary artery bypass grafting); ||Adjusted for acute coronary syndrome on admission.
CI indicates confidence interval; OR, odds ratio; ROC, receiver-operating characteristics.

Supplemental Table III. Impact of D-dimer Level on Short-term Ischemic Stroke Events Accounting for Competing Risk of Death

	Model 1*		Model 2†		Model 3‡		Model 4§	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
In-hospital Ischemic Stroke								
D-dimer, log	2.24 (1.57-3.20)	<0.001	2.47 (1.64-3.73)	0.001	2.35 (1.56-3.52)	<0.001	2.06 (1.49-2.84)	<0.001
D-dimer ≥3.5 μg/ml (according to ROC curve analysis)	4.43 (1.64-11.97)	0.003	4.73 (1.79-12.49)	0.002	4.62 (1.65-12.98)	0.004	4.39 (1.47-13.11)	0.008
30-day Ischemic Stroke								
D-dimer, log	1.69 (1.01-2.86)	0.048	2.10 (1.25-3.54)	0.005	1.83 (0.99-3.38)	0.051	2.08 (1.10-3.93)	0.025
D-dimer ≥3.5 μg/ml (according to ROC curve analysis)	3.16 (1.01-9.93)	0.048	4.79 (1.52-15.06)	0.007	3.57 (1.01-12.62)	0.048	4.72 (1.40-15.85)	0.012

* Unadjusted.
† Adjusted for major confounders; age, atrial fibrillation, and antithrombotic therapy (oral anticoagulant and aspirin).
‡ Adjusted for CHA_2DS_2-VASc score.
§ Adjusted for clinical variables which were associated with the ischemic stroke events in univariable analysis, and were as follows; use of loop diuretic, use of aspirin, and high-sensitive troponin T for in-hospital ischemic stroke, and use of loop diuretic and high-sensitive troponin T for 30-day ischemic stroke.
CI indicates confidence interval; HR, hazard ratio; ROC, receiver-operating characteristics.

Supplemental Figure I: Receiver-operating characteristics curve analysis