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Higher risk of deep vein thrombosis after hemorrhagic stroke than after acute ischemic stroke

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Patients with stroke are at particularly increased risk of developing deep vein thrombosis (DVT) during hospitalization. In this study, we aimed to compare the potential risk of in-hospital DVT by stroke subtypes. This study is based on a prospective cohort (in-hospital medical complication after acute stroke [iMCAS] registry) enrolling patients with acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). In-hospital DVT was diagnosed by clinical manifestations and verified by compression Doppler ultrasound. A logistic regression analysis was performed to assess the association between stroke subtypes and occurrence of DVT. A total number of 1,771 patients were enrolled in the iMCAS. The mean age was 57.1 ± 12.9 years, and 27.5% were female patients. The median length of stay was 14 days (interquartile range [IQR], 11–16). The median National Institutes of Health Stroke Scale score on admission for patients with AIS, ICH, and SAH was 4 (IQR: 2–8), 4 (IQR:1–10), and 0 (IQR:0–0), respectively. In-hospital DVT after AIS, ICH, and SAH was 1.9%, 5.7%, and 7.9%, respectively. The median time from stroke onset to DVT formation after AIS, ICH, and SAH was 10.5 days (IQR: 3.8–14.5), 7.5 days (IQR:4.0–9.5), and 7.0 days (IQR:5.0–12.5), respectively. After adjusting for potential confounders, patients with ICH (odds ratio = 7.350; 95% confidence interval = 2.411–22.13; P *< .001) and SAH (odds ratio = 11.92; 95% confidence interval = 5.192–27.38;* P *< .001) had significantly higher risk of in-hospital DVT than those patients with AIS. In conclusion, patients with hemorrhagic stroke (ICH and SAH) have significantly higher risk of in-hospital DVT than patients with AIS. Further studies on pathophysiologic mechanisms are warranted.* (J Vasc Nurs 2018;37:18-27)

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Venous thromboembolism (VTE) is common in hospitalized patients and associates with significant morbidity, mortality, and health-care cost.[1] Deep vein thrombosis (DVT) is the most prevalent presentation, and pulmonary embolism (PE) is the most severe form of VTE.[1,2]

Patients with stroke are at particularly increased risk of developing VTE during hospitalization.[3,4] It is estimated that stroke patients who have hemiplegia and do not receive VTE prophylaxis have as high as 75% likelihood of developing DVT and a 20% chance of developing PE.[2] VTE is thought to be responsible for early deaths after stroke in about 25% of cases and is fatal in 1%–2% of cases with acute stroke.

Several studies have focused on DVT after acute ischemic stroke (AIS),[5–13] intracerebral hemorrhage (ICH),[6,8,9,14–20] and subarachnoid hemorrhage (SAH).[21–24] A few studies indicated that the incidence of DVT after ICH is higher than that after AIS.[14,15] However, there is lack of study to make a face-to-face comparison on potential risks of developing DVT by different stroke subtypes (AIS, ICH, and SAH). In addition, time course of DVT formation after stroke, especially for different stroke subtypes, remains poorly understood despite its contribution to mortality and morbidity. As a result, the optimal time of VTE prophylaxis and duration of therapy are uncertain.[25,26] The answers to these questions might be helpful for making individualized VTE prophylaxis strategies and improving stroke outcomes.

In this study, we sought to compare the incidence of DVT during acute hospitalization after AIS, ICH, and SAH and to clarify the time course of in-hospital DVT formation after AIS, ICH, and SAH. We hypothesized that patients with hemorrhagic stroke (ICH and SAH) would have a higher risk of DVT than patients with ischemic stroke (AIS).

METHODS

Study population

This study is based on a cohort (in-hospital medical complication after acute stroke [iMCAS]), which is a prospective registry of consecutive stroke patients admitted to the department of vascular neurology of Beijing Tiantan hospital. Briefly, the primary aim of the iMCAS was to compare the potential risk of common in-hospital medical complications by stroke subtypes (AIS, ICH, and SAH); to investigate potential interrelationship among common in-hospital medical complications by stroke subtypes; and to explore biomarkers and neuroimaging markers for common in-hospital medical complications after stroke. In the iMCAS, information on following medical complications after stroke was recorded: DVT, stroke-associated pneumonia, urinary tract infection, gastrointestinal bleeding, recurrent stroke, epileptic seizure, hydrocephalous, myocardial infarction, atrial fibrillation/flutter, heart failure, sepsis, PE, and decubitus ulcer. Definitions of these medical complications after stroke were in accordance with definitions used in other studies.[27–29] To be eligible for the iMCAS, subjects had to meet the following criteria: (1) aged 18 years or older; (2) hospitalized with a primary diagnosis of AIS, ICH, or SAH according to the World Health Organization (WHO) criteria[30]; (3) stroke confirmed by head computerized tomography and/or brain magnetic resonance imaging; (4) time from stroke onset to hospital admission was less than 7 days; and (5) written informed consent obtained from patients or their legal representatives. The iMCAS was approved by the ethics committee of Beijing Tiantan hospital.

Data collection and definitions

A Web-based standardized case report form was established for clinical data collection and data management. The relevant data were extracted from medical records by trained research coordinators. Data completeness, correct coding, and proper application of diagnostic algorithm were checked by a research specialist. For the present study, the following patient variables were analyzed: (1) demographics (age and gender); (2) stroke risk factors including hypertension (history of hypertension or antihypertensive medication use), diabetes mellitus (history of diabetes mellitus or antidiabetic medication use), dyslipidemia (history of dyslipidemia or lipid-lowering medication use), atrial fibrillation (history of atrial fibrillation or documentation of atrial fibrillation on admission), coronary heart disease, history of stroke/transient ischemic attack, and current smoking; (3) preexisting comorbidities such as congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, peripheral artery disease, hepatic cirrhosis, peptic ulcer, renal failure, arthritis, and cancer; (4) index vascular event (AIS, ICH, and SAH); (5) prestroke dependence (modified Rankin Scale score > 3); (6) admission stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) score; (7) admission Hunt-Hess scale score (the Hunt and Hess scale is one of the grading systems used to classify the severity of an SAH with a higher grade correlating to lower survival rate) and World Federation of Neurologic Surgeons (WFNS) scale score (The WFNS scale was proposed by the WFNS and is intended to be a simple, reliable, and clinically valid way to grade a patient with SAH); (8) systolic and diastolic blood pressure; (9) body mass index; (10) admission blood tests measuring white blood cell count (10^9/L), red blood cell count (10^{12}/L), hemoglobin (g/L), platelet count (10^9/L), triglyceride (mmol/L), total cholesterol (mmol/L), high-density lipoprotein (mmol/L), low-density lipoprotein (mmol/L), glucose (mmol/L) (mmol/L $\times$ 18 = mg/dL), and creatine (mmol/L); (11) antithrombotic agents administered within 48 hours of admission; (12) VTE prophylaxis (anticoagulation [unfractionated heparin, low-molecular-weight heparin, warfarin, or non–vitamin K antagonist oral anticoagulants], intermittent pneumatic compression, or both); (13) time from stroke onset to hospital admission (days); and (14) length of hospital stay (LOS) (days).

Assessment of DVT

In the iMCAS, DVT was diagnosed by treating physicians based on clinical manifestations (such as swelling, pitting edema, redness, tenderness, and presence of collateral superficial veins and others) and verified by sequential compression Doppler ultrasound. Only DVTs that developed after hospital admission were counted. Time of initial ultrasound detecting DVT formation was recorded.

Statistical analysis

Continuous variables were summarized with mean and standard deviation or median and interquartile range (IQR). Categorical variables were summarized as proportions. In univariate analysis, chi-square or Fisher's exact test was used to compare categorical variables, and Mann-Whitney test was used to compare continuous variables. In multivariate analysis, logistic regression was performed to assess the association between stroke subtypes (AIS, ICH, and SAH) and occurrence of DVT and adjusted for demographics, stroke risk factors, preexisting comorbidities, prestroke dependence, admission NIHSS score, body mass index, admission blood pressure, blood tests, antithrombotic agents administered within 48 hours after admission, VTE prophylaxis, and LOS. All tests were two-tailed, and statistical significance was determined at α level of 0.05. Statistical analysis was performed using SAS 9.1 and SPSS 17.0.

RESULTS

Patient characteristics

Patient characteristics are shown in Tables 1 and 2. From January 20 to December 2016, a total of 1,771 patients (1,129 of AIS, 314 of ICH, and 328 of SAH) were enrolled in the iMCAS. The mean age was 57.1 $\pm$ 12.9 years, and 27.5% were female patients. The median LOS was 14 days (IQR, 11–16). The median NIHSS score on admission for patients with AIS, ICH, and SAH was 4 (IQR: 2–8), 4 (IQR:1–10), and 0 (IQR:0–0), respectively. The median Hunt-Hess scale score and WFNS scale score for patients with SAH were 2 (IQR:1–2) and 1 (IQR:1–1), respectively. Sixty-six (3.7%) of 1,771 patients were diagnosed with DVT, and only one patient (0.1%) developed symptomatic PE during hospitalization. In-hospital DVT was more frequent among older patients; female patients; patients who present a history of atrial fibrillation; noncurrent smokers; and patients with renal failure, index vascular event of ICH and SAH, higher level of admission white blood cell count, high-density lipoprotein and glucose, lower level of admission red blood cell count and hemoglobin, lower rate of antithrombotic agents administered within 48 hours after admission, higher rate of VTE prophylaxis, and longer hospital stay (Table 2).

TABLE 1

PATIENT CHARACTERISTICS STRATIFIED BY STROKE SUBTYPES

	AIS (N = 1,129)	*ICH (N = 314)*	*SAH (N = 329)*	**P** *value*
Demographics, n (%)				
Age, mean (SD)	58.7 ± 12.5	54.7 ± 14.2	54.2 ± 12.3	**<.001**
Gender (male)	230 (20.4)	93 (29.6)	164 (50.0)	**<.001**
Stroke risk factors, n (%)				
Hypertension	755 (66.9)	208 (66.2)	184 (56.1)	**.001**
Diabetes mellitus	341 (30.2)	41 (13.1)	29 (8.8)	**<.001**
Dyslipidemia	206 (18.2)	36 (11.5)	28 (8.5)	**<.001**
Atrial fibrillation	69 (6.1)	10 (3.2)	3 (0.9)	**<.001**
Coronary artery disease	151 (13.4)	26 (8.3)	20 (6.1)	**<.001**
History of stroke/TIA	266 (23.5)	48 (15.3)	30 (9.1)	**<.001**
Current smoking	628 (55.6)	120 (38.2)	118 (35.9)	**<.001**
Comorbidities, n (%)				
Congestive heart failure	6 (0.5)	3 (1.0)	0 (0.0)	.23
Valvular heart disease	10 (0.9)	2 (0.6)	1 (0.3)	.54
Chronic obstructive pulmonary disease	26 (2.3)	9 (2.9)	6 (1.8)	.68
Peripheral artery disease	8 (0.7)	0 (0.0)	0 (0.0)	.10
Hepatic cirrhosis	17 (1.5)	3 (1.0)	4 (1.2)	.73
Peptic ulcer	21 (1.9)	3 (1.0)	6 (1.8)	.53
Renal failure	7 (0.6)	2 (0.6)	1 (0.3)	.78
Arthritis	16 (1.4)	5 (1.6)	0 (0.0)	.09
Cancer	14 (1.2)	3 (1.0)	4 (1.2)	.92
Prestroke dependence (mRS ≤ 2), n (%)	1,110 (98.4)	309 (98.4)	324 (99.1)	.66
Admission NIHSS score, median (IQR)	4 (2–8)	4 (1–10)	0 (0–0)	**<.001**
Admission Hunt-Hess score	—	—	2 (1–2)	—
Admission WFNS score	—	—	1 (1–1)	—
Etiology, n (%)				
Large artery atherosclerosis	936 (82.9)	—	—	
Small vessel disease	13 (1.2)	—	—	
Cardioembolism	109 (10.0)	—	—	
Other determined etiology	19 (1.7)	—	—	
Undetermined etiology	52 (4.6)	—	—	
Primary intracerebral hemorrhage	—	277 (88.2)	—	
Secondary intracerebral hemorrhage	—	34 (10.8)	—	
Aneurysm subarachnoid hemorrhage	—	—	241 (73.3)	
Nonaneurysm subarachnoid hemorrhage	—	—	88 (26.7)	
Admission SBP (mm Hg), median (IQR)	151 (136–167)	158 (140–171)	148 (135–162)	**<.001**
Admission DBP (mm Hg), median (IQR)	87 (79–98)	93 (83–104)	89 (80–97)	**<.001**
BMI (kg/m^2), median (IQR)	25.2 (25.2–29.4)	25.2 (21.0–29.4)	25.2 (21.0–25.2)	**<.001**
Blood test				
WBC, (10^9/L), median (IQR)	7.38 (6.11–9.01)	8.83 (7.34–11.0)	10.0 (8.07–11.8)	**<.001**
RBC, (10^{12}/L), median (IQR)	4.61 (4.28–4.95)	4.81 (4.50–5.17)	4.51 (4.22–4.89)	**<.001**

(*Continued*)

TABLE 1

CONTINUED

	AIS (N = 1,129)	ICH (N = 314)	SAH (N = 329)	P value
HGB, (mmol/L), median (IQR)	142 (132–153)	148 (139–159)	139 (127–149)	**<.001**
Platelet, (10^9/L), median (IQR)	209 (175–245)	219 (187–254)	213 (180–245)	**.03**
TG, (mmol/L), median (IQR)	1.30 (0.96–1.76)	1.34 (1.01–1.85)	1.32 (1.02–1.75)	.32
TC, (mmol/L), median (IQR)	3.97 (3.38–4.68)	4.75 (4.11–5.46)	4.82 (4.30–5.58)	**<.001**
LDL, (mmol/L), median (IQR)	2.48 (1.88–3.06)	3.09 (2.46–3.70)	3.07 (2.47–3.68)	**<.001**
HDL, (mmol/L), median (IQR)	0.98 (0.85–1.16)	1.14 (1.00–1.36)	1.32 (1.10–1.50)	**<.001**
Glucose, (mmol/L), median (IQR)	5.07 (4.41–6.89)	5.04 (4.37–6.07)	5.15 (4.49–6.18)	.25
Creatine, (mmol/L), median (IQR)	64.9 (55.5–74.6)	61.7 (52.1–72.1)	51.0 (42.0–61.6)	**<.001**
Antiplatelet agents within administered 48 h after admission, n (%)	1,098 (97.3)	0 (0.0)	102 (31.0)	**<.001**
VTE prophylaxis during hospitalization, n (%)	715 (63.3)	198 (63.1)	207 (63.1)	.99
Time from onset to admission (d), median (IQR)	3 (1–5)	3 (1–4)	2 (1–3)	**<.001**
Length of hospital stay (d), median (IQR)	14 (11–16)	14 (12–18)	14 (11–18)	**<.001**
DVT, n (%)	22 (1.9)	18 (5.7)	26 (7.9)	**<.001**

AIS = acute ischemic stroke; BMI = body mass index; DBP = diastolic blood pressure; DVT = deep vein thrombosis; HDL = high-density lipoprotein; HGB = hemoglobin; ICH = intracerebral hemorrhage; IQR = interquartile range; LDL = low-density lipoprotein; mRS = modified rankin scale; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; RBC = red blood cell; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; TIA = transient ischemic attack; VTE = venous thromboembolism; WBC = white blood cell; WFNS = World Federation of Neurologic Surgeons.

Bolded values indicates that there is a significant difference between two groups (P < .001).

Time course of DVT formation stratified by stroke subtypes

Time course from stroke onset and hospital admission to initial ultrasound detecting DVT formation is shown in Table 3. The median time from stroke onset to DVT formation after AIS, ICH, and SAH was 10.5 days (IQR: 3.8–14.5), 7.5 days (IQR: 4.0–9.5), and 7.0 days (IQR: 5.0–12.5), respectively. The median time from hospital admission to DVT formation after AIS, ICH, and SAH was 5.0 days (IQR: 2.0–9.5), 4.0 days (IQR: 1.0–7.2 days), and 5.5 days (IQR: 3.0–10.0 days), respectively. Although there is a trend that time from stroke onset and hospital admission to DVT formation was shorter among patients with ICH and SAH than that among patients with AIS, it was not statistically significant (All $P > .05$).

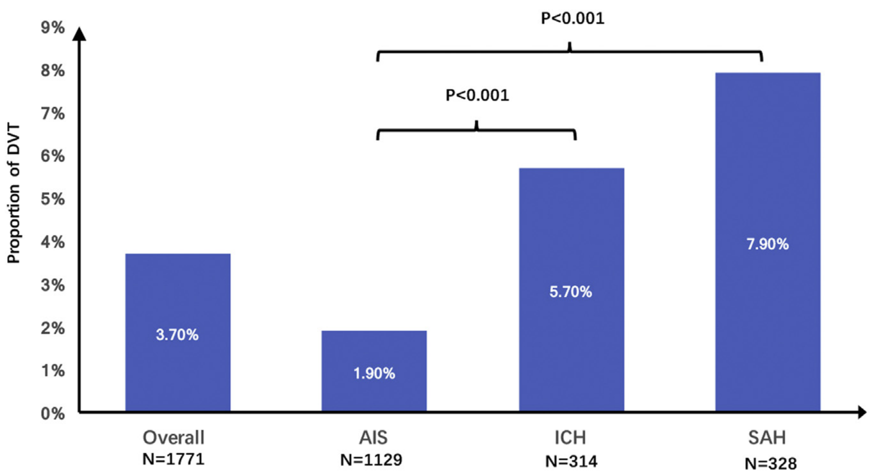

Figure 1. *Proportion of in-hospital deep vein thrombosis (DVT) stratified by stroke subtypes. In-hospital DVT after AIS, ICH, and SAH was 1.9%, 5.7%, and 7.9%, respectively. In-hospital DVT rate was significantly higher among patients with ICH (5.7% vs 1.9%;* P < .001*) and SAH (7.9% vs 1.9%;* P < .001*) than that among patients with AIS. AIS = acute ischemic stroke; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage.*

TABLE 2

PATIENT CHARACTERISTICS STRATIFIED BY OCCURRENCE OF VTE

	All (N = 1,771)	*Without VTE (N = 1,705)*	*With VTE (N = 66)*	**P** *value*
Demographics, n (%)				
Age, mean ± SD	57.1 ± 12.9	56.9 ± 12.9	62.4 ± 12.9	**.001**
Gender (female)	487 (27.5)	453 (26.6)	34 (51.5)	**<.001**
Stroke risk factors, n (%)				
Hypertension	1,147 (64.8)	1,104 (64.8)	43 (65.2)	.95
Diabetes mellitus	411 (23.2)	399 (23.4)	12 (18.2)	.32
Dyslipidemia	270 (15.2)	263 (15.4)	7 (10.6)	.29
Atrial fibrillation	82 (4.6)	75 (4.4)	7 (10.6)	.02
Coronary artery disease	197 (11.1)	185 (10.9)	12 (18.2)	.06
History of stroke/TIA	344 (19.4)	334 (19.6)	9 (13.6)	.23
Current smoking	866 (48.9)	854 (50.1)	12 (18.2)	**<.001**
Comorbidities, n (%)				
Congestive heart failure	9 (0.5)	9 (0.5)	0 (0.0)	.55
Valvular heart disease	13 (0.7)	12 (0.7)	1 (1.5)	.45
Chronic obstructive pulmonary disease	41 (2.3)	38 (2.2)	3 (4.5)	.22
Peripheral artery disease	8 (0.5)	7 (0.4)	1 (1.5)	.19
Hepatic cirrhosis	24 (1.4)	23 (1.3)	1 (1.5)	.91
Peptic ulcer	30 (1.7)	28 (1.6)	2 (3.0)	.39
Renal failure	10 (0.6)	8 (0.5)	2 (3.0)	.01
Arthritis	21 (1.2)	21 (1.2)	0 (0.0)	.36
Cancer	21 (1.2)	20 (1.2)	1 (1.5)	.80
Index vascular event				**<.001**
Acute ischemic stroke, n (%)	1,129 (63.7)	1,107 (64.9)	22 (33.3)	
Intracerebral hemorrhage, n (%)	314 (17.7)	296 (17.4)	18 (27.3)	
Subarachnoid hemorrhage, n (%)	328 (18.5)	302 (17.7)	26 (39.4)	
Prestroke dependence (mRS ≥ 3), n (%)	26 (1.5)	25 (1.5)	1 (1.5)	.98
Admission NIHSS score, median (IQR)	3 (1–7)	3 (1–7)	4 (0–12)	.36
Admission SBP (mm Hg), median (IQR)	151 (136–167)	151 (137–167)	153 (131–168)	.73
Admission DBP (mm Hg), median (IQR)	89 (80–99)	89 (80–99)	87 (78–97)	.33
BMI (kg/m^2), median (IQR)	25.2 (21.0–29.4)	25.2 (21.0–29.4)	25.2 (21.0–29.4)	.40
Blood test				
WBC, (10^9/L), median (IQR)	8.06 (6.45–10.1)	8.03 (6.43–10.3)	9.34 (7.42–11.8)	**<.001**
RBC, (10^{12}/L), median (IQR)	4.63 (4.30–4.97)	4.64 (4.30–4.98)	4.50 (4.15–4.76)	**.03**
HGB, (mmol/L), median (IQR)	143 (132–153)	143 (132–154)	138 (129–145)	**.008**
Platelet, (10^9/L), median (IQR)	212 (178–247)	211 (178–247)	230 (186–258)	.07
TG, (mmol/L), median (IQR)	1.31 (0.98–1.78)	1.31 (0.99–1.78)	1.24 (0.86–1.65)	.10
TC, (mmol/L), median (IQR)	4.28 (3.62–5.05)	4.28 (3.62–5.06)	4.38 (3.65–5.12)	.50
LDL, (mmol/L), median (IQR)	2.66 (2.06–3.34)	2.66 (2.06–3.34)	2.68 (1.91–3.28)	.94
HDL, (mmol/L), median (IQR)	1.06 (0.90–1.28)	1.05 (0.89–1.27)	1.20 (0.95–1.51)	**.002**
Glucose, (mmol/L), median (IQR)	5.08 (4.41–6.46)	5.05 (4.40–6.45)	5.68 (4.84–7.54)	**.001**
Creatine, (mmol/L), median (IQR)	61.8 (51.6–72.1)	61.9 (51.9–72.1)	56.7 (45.0–74.2)	.08

(*Continued*)

TABLE 2

CONTINUED

	All (N = 1,771)	*Without VTE (N = 1,705)*	*With VTE (N = 66)*	P *value*
Antithrombotic agents within administered 48 h of admission, n (%)	1,200 (67.8)	1,167 (68.4)	33 (50%)	**.002**
DVT prophylaxis within 48 h of admission, n (%)	1,120 (63.2)	1,067 (62.6)	53 (80.3)	**.003**
Time from onset to admission (d), median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	.15
Length of hospital stay (d), median (IQR)	14 (11–16)	14 (11–16)	17 (12–26)	**<.001**

BMI = body mass index; DBP = diastolic blood pressure; DVT = deep vein thrombosis; HDL = high-density lipoprotein; HGB = hemoglobin; IQR = interquartile range; LDL = low-density lipoprotein; mRS = modified rankin scale; NIHSS = National Institutes of Health Stroke Scale; RBC = red blood cell; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG, triglyceride; TIA, transient ischemic attack; VTE = venous thromboembolism; WBC = white blood cell.

Bolded values indicates that there is a significant difference between two groups (P < .001).

Incidence of DVT stratified by stroke subtypes

Incidence of in-hospital DVT stratified by stroke subtypes is shown in Figure 1. In-hospital DVT rate after AIS, ICH, and SAH was 1.9%, 5.7%, and 7.9%, respectively. In-hospital DVT rate was significantly higher among patients with ICH (5.7% vs 1.9%; $P < .001$) and SAH (7.9% vs 1.9%; $P < .001$) than that among patients with AIS (Figure 1).

Association between stroke subtypes and occurrence of VTE

The association between stroke subtypes and the occurrence of in-hospital DVT is shown in Table 4. In unadjusted analysis, patients with ICH (odds ratio [OR] = 3.060; 95% confidence interval [CI] = 1.620–5.780; $P < .001$) and SAH (OR = 4.332; 95% CI = 2.421–7.752; $P < .001$) had significantly higher risk of in-hospital DVT than those patients with AIS. After adjusting for all potential confounders, patients with ICH (OR = 7.350; 95% CI = 2.411–22.13; $P < .001$) and SAH (OR = 11.92; 95% CI = 5.192–27.38; $P < .001$) still had significantly higher risk of in-hospital DVT than those patients with AIS (Table 4).

Risk factors for in-hospital DVT after acute stroke

Multivariate analysis data for risk factors of in-hospital DVT after acute stroke are shown in Table 5. Age ($P = .02$), current smoking ($P < .001$), index vascular event of ICH ($P < .001$) and SAH ($P < .001$), admission NIHSS score ($P = .003$), antithrombotic agents administered within 48 hours after admission ($P = .02$), and LOS ($P < .001$) were identified as independent predictors of in-hospital DVT after acute stroke. C-statistic of the model was 0.837 (Table 5).

DISCUSSION

In the present study, we aimed to compare the potential risk of in-hospital DVT by stroke subtypes (AIS, ICH, and SAH). It was found that patients with ICH had a 7.35-fold and those with SAH had an 11.9-fold greater risk of developing in-hospital DVT than patients with AIS. The highest risk of DVT formation was within the first 2 weeks, especially the first weeks after onset. Age, current smoking, stroke subtypes, admission NIHSS score, antithrombotic agents administered within 48 hours after admission, and LOS were identified as independent predictors of in-hospital DVT after stroke.

The time course of DVT formation after stroke, especially for different stroke subtypes, remains poorly understood despite its contribution to mortality and morbidity. As a result, optimal time of VTE prophylaxis and duration of therapy are uncertain. In the study, it was found that the median time from stroke onset to DVT formation after AIS, ICH, and SAH was 10.5 days (IQR: 3.8–14.5), 7.5 days (IQR: 4.0–9.5), and 7.0 days (IQR: 5.0–12.5), respectively. These data indicated that three quarters of in-hospital DVT occurred within the first 2 weeks, and one half developed around the first week after onset. In addition, there was a trend that in-hospital DVT formation was earlier among patients with hemorrhagic stroke (ICH and SAH) than that among patients with AIS. It is helpful to take these kinds of information into account when making individualized VTE prophylaxis strategies after stroke.

Clarifying the potential risk of DVT by stroke subtypes will be an important step toward determining the most effective and safest prophylaxis strategies. A prior study has shown higher incidence of DVT in patients with hemorrhagic stroke than in patients with ischemic stroke.[14,15] However, these studies were based on either the National Hospital Discharge Survey[15] or Maryland Health Services Cost Review Commission data base.[14] Relevant information on important confounders, such as antithrombotic therapy and NIHSS score, was not collected. To the best of our knowledge, we are the first to make a systematic face-to-face comparison on the potential risk of in-hospital DVT by three different stroke subtypes (AIS, ICH, and SAH). After adjusting for potential confounders (including antithrombotic therapy and NIHSS score), it was shown that patients with ICH had a 7.35-fold and SAH 11.9-fold greater risk of in-hospital DVT than patients with AIS (Table 4). These data point

TABLE 3

TIMING OF IN-HOSPITAL DVT FORMATION STRATIFIED BY STROKE SUBTYPES (N = 66)

	Time From Stroke Onset to DVT Detection (D)		*Time From Admission to DVT Detection (D)*	
	Mean ± SD	***Median (IQR)***	***Mean ± SD***	***Median (IQR)***
AIS cohort	12.3 ± 11.1	10.5 (3.8–14.5)	7.7 ± 9.7	5.0 (2.0–9.5)
ICH cohort	8.0 ± 5.6	7.5 (4.0–9.5)	5.8 ± 6.1	4.0 (1.0–7.2)
SAH cohort	8.4 ± 4.9	7.0 (5.0–12.5)	6.7 ± 5.0	5.5 (3.0–10.0)

AIS = acute ischemic stroke; DVT = deep vein thrombosis; ICH = intracerebral hemorrhage; IQR = interquartile range; SAH = subarachnoid hemorrhage; SD = standard deviation.

out the need for more aggressive VTE prophylaxis among patients with ICH and SAH than in patients with AIS. It is more significant for ICH management because that treatment for ICH remains strictly supportive with not many evidence-based interventions currently available. According to the American Heart Association/American Stroke Association guidelines for ICH management, patients with ICH should have intermittent pneumatic compression for prevention of VTE from the day of hospital admission (class I; level of evidence, A). After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-

TABLE 4

ASSOCIATION BETWEEN STROKE SUBTYPES AND OCCURRENCE OF IN-HOSPITAL VTE (N = 1,771)

	Category	*OR*	*95% CI*	*P*
Unadjusted model	ICH vs AIS	3.060	1.620–5.780	<.001
	SAH vs AIS	4.332	2.421–7.752	<.001
Adjusted models				
Model 1	ICH vs AIS	3.310	1.732–6.325	<.001
	SAH vs AIS	4.387	2.354–8.173	<.001
Model 2	ICH vsAIS	3.186	1.609–6.307	<.001
	SAH vs AIS	4.537	2.313–8.900	<.001
Model 3	ICH vs AIS	3.090	1.544–6.186	.001
	SAH vs AIS	6.606	3.224–13.53	<.001
Model 4	ICH vs AIS	3.867	1.723–8.682	.001
	SAH vs AIS	7.227	2.966–17.61	<.001
Model 5	ICH vs AIS	7.305	2.411–22.13	<.001
	SAH vs AIS	11.92	5.192–27.38	<.001

AIS = acute ischemic stroke; BMI = body mass index; CI = confidence interval; DVT = deep vein thrombosis; HDL = high-density lipoprotein; HGB = hemoglobin; ICH = intracerebral hemorrhage; LDL = low-density lipoprotein; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; SAH = subarachnoid hemorrhage; TC = total cholesterol; TG, triglyceride; TIA, transient ischemic attack; VTE = venous thromboembolism; WBC = white blood cell.

Model 1 adjusted for demographics (age and gender).

Model 2 adjusted for demographics, stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, history of stroke/TIA, and current smoking), comorbidities (congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, peripheral artery disease, hepatic cirrhosis, peptic ulcer or previous gastrointestinal bleeding, renal failure, arthritis, dementia, and cancer), and prestroke dependence (mRS > 3).

Model 3 adjusted for demographics, stroke risk factors, comorbidities, prestroke dependence, and admission NIHSS score.

Model 4 adjusted for demographics, stroke risk factors, comorbidities, prestroke dependence, admission NIHSS score, BMI, admission blood pressure, and admission blood tests (WBC, HGB, platelet, TG, TC, LDL, HDL, glucose, and creatine).

Model 5 adjusted for demographics, stroke risk factors, comorbidities, prestroke dependence, admission NIHSS score, BMI, admission blood pressure, blood tests, antiplatelet agents administered within 48 hours after admission, DVT prophylaxis, and length of hospital stay.

TABLE 5

MULTIVARIATE ANALYSIS OF RISK FACTORS FOR IN-HOSPITAL DVT AFTER ACUTE STROKE (N = 1,771)

	B	*SE*	*OR*	*95% CI*	P
Age (per year increase)	0.0264	0.0115	1.027	1.004–1.050	.02
Current smoking (yes)	−1.3490	0.4028	0.260	0.118–0.572	<.001
Index vascular event					
Acute ischemic stroke	—	—	1.000	—	—
Intracerebral hemorrhage	1.9885	0.5656	7.305	2.411–22.13	<.001
Subarachnoid hemorrhage	2.4784	0.4241	11.92	5.192–27.38	<.001
Admission NIHSS score (per score increase)	0.0594	0.0199	1.061	1.021–1.103	.003
Antithrombotic agents administered within 48 h of admission (yes)	−0.9631	0.4297	0.382	0.164–0.886	.02
Length of stay (per day increase)	0.0696	0.0161	1.072	1.039–1.106	<0.0001
c-statistic	0.837				

BMI = body mass index; CI = confidence interval; DVT = deep vein thrombosis; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; SE = standard error.

Adjusted for demographics, stroke risk factors, comorbidities, prestroke dependence, admission NIHSS score, BMI, admission blood pressure, blood tests, antithrombotic agents administered within 48 hours after admission, DVT prophylaxis, and length of hospital stay.

Probability of in-hospital DVT is calculated by $P = e^Y/(1 + e^Y)$, where $Y = a + b_1X_1 + b_2X_2 + \ldots + b_iX_i$.

weight heparin or unfractionated heparin may be considered for prevention of VTE in patients with lack of mobility after 1 to 4 days from onset (class IIb; level of evidence, B). Further studies focusing on the optimal time of initiating the anticoagulation therapy, type and dosage of anticoagulation medications, and duration of treatment for VTE prophylaxis for hemorrhagic stroke (ICH and SAH) are warranted.[19]

Potential mechanisms underlying the phenomenon that hemorrhagic stroke (ICH and SAH) has a significantly higher risk of developing in-hospital DVT than AIS are unclear. One might argue that it was due to the higher rate of antithrombotic therapy among patients with ischemic stroke and more severe neurological deficit for patients with hemorrhagic stroke. In this study, we systematically adjusted for demographics, stroke risk factors, coexisting comorbidities, admission NIHSS score, antithrombotic therapy, VTE prophylaxis, and LOS when investigating the association between stroke subtypes and occurrence of in-hospital DVT (Table 3). It is interesting that patients with SAH had the lowest level of focal neurological deficit measured with NIHSS score at admission (Table 1); however, they had the highest risk of in-hospital DVT after onset. Together, these data indicated that besides traditional risk factors of developing DVT after stroke, such as paralysis or hemiparesis, there might be some other predisposing factors. Previous studies have suggested that there would be a sequential response involving activation of the coagulation cascade, platelet plug formation, and upregulation of endogenous defense mechanisms after hemorrhagic stroke.[31–34] We speculated that activation of an endogenous coagulation system might play an important role in increasing the risk of in-hospital DVT after hemorrhagic stroke compared with after ischemic stroke. Hemostasis, a defense system to maintain the integrity of the circulatory system, occurs through a process of blood clotting and subsequent dissolving of the clot after repair of the injured tissue. In the setting of hemorrhagic stroke, hemostasis would be a protector of brain from rebleeding; however, it might be a potential risk factor for developing DVT in peripheral venous circulation at the same time. Pathophysiologic mechanisms on higher risk of in-hospital DVT after hemorrhagic stroke than after ischemic stroke need to be further investigated.

Currently, there is a lack of evidence-based method for predicting the potential risk of DVT after stroke. Prior studies have indicated several factors associated with the occurrence of DVT, such as age,[11,17,23,35] smoking,[22,35–37] congestive heart failure,[23,35] obesity,[11,23,35] severity of paralysis,[5,8,11,17,23,38] dehydration,[35,39] prothrombotic state,[1,23] malignancy,[11] kidney disease,[40] and LOS.[22,24] Consistent with these studies, we confirmed that age, current smoking, index vascular event of ICH and SAH, admission NIHSS score, antithrombotic agents administered within 48 hours after admission, and LOS were independent predictors of in-hospital DVT after stroke. C-statistics of the model for predicting in-hospital DVT was 0.837. It might be a useful tool to identify a population at high risk for developing in-hospital DVT after stroke. Further studies to validate the model in larger samples are warranted.

Limitations

Our study has limitations that deserve mention. First, similar to all observational studies, we cannot rule out the possibility that additional variables (unmeasured confounders) might have some impact on the potential risk of developing in-hospital DVT after stroke, such as markers of hemostatic activation. Second, detailed information on type, dosage, frequency, duration, and combination of different VTE prophylaxis treatments (chemical vs mechanical prophylaxis) was not recorded. In comparison with patients with ischemic stroke, hemorrhagic stroke patients are often not receiving antithrombotic therapy due to the risk of extending intracranial hemorrhage, and mechanical prophylaxis is the preferred choice. A prior study indicated that chemical prophylaxis is superior to mechanical prophylaxis for VTE prevention.[41] This might be, at least partially, a potential reason for the higher risk of in-hospital DVT among patients with hemorrhagic stroke than that among patients with ischemic stroke. Finally, our study included only hospitalized patients, and those patients died in emergency room or treated in outpatient clinics were not included. In addition, this study focused on the risk of DVT during acute hospitalization after stroke. It is important for further studies to clarify the potential risk of DVT in subacute and chronic phases by stroke subtypes.

CONCLUSION

In conclusion, patients with hemorrhagic stroke (ICH and SAH) have significantly higher risk of in-hospital DVT than patients with AIS. Further studies to clarify potential pathophysiological mechanisms underlying this phenomenon are warranted as it would pave ways to develop individualized VTE prophylaxis strategies and improve stroke outcome.

REFERENCES

1. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016;388:3060-73.
2. Goshgarian C, Gorelick PB. Dvt prevention in stroke. Curr Neurol Neurosci Rep 2017;17:81.
3. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol 2010;9:105-18.
4. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an evidence-based guideline: a statement for healthcare professionals from the neurocritical care society. Neurocrit Care 2016;24:47-60.
5. Sherman DG, Albers GW, Bladin C, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (prevail study): an open-label randomised comparison. Lancet 2007;369:1347-55.
6. Collaboration CTDennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (clots trial 1): a multicentre, randomised controlled trial. Lancet 2009;373:1958-65.
7. Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep-vein thrombosis and pulmonary embolism in patients with acute ischemic stroke? Thromb Res 2007;119:265-74.
8. Collaboration CT. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. Ann Intern Med 2010;153:553-62.
9. Collaboration CTDennis M, Sandercock P, Reid J, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (clots 3): a multicentre randomised controlled trial. Lancet 2013;382:516-24.
10. Douds GL, Hellkamp AS, Olson DM, et al. Venous thromboembolism in the get with the guidelines-stroke acute ischemic stroke population: incidence and patterns of prophylaxis. J Stroke Cerebrovasc Dis 2014;23:123-9.
11. Liu LP, Zheng HG, Wang DZ, et al. Risk assessment of deep-vein thrombosis after acute stroke: a prospective study using clinical factors. CNS Neurosci Ther 2014;20:403-10.
12. Li Z, Liu L, Wang Y, et al. Factors impact the adherence rate of prophylaxis for deep venous thrombosis in acute ischaemic stroke patients: an analysis of the china national stroke registry. Neurol Res 2015;37:427-33.
13. Rinde LB, Smabrekke B, Mathiesen EB, et al. Ischemic stroke and risk of venous thromboembolism in the general population: the Tromso study. J Am Heart Assoc 2016;5:e004311.
14. Gregory PC, Kuhlemeier KV. Prevalence of venous thromboembolism in acute hemorrhagic and thromboembolic stroke. Am J Phys Med Rehabil 2003;82:364-9.
15. Skaf E, Stein PD, Beemath A, et al. Venous thromboembolism in patients with ischemic and hemorrhagic stroke. Am J Cardiol 2005;96:1731-3.
16. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. Neurologist 2009;15:329-31.
17. Kim KS, Brophy GM. Symptomatic venous thromboembolism: incidence and risk factors in patients with spontaneous or traumatic intracranial hemorrhage. Neurocrit Care 2009;11:28-33.
18. Wu TC, Kasam M, Harun N, et al. Pharmacological deep vein thrombosis prophylaxis does not lead to hematoma expansion in intracerebral hemorrhage with intraventricular extension. Stroke 2011;42:705-9.
19. Masotti L, Godoy DA, Di Napoli M, et al. Pharmacological prophylaxis of venous thromboembolism during acute phase of spontaneous intracerebral hemorrhage: what do we know about risks and benefits? Clin Appl Thromb Hemost 2012;18:393-402.
20. Cherian LJ, Smith EE, Schwamm LH, et al. Current practice trends for use of early venous thromboembolism prophylaxis after intracerebral hemorrhage. Neurosurgery 2018;82:85-92.
21. Henwood PC, Kennedy TM, Thomson L, et al. The incidence of deep vein thrombosis detected by routine surveillance ultrasound in neurosurgery patients receiving dual modality prophylaxis. J Thromb Thrombolysis 2011;32:209-14.
22. Serrone JC, Wash EM, Hartings JA, et al. Venous thromboembolism in subarachnoid hemorrhage. World Neurosurg 2013;80:859-63.
23. Kshettry VR, Rosenbaum BP, Seicean A, et al. Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage. J Clin Neurosci 2014;21:282-6.
24. Liang CW, Su K, Liu JJ, et al. Timing of deep vein thrombosis formation after aneurysmal subarachnoid hemorrhage. J Neurosurg 2015;123:891-6.
25. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a

guideline for healthcare professionals from the american heart association/american stroke association. Stroke 2013; 44:870-947.

26. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke 2015;46:2032-60.
27. Weimar C, Roth MP, Zillessen G, et al. Complications following acute ischemic stroke. Eur Neurol 2002;48: 133-40.
28. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. Stroke 2000;31: 1223-9.
29. Ji R, Wang D, Shen H, et al. Interrelationship among common medical complications after acute stroke: pneumonia plays an important role. Stroke 2013;44:3436-44.
30. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the who task force on stroke and other cerebrovascular disorders. Stroke 1989; 20:1407-31.
31. Keep RF, Xi G, Hua Y, et al. Clot formation, vascular repair and hematoma resolution after ich, a coordinating role for thrombin? Acta Neurochir Suppl 2011;111:71-5.
32. Ebihara T, Kinoshita K, Utagawa A, et al. Changes in coagulative and fibrinolytic activities in patients with intracranial hemorrhage. Acta Neurochir Suppl 2006;96:69-73.
33. Miao W, Zhao K, Deng W, et al. Coagulation factor hyperfunction after subarachnoid hemorrhage induces deep venous thrombosis. World Neurosurg 2018;110:e46-52.
34. von der Brelie C, Subai A, Limperger V, et al. In vitro analysis of platelet function in acute aneurysmal subarachnoid haemorrhage. Neurosurg Rev 2018;41:531-53.
35. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107:I9.
36. Golomb BA, Chan VT, Denenberg JO, et al. Risk marker associations with venous thrombotic events: a cross-sectional analysis. BMJ Open 2014;4:e003208.
37. Mi Y, Yan S, Lu Y, et al. Venous thromboembolism has the same risk factors as atherosclerosis: a prisma-compliant systemic review and meta-analysis. Medicine (Baltimore) 2016;95:e4495.
38. Balogun IO, Roberts LN, Patel R, et al. Clinical and laboratory predictors of deep vein thrombosis after acute stroke. Thromb Res 2016;142:33-9.
39. Kelly J, Hunt BJ, Lewis RR, et al. Dehydration and venous thromboembolism after acute stroke. QJM 2004;97:293-6.
40. Cheung KL, Zakai NA, Folsom AR, et al. Measures of kidney disease and the risk of venous thromboembolism in the regards (reasons for geographic and racial differences in stroke) study. Am J Kidney Dis 2017;70:182-90.
41. Gaspard D, Vito K, Schorr C, et al. Comparison of chemical and mechanical prophylaxis of venous thromboembolism in nonsurgical mechanically ventilated patients. Thrombosis 2015;2015:849142.