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 oral antagonists [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=0.0279) 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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doi: 10.2169/internalmedicine.8113-21
Intern Med Advance Publication
http://internmed.jp
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, vitamin K antagonist

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 oral antagonists (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 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 CHADS2, CHA2DS2-VASc, or HAS-BLED score. Cardiovascular risk factors were defined as (1) hypertension: history of using antihypertensive agents, systolic blood pressure \(\geq 140\) mm Hg, or diastolic blood pressure \(\geq 90\) mm Hg before 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).
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 CHADS2, CHA2DS2-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 Inc., Cary, NC, 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 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 CHADS2 (p=0.0123) and CHA2DS2-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
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 CHADS2, CHA2DS2-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
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 CHADS2 and CHA2DS2-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, APPT, 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-
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

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

| Variable                      | NOAC | VKA |
|-------------------------------|------|-----|
| IS/TIA n=462                  |      |     |
| 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 |
| CHADS2 score, median (IQR)    | 3 (2-4) | 3 (2-4) | 0.6307 | 3 (2-4) | 2 (1-3) | 0.0001 |
| HAS-BLED score, median (IQR)  | 3 (2-3) | 3 (2-3) | 0.0532 | 3 (2-4) | 3 (3-3) | 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, sec, median (IQR)       | 32 (28-36) | 32 (28-36) | 0.6415 | 32 (28-38) | 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 (28.9) | <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) | 0.0013 | 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, 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 >1.0μg/mL or more. High BNP or NT-proBNP† was defined as >100 or >300 pg/mL, respectively.
Figure 2. Distribution of patients according to clinical characteristics. Patients were stratified based on (A) age, (B) CHA2DS2-VASc scores, (C) HAS-BLED scores, (D) PT-INR, and (E) CMBs according to the prior use of non-vitamin K oral antagonists (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.

| Variables                        | Prior NOAC prescription cohort | Prior VKA prescription cohort |
|----------------------------------|--------------------------------|--------------------------------|
|                                  | 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 | 0.2465 |
| 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-proBNP²              | 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 antagonists, 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-dimer² was defined as 1.0μg/mL or more. High BNP or NT-proBNP² 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 Co., Ltd.; Research funding, the All Japan Coffee Association, Yasuyuki Iguchi: Honoraria, Sanofi Co., Ltd., Daiichi-Sankyo Co., Ltd, Nippon Boehringer Ingelheim Co. Ltd, Bayer Healthcare Co. Ltd, Pfizer Inc Co. Ltd and Bristol-Myers Squibb Co. Ltd. Yoshiki Yagita: Honoraria, Daiichi-Sankyo Co., Ltd. Takao Kanzawa: Honoraria, Daiichi-Sankyo Co., Ltd. Shigeru Fujimoto: Honoraria, Takeda Pharmaceutical Co., Ltd., Bayer Yakuhin, Co., Ltd. and Daiichi-Sankyo Co., Ltd. Makoto Nakajima: Honoraria, Daiichi-Sanky Co. Ltd. Takehiko Nagao: Honoraria, Bayer Yakuhin, Co., Ltd. Kazumi Kimura: Honoraria, Bristol-Myers Squibb Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bayer Healthcare Co. Ltd. and Daiichi Sankyo Co. Ltd.; Research funding, Nippon Boehringer Ingelheim Co. Ltd. and Daiichi Sankyo Co. Ltd. Yu Kono: Research funding, Sanofi Co., Ltd.

Acknowledgement

We thank the following PASTA investigators and their hospitals for participating in this study: Rinko Kokubo, Tomoyuki Kono, Takafumi Mashiho, Hiroshi Okada, Naoki Oyama, Kenichiro Sakai, Tomonari Saito, Masayuki Suzuki, Kenichi Todo, and Masayuki Ueda.
Funding Sources
This research was supported by Nippon Boehringer Ingelheim Co., Ltd.

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