Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8113-21
Intern Med 61: 801-810, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Characteristics of Ischemic Versus Hemorrhagic Stroke in Patients Receiving Oral Anticoagulants: Results of the PASTA Study

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Abstract:

Objective Limited data exist regarding the comparative detailed clinical characteristics of patients with ischemic stroke (IS)/transient ischemic attack (TIA) and intracerebral hemorrhage (ICH) receiving oral anticoagulants (OACs).

Methods The prospective analysis of stroke patients taking oral anticoagulants (PASTA) registry, a multicenter registry of 1,043 stroke patients receiving OACs [vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulant (NOACs)] across 25 medical institutions throughout Japan, was used. Univariate and multivariable analyses were used to analyze differences in clinical characteristics between IS/TIA and ICH patients with atrial fibrillation (AF) who were registered in the PASTA registry.

Results There was no significant differences in cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking, or alcohol consumption (all $p>0.05$), between IS/TIA and ICH among both NOAC and VKA users. Cerebral microbleeds (CMBs) [odds ratio (OR), 4.77; $p<0.0001$] were independently associated with ICH, and high brain natriuretic peptide/N-terminal pro B-type natriuretic peptide levels (OR, 1.89; $p=0.0390$) were independently associated with IS/TIA among NOAC users. A history of ICH (OR, 13.59; $p=0.0279$) and the high prothrombin time-international normalized ratio (PT-INR) (OR, 1.17; $p<0.0001$) were independently associated with ICH, and a history of IS/TIA (OR, 3.37; 95% CI, 1.34-8.49; $p=0.0101$) and high D-dimer levels (OR, 2.47; 95% CI, 1.05-5.82; $p=0.0377$) were independently associated with IS/TIA among VKA users.

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Received: June 8, 2021; Accepted: July 20, 2021; Advance Publication by J-STAGE: September 4, 2021

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Conclusion The presence of CMBs, a history of stroke, natriuretic peptide and D-dimer levels, and PT-INR may be useful for risk stratification of either IS/TIA or ICH development in patients with AF receiving OACs.

Key words: atrial fibrillation, intracerebral hemorrhage, ischemic stroke, non-vitamin K antagonist oral anticoagulant, vitamin K antagonist

(Intern Med 61: 801-810, 2022)
(DOI: 10.2169/internalmedicine.8113-21)

Introduction

Atrial fibrillation (AF)-related stroke and acute venous thromboembolism are associated with substantial morbidity and mortality and are increasing in prevalence in Japan (1-3). Vitamin K antagonists (VKAs) have been the cornerstone of therapy for the prevention of thromboembolism in patients with AF and deep vein thrombosis. However, while inexpensive, VKAs have a narrow therapeutic window, require frequent monitoring, and have many interactions with food and drugs, resulting in poor adherence (4). Non-vitamin K antagonist oral anticoagulant (NOACs) are confirmed to be as effective as VKAs and are associated with a lower risk of intracranial hemorrhage (5-7). Recent guidelines specify NOACs as first-line drugs for the prevention of embolism in patients with AF (8, 9).

NOACs are prescribed liberally in clinical practice (10), and the incidences of ischemic stroke (IS)/transient ischemic attack (TIA) and intracerebral hemorrhage (ICH) related to NOACs are expected to increase. Stroke prevention using OACs must balance the benefit of reducing the risk of IS against the increased risk of major bleeding, including ICH. A better distinction between patients who are primarily at risk of experiencing either IS/TIA or ICH is desirable, but the criteria of the most widely used clinical risk scores for thromboembolism and bleeding overlap considerably (11, 12). Furthermore, the recommended international normalized ratio (INR) values for VKA and the criteria for NOAC dosing differ between Japan and Western countries (13). Previous studies showing the characteristics or outcomes of patients with stroke who received OACs were predominantly retrospective, single-center, relatively small-sample studies that enrolled patients with IS and ICH separately (14-18). Therefore, we established the multicenter PASTA registry to support current research on the status of stroke in patients receiving OACs in Japan (19).

The present study is the first to analyze the PASTA registry data, aiming to clarify the differences in clinical characteristics between IS/TIA and ICH patients with AF who are receiving NOACs and VKAs.

Materials and Methods

Standard protocol approvals, registrations, and patient consent

This investigator-initiated, multicenter, prospective, cohort study utilized the PASTA registry as previously reported (19). IS, TIA, and ICH patients receiving OACs were prospectively enrolled across 25 medical institutions throughout Japan between April 2016 and September 2019. Patients were divided into the IS/TIA and ICH groups.

This study was approved by the ethics committee of Nippon Medical School and conformed to the tenets of the Declaration of Helsinki. All participants or their family members provided their written informed consent prior to study participation.

Clinical characteristics

We collected data on clinical characteristics, including the sex, age, cardiovascular risk factors, pre-morbid modified Rankin scale (mRS) score, and pre-stroke $CHADS_2$, CHA_2DS_2-VASc, or HAS-BLED score. Cardiovascular risk factors were defined as 1) hypertension: history of using antihypertensive agents, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg before or ≥2 weeks after stroke onset; 2) diabetes mellitus: use of hypoglycemic agents, random glucose level ≥200 mg/dL, or glycosylated hemoglobin ≥6.0% on admission; 3) hyperlipidemia: use of antihyperlipidemic agents, or a serum total cholesterol level ≥220 mg/dL; and 4) current smoker. The prestroke $CHADS_2$ or CHA_2DS_2VASc score was calculated for each patient based on the published guideline (20). The blood pressure (BP) status one month before the onset of stroke was also recorded. A poor BP control was defined as a systolic BP ≥ 140 mmHg and/or diastolic BP ≥90 mmHg with or without pre-stroke antihypertensive medication. The presence of an abnormal renal function, abnormal liver function, and alcohol intake defined by the HAS-BLED score was also evaluated (20, 21).

Routine blood biochemistry examinations were performed on admission. A high D-dimer level was defined as >1.0 μg/mL (22-24). High brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were defined as >100 or >300 pg/mL, respectively (25, 26).

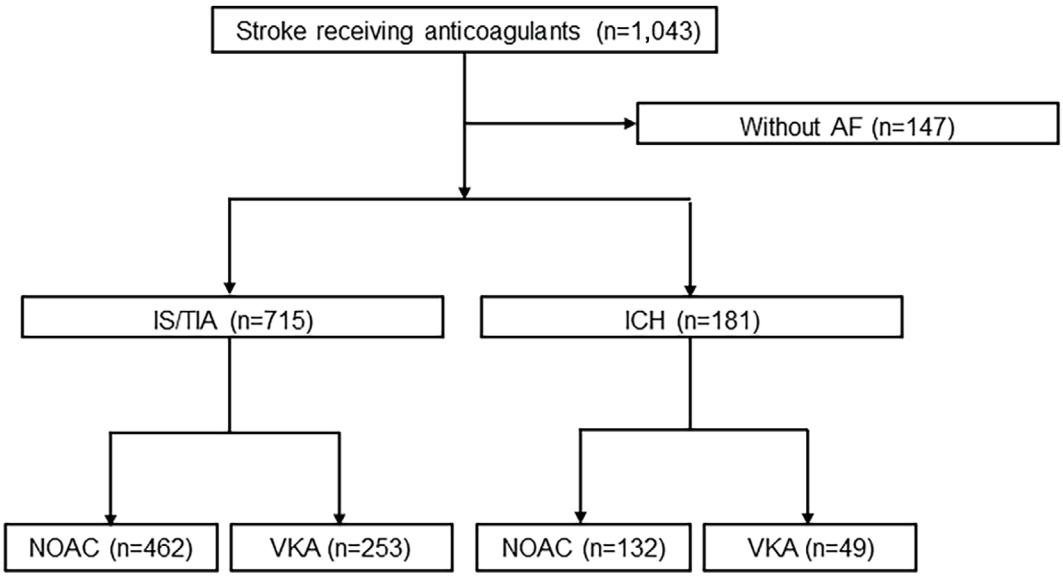

Figure 1. **Study flowchart. ICH: intracerebral hemorrhage, IS: ischemic stroke, NOAC: non-vitamin K antagonist oral anticoagulant, TIA: transient ischemic attack, VKA: vitamin K antagonist**

Gradient-recalled echo T2*-weighted images were assessed for evidence of cerebral microbleeds (CMBs), defined as parenchymal hemorrhage ≤10 mm in diameter (27). Stroke severity on admission and on discharge was assessed using the National Institutes of Health Stroke Scale (NIHSS) score and the mRS score, respectively.

Statistical analyses

We roughly compared the clinical characteristics between the IS/TIA and ICH groups, and then according to prior NOAC or VKA use. Univariate analyses were performed using the chi-squared test or Wilcoxon's rank-sum test. Data are presented as medians (interquartile range) or numbers (%). A multivariable logistic regression analysis was performed to identify independent factors associated with an increased incidence of ICH or IS/TIA. Sex, age, and all clinical characteristics with $p<0.05$ in the univariate analyses were entered into the model. The $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were excluded due to variable duplication, and the initial NIHSS score was excluded because these parameters were consequences of stroke. A two-tailed p value of <0.05 was considered significant. Analyses were performed using the JMP version 13 statistical software program (SAS Institute, Cary, USA).

Results

Differences in clinical characteristics between IS/TIA and ICH

A total of 1,043 patients with IS/TIA or ICH [women, 415 patients; median age, 79 (interquartile range, 72-84) years old; and NIHSS score, 6 (interquartile range, 2-18)] were enrolled in the PASTA study. The final cohort for the present analysis comprised 896 patients (Fig. 1). There were 715 (79.8%) and 181 (20.2%) patients in the IS/TIA and ICH groups, respectively. Among IS/TIA patients, NOACs and VKAs were prescribed in 462 [64.6% (dabigatran, n=67; rivaroxaban, n=139; apixaban, n=143; or edoxaban, n=113)] and 253 (35.4%), respectively. Among ICH patients, NOACs and VKAs were prescribed in 132 [62.9% (dabigatran, n=4; rivaroxaban, n=47; apixaban, n=46; or edoxaban, n=35)] and 49 (37.1%), respectively.

Table 1 presents the clinical characteristics of both groups. IS/TIA patients were older than ICH patients ($p<0.0001$). Male sex ($p=0.0456$), prior NOAC plus antiplatelet therapy ($p=0.0447$), a history of ICH ($p<0.0001$), poor pre-stroke BP control ($p<0.0001$), alcohol use ($p=0.0141$), and CMBs ($p<0.0001$) were more prevalent among ICH patients than among IS/TIA patients. The creatinine clearance (Ccr) ($p<0.0001$), glycated hemoglobin A1c (HbA1c) level ($p=0.0268$), APTT ($p=0.0254$), NIHSS score on admission ($p<0.0001$), mRS score on discharge ($p<0.0001$), and in-hospital mortality ($p=0.0012$) were also significantly higher among ICH patients than among IS/TIA patients. The prevalence of comorbidities associated with stroke, such as hypertension, diabetes mellitus, dyslipidemia, and smoking, and HAS-BLED scores did not significantly differ between both groups (all $p>0.05$). Furthermore, the $CHADS_2$ ($p=0.0123$) and CHA_2DS_2-VASc ($p=0.0011$) scores and the D-dimer ($p<0.0001$) and BNP/NT-proBNP levels ($p=0.0005$) were higher among IS/TIA patients than ICH patients.

Factors associated with ICH or IS/TIA

Table 2 presents the findings of the multivariable logistic regression analysis of factors associated with ICH. A history of ICH [odds ratio (OR), 4.03; 95% confidence interval (CI), 1.64-9.92; $p=0.0024$], a high APTT (OR, 1.02; 95% CI, 1.00-1.04; $p=0.0317$), and CMBs (OR, 3.64; 95% CI, 2.25-5.87; $p<0.0001$) were independently associated with

Table 1. Comparison of Clinical Characteristics between IS/TIA and ICH.

Variable	Total n=896	IS/TIA n=715	ICH n=181	p value
Age, years, median (IQR)	79 (73-84)	80 (74-85)	77 (70-82)	<0.0001
Female gender, n (%)	345 (38.5)	287 (40.1)	58 (32.0)	0.0456
Prior antithrombotic therapy, n (%)				
NOAC	510 (56.9)	402 (56.2)	108 (59.7)	0.4031
NOAC plus APT	84 (9.4)	60 (8.4)	24 (13.3)	0.0447
VKA	233 (26.0)	194 (27.1)	39 (21.6)	0.1259
VKA plus APT	69 (7.7)	59 (8.3)	10 (5.5)	0.2190
Risk factors, n (%)				
Previous IS/TIA	388 (43.3)	319 (44.6)	69 (38.1)	0.1152
Previous ICH	33 (3.7)	14 (1.96)	19 (10.5)	<0.0001
Hypertension	721 (80.5)	569 (79.6)	152 (84.0)	0.1825
Diabetes mellitus	243 (27.1)	201 (28.1)	42 (23.2)	0.1846
Congestive heart failure	248 (27.7)	202 (28.3)	46 (25.4)	0.4460
Dyslipidemia	323 (36.1)	260 (36.4)	63 (34.8)	0.6967
Smoking	209 (23.3)	168 (23.5)	41 (22.7)	0.8103
Alcohol	166 (18.5)	121 (16.9)	45 (24.9)	0.0141
History of vascular disease, n (%)	129 (14.4)	103 (14.4)	26 (14.4)	0.9888
Abnormal renal function, n (%)	24 (2.7)	18 (2.5)	6 (3.3)	0.5528
Abnormal liver function, n (%)	25 (2.8)	16 (2.2)	9 (5.0)	0.0460
Poor BP control prior to admission, n (%)	171 (19.6)	119 (17.0)	52 (30.2)	<0.0001
$CHADS_2$ score, median (IQR)	3 (2-4)	3 (2-4)	2 (2-4)	0.0123
CHA_2DS_2-VASc score, median (IQR)	4 (3-5)	5 (3-6)	4 (3-5)	0.0011
HAS-BLED score, median (IQR)	3 (2-3)	3 (2-3)	4 (3-4)	0.6465
Preadmission mRS, median (IQR)	0 (0-2)	0 (0-2)	0 (0-2)	0.4561
NIHSS score on admission, median (IQR)	7 (2-18)	6 (2-18)	12 (4-23)	<0.0001
Laboratory at admission				
LDL, mg/dL, median (IQR)	100 (82-121)	100 (83-121)	97 (80-117)	0.4083
Ccr, mL/min, median (IQR)	53 (37-71)	52 (36-68)	58 (43-83)	<0.0001
Blood glucose, mg/dL, median (IQR)	126 (108-154)	126 (108-152)	131 (109-159)	0.1136
HbA1c, (%), median (IQR)	6.0 (5.6-6.4)	6.0 (5.7-6.4)	5.9 (5.5-6.3)	0.0268
APTT, s, median (IQR)	32 (28-37)	32 (28-37)	33 (29-38)	0.0254
PT-INR, median (IQR)	1.21 (1.08-1.50)	1.21 (1.08-1.48)	1.23 (1.08-1.81)	0.1242
High D-dimer*, n (%)	439 (50.6)	384 (55.0)	55 (32.4)	<0.0001
High BNP/NT-proBNP†, n (%)	646 (77.9)	543 (80.3)	103 (67.3)	0.0005
Cerebral microbleeds, n (%)	221 (31.3)	149 (26.0)	72 (54.1)	<0.0001
mRS at discharge, median (IQR)	3 (1-5)	3 (1-4)	4 (3-5)	<0.0001
Mortality during hospitalization, n (%)	57 (6.4)	36 (5.0)	21 (11.6)	0.0012

aPTT: activated partial thromboplastin time, BNP: brain natriuretic peptide, BP: blood pressure, Ccr: creatinine clearance, ICH: intracerebral hemorrhage, IQR: interquartile range, IS: ischemic stroke, LDL: low-density lipoprotein cholesterol, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, NOAC: non-vitamin K antagonist oral anticoagulant, NT-proBNP: N-terminal B-type natriuretic peptide, PT-INR: prothrombin time-international normalized ratio, T-cho: total cholesterol, TG: triglycerides, TIA: transient ischemic attack, VKA: vitamin K antagonist. High D-dimer* was defined as 1.0 μg/mL or more. High BNP or NT-proBNP†was defined as >100 or >300 pg/mL, respectively.

ICH, while high BNP/NT-proBNP (OR, 1.69; 95% CI, 1.01-2.80; p=0.0486) and high D-dimer levels (OR, 2.38; 95% CI, 1.41-4.02; p=0.0010) were independently associated with IS/TIA.

Differences in clinical characteristics according to prior NOAC and VKA use

Table 3 presents the clinical characteristics of patients in both groups according to prior NOAC and VKA use, while Fig. 2 illustrates the distribution of IS/TIA and ICH patients according to the clinical characteristics. Among prior NOAC users, ICH patients were younger than IS/TIA patients (Fig. 2A; p=0.0073). Furthermore, a history of ICH, poor pre-stroke BP control, CMBs, and high Ccr (Fig. 2E) were more common among ICH patients than among IS/TIA patients (p=0.0003, p<0.0001, p<0.0001, and p=0.0200, respectively). Although the $CHADS_2$, CHA_2DS_2-VASc (Fig. 2B), and HAS-BLED scores (Fig. 2C) as well as APTT and PT-INR (Fig. 2D) did not significantly differ between the groups (all p>0.05), the BNP/NT-proBNP and D-dimer levels were higher among IS/TIA patients than among ICH patients (p=0.0042 and p=0.0008, respectively). Stroke

Table 2. Multivariable Logistic Regression Analysis for the Development of Intracerebral Hemorrhage.

Variables	OR	95% CI	p value
Age (per 10 years)	0.80	0.57-1.13	0.2052
Female gender	0.75	0.44-1.29	0.3024
NOAC plus APT	1.28	0.79-2.07	0.3249
Previous ICH	4.03	1.64-9.92	0.0024
Poor BP control prior to admission	1.34	0.75-2.32	0.2988
Alcohol	1.42	0.79-2.86	0.2319
Abnormal liver fnction	1.74	0.51-5.97	0.3773
Ccr (per 10)	1.04	0.93-1.18	0.4820
HbA1c (per 1)	0.83	0.60-1.11	0.2139
APTT (per 1)	1.02	1.00-1.04	0.0317
High D-dimer*	0.42	0.25-0.71	0.0010
High BNP/NT-proBNP†	0.59	0.35-0.99	0.0486
Cerebral microbleeds	3.64	2.25-5.87	<0.0001

BNP: brain natriuretic peptide, BP: blood pressure, CI confidence interval, Ccr: creatinine clearance, ICH: intracerebral hemorrhage, IS: ischemic stroke, NT-proBNP: N-terminal B-type natriuretic peptide, OR: odds ratio, PT-INR: prothrombin time-international normalized ratio. TIA: transient ischemic attack. High D-dimer* was defined as 1.0 μg/mL or more. High BNP or NT-proBNP† was defined as >100 or >300 pg/mL, respectively.

severity, including the NIHSS score on admission (p< 0.0001), the mRS score on discharge (p<0.0001), and mortality (p=0.0043) during hospitalization were higher in the ICH group than in the IS/TIA group.

Among prior VKA users, IS/TIA patients were older than ICH patients (Fig. 2A; p=0.0005). Furthermore, a history of IS/TIA and high D-dimer levels (p=0.0020 and p<0.0001, respectively) as well as high $CHADS_2$ and CHA_2DS_2-VASc scores (Fig. 2B) (p=0.0001 and p<0.0001, respectively) were significantly more common among IS/TIA patients than among ICH patients. However, the incidence of previous ICH and alcohol use were higher among ICH patients than among IS/TIA patients (p<0.0001 and p=0.0125, respectively). The HAS-BLED score did not differ markedly between the groups (Fig. 2C; p=0.1763). The Ccr, APTT, and PT-INR were significantly higher among ICH patients than among IS/TIA patients (p=0.0023, p<0.0001, and p<0.0001, respectively). A PT-INR of <1.6 was more common among IS/TIA patients, whereas a PT-INR of 2.0-2.5 was more common among ICH patients (Fig. 2D). There were no significant differences in the proportion of the presence of CMBs (Fig. 2E) between the IS/TIA and ICH groups (p= 0.2397 and p=0.2212, respectively). The level of stroke severity, including the discharge mRS score (p=0.0333), and the mortality rate during hospitalization (p=0.0477) but not the NIHSS score on admission (p=0.3268) were higher in the ICH group than in the IS/TIA group.

Factors associated with ICH or IS/TIA according to prior NOAC and VKA use

Table 4 presents the findings of the multivariable logistic regression analysis of predictors of ICH according to prior OAC use. Among prior NOAC users, the occurrence of CMBs (OR, 4.77; 95% CI, 2.69-8.47; p<0.0001) was independently associated with ICH. Furthermore, high BNP/NT-proBNP levels (OR, 1.89; 95% CI, 1.03-3.45; p=0.0390) were independently associated with IS/TIA. Among prior VKA users, a history of ICH (OR, 13.59; 95% CI, 1.33-139.17; p=0.0279) and a high PT-INR (OR, 1.17; 95% CI, 1.10-1.26; p<0.0001) were independently associated with ICH, while a history of IS/TIA (OR, 3.37; 95% CI, 1.34-8.49; p=0.0101) and high D-dimer levels (OR, 2.47; 95% CI, 1.05-5.82; p=0.0377) were independently associated with IS/TIA.

Discussion

This study yielded several major findings. First, during the study period, NOACs were prescribed to more than 60% of patients with both IS/TIA and ICH during OAC therapy. Second, although the prevalence of cardiovascular risk factors was similar between IS/TIA and ICH, the presence of CMBs was independently associated with ICH, and high BNP/NT-proBNP levels were independently associated with IS/TIA among NOAC users. Third, among VKA users, a history of ICH and the PT-INR were independently associated with ICH, while a history of IS/TIA and high D-dimer levels were independently associated with IS/TIA.

In the present study, the presence of CMBs was independently associated with ICH among prior NOAC users. A previous meta-analysis of 15 prospective studies, including patients with IS or TIA, suggested a higher risk of future ICH than IS in patients with CMBs (28). Recently, an observational cohort study in Europe, similar to our study, found that patients with NOAC-related ICH are more likely to have more CMBs than patients with NOAC-related IS; however, the sample of that study was relatively small (n=116). A retrospective cohort study suggested that NOACs might trigger ICH only in patients at particularly high risk of ICH, such as those with CMBs and high small-vessel disease scores (18, 29). However, in our study, we did not systematically collect data on the location of the CMBs. Further studies are therefore needed to ascertain how best to manage patients with CMBs who require OACs and to determine the characteristics of patients in whom OACs should be prescribed or avoided.

We found that high D-dimer levels among patients receiving VKAs and high BNP/NT-proBNP levels among patients receiving NOACs were independently associated with IS/TIA. Previous reports suggest that elevated D-dimer levels are common in patients with AF and are an additional risk factor for stroke. D-dimer levels are suppressed by anticoagulant therapy, but even in patients receiving oral anticoagulation, D-dimer levels can independently predict stroke or systemic embolism, cardiovascular mortality, and bleeding (30-32). These present and previous findings suggest that D-dimer levels may also be a clinically useful risk marker of IS in AF during OAC therapy. A pooled data meta-analysis demonstrated increased BNP/NT-proBNP lev-

Table 3. Comparison of Clinical Background Characteristics according to Prior Direct Oral Anticoagulant or Warfarin Use.

Variable	NOAC			VKA		
	IS/TIA n=462	ICH n=132	p value	IS/TIA n=253	ICH n=49	p value
Age, years, median (IQR)	79 (73-85)	77 (70-82)	0.0073	81 (76-85)	75 (70-83)	0.0005
Female gender, n (%)	177 (38.3)	44 (33.3)	0.2967	110 (43.4)	14 (28.6)	0.0522
Risk factors, n (%)						
Previous IS/TIA	202 (43.7)	58 (43.9)	0.9647	117 (46.3)	11 (22.5)	0.0020
Previous ICH	12 (2.6)	13 (9.9)	0.0003	2 (0.8)	6 (12.2)	<0.0001
Hypertension	368 (79.7)	114 (86.4)	0.0822	201 (79.5)	38 (77.6)	0.7650
Diabetes mellitus	134 (29.0)	30 (22.7)	0.1548	67 (26.5)	12 (24.5)	0.7715
Congestive heart failure	116 (25.1)	33 (25.0)	0.9798	86 (34.0)	13 (26.5)	0.3085
Dyslipidemia	164 (35.5)	49 (37.1)	0.7316	96 (37.9)	14 (28.6)	0.2120
Smoking	118 (25.5)	30 (22.7)	0.5098	50 (19.8)	11 (22.5)	0.6682
Alcohol	89 (19.3)	32 (24.2)	0.2104	32 (12.7)	13 (26.5)	0.0125
History of vascular disease, n (%)	62 (13.4)	16 (12.1)	0.6968	41 (16.2)	10 (20.4)	0.4723
Abnormal renal function, n (%)	4 (0.9)	1 (0.8)	0.9045	14 (5.5)	5 (10.2)	0.2178
Abnormal liver function, n (%)	11 (2.4)	7 (5.3)	0.0841	5 (2.0)	2 (4.1)	0.3700
Poor BP control prior to admission, n (%)	78 (17.1)	42 (33.1)	<0.0001	41 (16.6)	10 (22.2)	0.3609
$CHADS_2$ score, median (IQR)	3 (2-4)	3 (2-4)	0.6307	3 (2-4)	2 (1-3)	0.0001
CHA_2DS_2-VASc score, median (IQR)	4 (3-6)	4 (3-5)	0.2423	5 (4-6)	3 (3-5)	<0.0001
HAS-BLED score, median (IQR)	3 (2-3)	3 (2-3)	0.0532	3 (2-4)	3 (3-5)	0.1763
Concomitant use of antiplatelet therapy, n (%)	60 (13.0)	24 (18.2)	0.1309	59 (23.3)	10 (20.4)	0.6568
Preadmission mRS, median (IQR)	0 (0-2)	0 (0-2)	0.6827	1 (0-3)	0 (0-2)	0.0877
NIHSS score on admission, median (IQR)	5 (2-16)	11 (4-23)	<0.0001	8 (3-21)	13 (4-22)	0.3268
Biochemistry sign at admission						
LDL, mg/dL, median (IQR)	100 (84-122)	97 (79-116)	0.2358	100 (80-118)	97 (82-120)	0.7492
Ccr, mL/min, median (IQR)	55 (39-72)	57 (43-84)	0.0200	44 (32-63)	59 (37-77)	0.0023
Blood glucose, mg/dL, median (IQR)	128 (109-155)	133 (114-157)	0.2471	123 (105-149)	127 (103-166)	0.4550
HbA1c, (%), median (IQR)	6.0 (5.7-6.4)	5.9 (5.5-6.3)	0.0286	6.0 (5.6-6.4)	5.9 (5.5-6.2)	0.4004
APTT, s, median (IQR)	32 (28-36)	32 (28-36)	0.6415	32 (28-37)	38 (34-45)	<0.0001
PT-INR, median (IQR)	1.14 (1.04-1.30)	1.14 (1.05-1.29)	0.8983	1.43 (1.23-1.83)	2.23 (1.84-2.71)	<0.0001
High D-dimer*, n (%)	227 (50.4)	41 (33.3)	0.0008	157 (63.3)	14 (29.8)	<0.0001
High BNP/NT-proBNP†, n (%)	337 (77.5)	72 (64.3)	0.0042	206 (85.5)	31 (75.6)	0.1107
Cerebral microbleeds, n (%)	95 (25.1)	58 (60.4)	<0.0001	54 (27.8)	14 (37.8)	0.2212
mRS at discharge, median (IQR)	3 (1-4)	4 (3-5)	<0.0001	4 (1-5)	4 (3-5)	0.0333
Mortality during hospitalization, n (%)	17 (3.7)	13 (9.9)	0.0043	19 (7.5)	8 (16.3)	0.0477

aPTT: activated partial thromboplastin time, BNP: brain natriuretic peptide, BP: blood pressure, Ccr: creatinine clearance, ICH: intracerebral hemorrhage, IQR: interquartile range, IS: ischemic stroke, LDL: low-density lipoprotein cholesterol, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, NOAC: non-vitamin K antagonist oral anticoagulant, NT-proBNP: N-terminal B-type natriuretic peptide, PT-INR: prothrombin time-international normalized ratio, T-cho: total cholesterol, TG: triglycerides, TIA: transient ischemic attack, VKA: vitamin K antagonist. High D-dimer* was defined as 1.0 μg/mL or more. High BNP or NT-proBNP† was defined as >100 or >300 pg/mL, respectively.

els in patients with cardioembolic stroke (33). A previous prospective study also showed that the plasma BNP level was significantly higher in the acute phase of stroke than in the subacute phase, suggesting that heart failure may be associated with the onset of IS in patients with AF (34). Although the levels of D-dimer and BNP/NT-pro BNP on admission may be influenced by stroke itself and other concomitant confounders, the present study suggests that combined strategies for managing modifiable factors, such as coagulation and heart failure, may be effective for preventing stroke in patients receiving OACs.

Among patients receiving VKAs, the PT-INR was associated with ICH. A previous study identified Asian ethnicity as a risk factor for VKA-associated ICH, which may be partly attributed to genetic differences affecting VKA metabolism or the treatment response (35-37). Unlike in western countries, the Japanese domestic guidelines recommend a PT-INR value of 1.6-2.6 for patients with non-valvular AF (38, 39). Unlike NOAC users, there was no significant difference in the presence of CMBs between IS/TIA and ICH patients among VKA users. A systematic review and meta-analysis suggested that CMBs are associated with an increased risk of future ICH, particularly in patients receiving VKAs (40). This may be because physicians tend to choose NOACs over VKAs for patients with a high ICH risk, such as those with CMBs. Another possible reason is that VKAs may be used while keeping PT-INR low in patients with CMB and a history of ICH, which may increase the IS and diminish the impact of the presence of CMBs on VKA-related ICH. Furthermore, there may be differences in

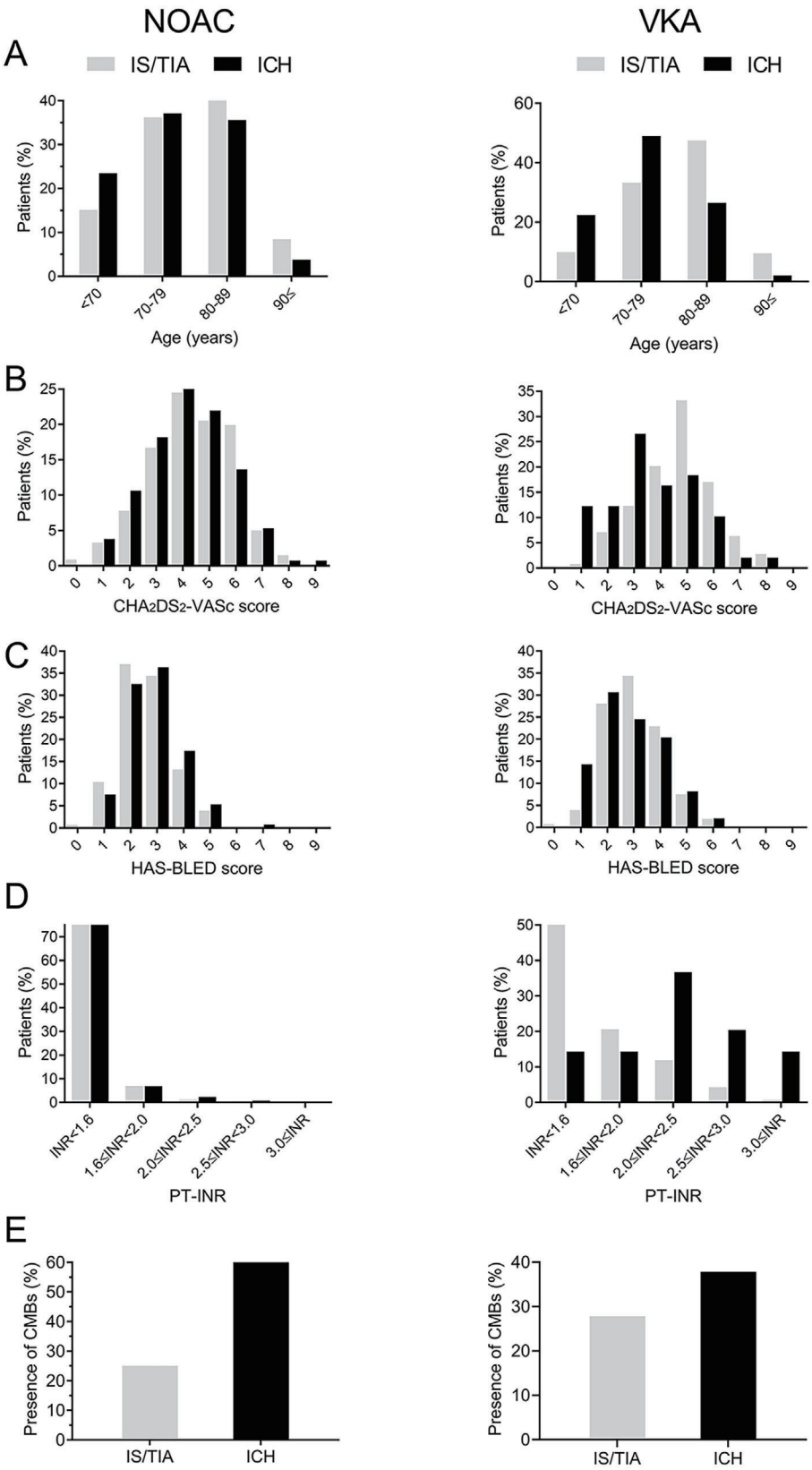

Figure 2. **Distribution of patients according to clinical characteristics. Patients were stratified based on (A) age, (B) CHA_2DS_2-VASc scores, (C) HAS-BLED scores, (D) PT-INR, and (E) CMBs according to the prior use of non-vitamin K antagonist oral anticoagulant (NOACs) and vitamin K antagonists (VKAs). CMBs: cerebral microbleeds, ICH: intracerebral hemorrhage, IS: ischemic stroke, PT-INR: prothrombin time-international normalized ratio, TIA: transient ischemic attack**

Table 4. Multivariable Logistic Regression Analysis for the Development of Intracerebral Hemorrhage According to Prior NOAC or VKA Use.

	Prior NOAC prescription cohort			Prior VKA prescription cohort		
Variables	OR	95% CI	p value	OR	95% CI	p value
Age (per 10 years)	0.78	0.52-1.17	0.2270	0.65	0.39-1.08	0.0986
Female gender	0.81	0.44-1.48	0.4968	0.56	0.21-1.49	0.2463
Previous IS/TIA	-	-	-	0.30	0.12-0.75	0.0101
Previous ICH	2.11	0.76-5.90	0.1521	13.59	1.33-139.17	0.0279
Alcohol	-	-	-	1.30	0.49-3.46	0.5957
Poor BP control prior to admission	1.36	0.72-2.58	0.3456	1.58	0.61-4.11	0.3497
Ccr (per 10)	1.00	0.87-1.16	0.9672	-	-	-
HbA1c (per 1)	0.31	0.57-1.14	0.2552	-	-	-
PT-INR (per 0.1)	-	-	-	1.17	1.10-1.26	<0.0001
High D-dimer*	0.56	0.31-1.01	0.0540	0.40	0.17-0.95	0.0377
High BNP/NT-proBNP†	0.53	0.29-0.97	0.0390	-	-	-
Cerebral microbleeds	4.77	2.69-8.47	<0.0001	-	-	-

BNP: brain natriuretic peptide, BP: blood pressure, CI confidence interval, Ccr: creatinine clearance, ICH: intracerebral hemorrhage, IS: ischemic stroke, NOAC: non-vitamin K antagonist oral anticoagulant, NT-proBNP: N-terminal B-type natriuretic peptide, OR: odds ratio, PT-INR: prothrombin time-international normalized ratio. TIA: transient ischemic attack, VKA: vitamin K antagonist. High D-dimer* was defined as 1.0 μg/mL or more. High BNP or NT-proBNP† was defined as >100 or >300 pg/mL, respectively.

the strictness of blood pressure control prior to stroke between patients on NOACs and VKAs. As we have no data on the detailed location and number of CMBs and duration of OAC medication, longitudinal prospective studies are needed to confirm the relationship between development of new CMB/ICH and OAC treatment.

Several limitations associated with the present study warrant mention. Due to the cross-sectional design and the fact that nearly half of the patients in this cohort had a history of stroke, there was potential selection bias, and we merely compared ICH and IS/TIA rather than demonstrating a causative relationship. Thus, firm conclusions regarding the absolute risk factors cannot be drawn. A recent analysis of the National Health Insurance Database from the Tsugaru region of Aomori Prefecture in Japan showed that among AF patients on OAC, 32% were on warfarin in 2016 and 27% in 2017 (41). In the present study, the proportion of AF patients prescribed warfarin was 34%, which is relatively high. This may be explained by two possible reasons: 1) patients that had been diagnosed with AF before 2011 were started on VKA and did not switch to NOACs, and 2) patients taking warfarin were more likely to develop stroke than those taking NOACs. Unfortunately, we were unable to gather data regarding the pre-stroke duration of AF burden, OAC therapy, or time since the last stroke. Finally, almost all enrolled patients were Japanese; thus, the results of this study may not be generalizable to all ethnicities.

Nevertheless, our study has certain strengths, including a multicenter setting, a relatively large sample size, and the analysis of combined ischemic and hemorrhagic stroke data.

Conclusion

Our findings suggest that the presence of CMBs and natriuretic peptides may be useful for risk stratification of either IS or ICH development in patients receiving NOACs. In contrast, a history of stroke, the PT-INR, and D-dimer levels may be useful for risk stratification of either IS or ICH development in patients receiving VKAs. Further longitudinal studies and validation of these findings in other cohorts are required to investigate the role of a stroke history, neuroimaging, and cardiac and coagulation laboratory markers in the selection or management of patients regarding OAC therapy.

Author's disclosure of potential Conflicts of Interest (COI).

Satoshi Suda: Honoraria, Eisai; Research funding, the All Japan Coffee Association. Yasuyuki Iguchi: Honoraria, Sanofi, Daiichi-Sankyo, Nippon Boehringer Ingelheim, Bayer Healthcare, Pfizer and Bristol-Myers Squibb. Yoshiki Yagita: Honoraria, Daiichi-Sankyo. Takao Kanzawa: Honoraria, Daiichi-Sankyo. Shigeru Fujimoto: Honoraria, Takeda Pharmaceutical, Bayer Yakuhin and Daiichi-Sankyo. Yu Kono: Research funding, Sanofi. Makoto Nakajima: Honoraria, Daiichi-Sankyo. Takehiko Nagao: Honoraria, Bayer Yakuhin, Kazumi Kimura: Honoraria, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer Healthcare and Daiichi Sankyo; Research funding, Nippon Boehringer Ingelheim and Daiichi Sankyo.

Financial Support

This research was supported by Nippon Boehringer Ingelheim Co., Ltd.

Acknowledgement

We thank the following PASTA investigators and their hospitals for participating in this study: Rinko Kokubo, Tomoyuki Kono, Takafumi Mashiko, Hiroshi Okada, Naoki Oyama, Kenichiro Sakai, Tomonari Saito, Masayuki Suzuki, Kenichi

Todo, and Masayuki Ueda.

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