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Stroke-Specific Predictors of Major Bleeding in Anticoagulated Patients With Stroke and Atrial Fibrillation: A Nationwide Multicenter Registry-Based Study

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Background and Purpose The congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack (CHA_2DS_2-VASc) and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol (HAS-BLED) scores have been validated in estimating the risks of ischemic stroke and major bleeding, respectively, in patients with atrial fibrillation (AF). This study investigated stroke-specific predictors of major bleeding in patients with stroke and AF who were taking oral anticoagulants (OACs).

Methods Subjects were selected from patients enrolled in the Korean ATrial fibrillaTion EvaluatioN regisTry in Ischemic strOke patieNts (K-ATTENTION) nationwide multicenter registry between 2013 and 2015. Patients were excluded if they were not taking OACs, had no brain imaging data, or had intracranial bleeding directly related to the index stroke. Major bleeding was defined according to International Society of Thrombosis and Haemostasis criteria. Cox regression analyses were performed to assess the associations between clinical variables and major bleeding and Kaplan-Meier estimates were performed to analyze event-free survival.

Results Of a total of 3,213 patients, 1,414 subjects (mean age of 72.6 years, 52.5% males) were enrolled in this study. Major bleeding was reported in 34 patients during the median follow-up period of 1.73 years. Multivariable analysis demonstrated that initial National Institutes of Health Stroke Scale scores (hazard ratio [HR] 1.07, p=0.006), hypertension (HR 3.18, p=0.030), persistent AF type (HR 2.51, p=0.016), and initial hemoglobin level (HR 0.74, p=0.001) were independently associated with major bleeding risk. Except for hypertension, these associations remained significant after adjusting for the HAS-BLED score. Intracranial atherosclerosis presented a trend of association without statistical significance (HR 2.21, p=0.050).

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Conclusions This study found that major bleeding risk was independently associated with stroke-specific factors in anticoagulated patients with stroke and AF. This has the clinical implication that baseline characteristics of patients with stroke and AF should be considered in secondary prevention, which would bring the net clinical benefit of balancing recurrent stroke prevention with minimal bleeding complications.

Key Words anticoagulation; atrial fibrillation; ischemic stroke; hemorrhage; bleeding.

INTRODUCTION

Prevention of thromboembolism in patients with atrial fibrillation (AF) is essential because AF is associated with near fivefold increase in the risk of ischemic stroke.[1] Effective stroke prevention typically refers to anticoagulation therapy that requires balancing efforts to reduce the risks of stroke and major bleeding. Patients with stroke are vulnerable to bleeding due to complex comorbid conditions, and countermeasures are needed that provide a net clinical benefit between secondary stroke prevention and bleeding complications. In particular, marked differences were found in the initial neurological severity, incidence of major adverse cardiovascular events, and mortality between patients with stroke taking and not taking oral anticoagulants (OACs).[2]

The main safety concern posed by anticoagulation therapy is the increased risk of bleeding, especially major bleeding, which requires hospitalization or surgical treatment as well as transfusion, or involves a critical anatomical area. Assessment of the bleeding risk of individuals prior to administering anticoagulant agents should be followed by treatment and stroke prevention. Several risk stratification scores for bleeding have been validated among patients with AF, including hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol (HAS-BLED), anticoagulation and risk factors in atrial fibrillation (ATRIA), age, biomarkers, and clinical history (ABC), outcomes registry for better informed treatment of atrial fibrillation (ORBIT), hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk and stroke (HEMMORR$_2$HAGES), and Shireman.[3-7]

However, unlike general patients with AF, those with stroke and AF have various underlying medical conditions that include vascular risk factors. Given these characteristics of patients with stroke, the existing tools for assessing the bleeding risk in general patients with AF might not be effective. There are still few studies of risk assessment tools for bleeding in patients with stroke and AF that require anticoagulant treatment.

Therefore, the purpose of this study was to determine independent predictors of major bleeding in patients with stroke and AF by using real-world data and focusing on their neurological characteristics.

METHODS

Study design and settings

This study retrospectively analyzed the nationwide, multicenter Korean ATrial fibrillaTion EvaluatioN regisTry in Ischemic strOke patieNts (K-ATTENTION) registry. Clinical data were collected on 3,213 consecutive patients with acute ischemic stroke and AF who attended 11 comprehensive stroke centers in South Korea between January 2013 and December 2015. This registry includes information on demographics, risk factors, stroke subtypes and severity scale scores, concomitant cerebral atherosclerosis, accompanying bleeding events during the follow-up period, brain imaging findings, initial laboratory findings, and types of OACs in the acute phase and at discharge. The study protocol was approved by the institutional review board of each center (Samsung Medical Center, 2016-07-011). The need to obtain informed consent from each participant was waived due to the retrospective observational design of the study.

Patient selection

Eligible patients were those diagnosed with acute ischemic stroke and AF who were 20 years of age or older and were taking OACs after index stroke. Patients were excluded if they were not taking OACs, had no brain imaging data or missing data on initial National Institutes of Health Stroke Scale (NIHSS), or had intracranial bleeding directly related to the index stroke.

Data collection

The methods of clinical data acquisition have been mentioned in previous research reports related to K-ATTENTION.[8] Demographics; clinical, laboratory, and brain imaging data at baseline; vascular comorbidity data; concomitant

medications; and the type and location of the index bleeding event were collected. Follow-up data were obtained by reviewing electronic medical records.

Paroxysmal AF was defined as AF that terminated spontaneously or through intervention within 7 days of onset, and persistent AF was defined as AF that was continuously sustained beyond 7 days or terminated by cardioversion after more than 7 days.[9] Cerebral atherosclerosis, generally classified as extracranial carotid artery stenosis (ECAS) and intracranial carotid artery stenosis (ICAS), was defined as greater than 50% reduction or occlusion in the luminal diameter. CHA_2DS_2-VASc is an acronym for Congestive heart failure, Hypertension, Age (>65 years=1 point, >75 years=2 points), Diabetes, previous stroke/transient ischemic attack (2 points). HAS-BLED is an acronym for Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal liver and/or renal function, stroke history, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>65 years), and drugs and/or alcohol concomitant use. The HAS-BLED score was calculated in this study as follows: for 'hypertension,' instead of tracking the blood pressure trend of the patients, 1 point was given for a previous diagnosis of hypertension. For 'abnormal renal function,' 1 point was given for undergoing renal replacement therapy or patients with an estimated glomerular filtration rate of less than 15 mL/min/1.73 m^2. For 'abnormal liver function,' 1 point was given for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels higher than three times the normal values. For 'alcohol consumption,' 1 point was given for consuming more than eight drinks per week or more than four times a week (beyond so-called social drinking).

Outcome measures

The outcome measure was the first major bleeding event after index stroke in patients with stroke and AF taking OACs. However, intracranial bleeding directly associated with the index stroke was excluded. Major bleeding was defined according to the following International Society on Thrombosis and Haemostasis (ISTH) criteria:[10]

1) Fatal bleeding, and/or

2) Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or

3) Bleeding causing a decrease in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of at least 2 units of packed red blood cells.

To avoid ambiguity, patients with intracranial bleeding or hemorrhagic transformation directly related to an initial infarct lesion were not considered to have intracranial bleeding.

Data management and quality control

All data were collected and uploaded via a web-based electronic data capturing system. All investigators accessed this secure database system and registered mandatory variables. The collected data were monitored and audited by the quality control team.

Statistical analysis

Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as frequencies and percentages. To minimize bias from missing data, the mean value of a variable was used in place of the missing value (Supplementary Table 1 in the online-only Data Supplement). Two missing values for AF type were imputed as paroxysmal AF, but these cases were eventually excluded due to other missing values.

To compare baseline characteristics between the major bleeding and non-major bleeding groups, chi-square test or Fisher's exact test was applied for categorical variables, and Student's *t*-test or the Mann-Whitney U test was applied for continuous variables.

Cox regression analyses were performed to estimate the associations between clinical variables and major bleeding risk. The independent effects of clinical variables on major bleeding were calculated using Cox proportional hazards regression; the multivariable model included variables for which $p<0.05$ in the univariable analysis. Multivariable regression was performed using the stepwise method. Kaplan-Meier estimates were used to analyze event-free survival, and the log-rank test was used to make comparisons between groups. To compare event-free survival probability between groups, the initial NIHSS score and hemoglobin level were dichotomized into two groups (score ≥7 versus <7, and ≥13 versus <13 g/dL, respectively) using the median as the cut-off. Subjects were considered to be censored if they had no major bleeding events, died prematurely, or were lost to follow-up during the follow-up period. The unadjusted and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. A two-sided *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC, USA) and SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

Among the 3,213 patients registered in the K-ATTENTION

registry from January 2013 to December 2015, 874 who had not been prescribed an OAC after index stroke were excluded (Fig. 1). Of the remaining 2,339 patients, 264 patients with no data on bleeding events, 597 patients without brain imaging data, and 64 patients with missing NIHSS or HAS-BLED scores or no information on ICAS or ECAS were all excluded. We finally enrolled 1,414 patients (mean age, 72.6±9.78 years; 52.5% males) with median NIHSS and HAS-BLED scores of 7 (interquartile range [IQR] 2–14) and 2 (IQR 2–3), respectively. The baseline characteristics of finally enrolled and excluded patients taking OACs are compared in Supplementary Table 2 (in the online-only Data Supplement). Of the 1,414 patients, 34 (2.40%) experienced major bleeding as defined by ISTH criteria during follow-up period. The median follow-up period was 1.74 years (IQR 0.58–2.83 years), and the median time-to-event was 1.73 years (IQR 0.56–2.83 years). During the follow-up period, 6 patients experienced fatal bleeding, 7 experienced critical organ bleeding, and 21 experienced bleeding that lowered the hemoglobin level or required a transfusion.

The overall incidence rate of major bleeding was 1.35 per 100 patient-years (95% CI 1.31–1.40). According to the Kaplan–Meier estimates, the cumulative incidence rate of major bleeding at 1 and 3 years were 1.3% and 2.1%, respectively, indicating a steady increase in the incidence rate of major bleeding from the beginning of the study. Intracranial hemorrhage (ICH) independent of index stroke occurred in 19 (1.34%) of the 1,414 patients, 2 of whom died and 2 of whom

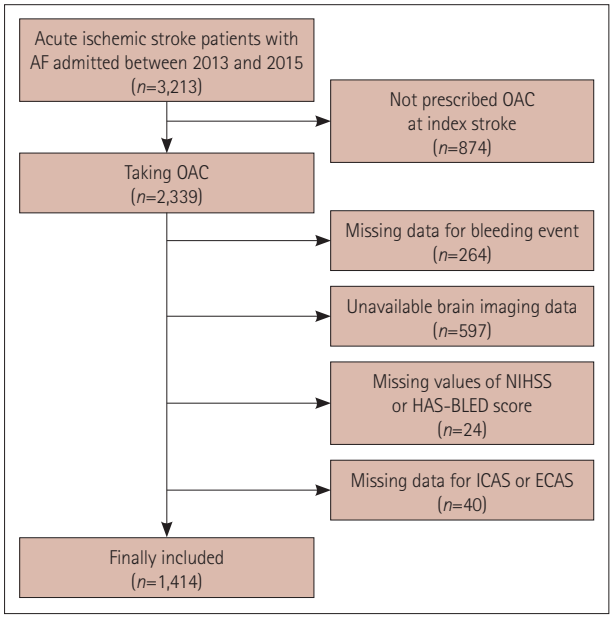

Fig. 1. Flow chart of inclusion and exclusion criteria for the study patients. AF, atrial fibrillation; ECAS, extracranial atherosclerosis; HAS-BLED, Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal liver and/or renal function, Stroke history, Bleeding history or predisposition, labile international normalized ratio, Elderly (>65 years), Drugs and/or alcohol concomitant usage; ICAS, intracranial atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant.

Table 1. Baseline characteristics of study patients

	Major ISTH bleeding (*n*=34)	Non-major bleeding (*n*=1,380)	*p*
Demographics			
Age, years	75.15±8.27	72.56±9.81	0.156
Sex, male	17 (50.00)	725 (52.54)	
AF type			
Paroxysmal	10 (29.41)	709 (51.38)	
Persistent	24 (70.59)	671 (48.62)	0.014*
Oral anticoagulation therapy			
Warfarin	26 (76.47)	1,129 (81.81)	0.499
NOAC	8 (23.53)	251 (18.19)	0.499
Comorbidities			
ICAS	25 (73.53)	747 (54.13)	0.035*
ECAS	5 (14.71)	301 (21.81)	0.403
History of stroke/TIA	11 (32.35)	464 (33.62)	1.000
History of CHF	2 (5.88)	52 (3.77)	0.376
History of CAD	7 (20.59)	195 (14.13)	0.317
Hypertension	30 (88.24)	928 (67.25)	0.009*
Diabetes mellitus	9 (26.47)	340 (24.64)	0.841
Dyslipidemia	8 (23.53)	306 (22.17)	0.835
Current smoking	3 (8.82)	192 (13.91)	0.613
Initial NIHSS score, point	11 [6–17]	6 [2–14]	0.018*
CHA_2DS_2-VASc score, point	5 [5–6]	5 [4–6]	0.033*
HAS-BLED score, point	3 [3–3]	2 [2–3]	<0.001*
Laboratory measurements			
Hemoglobin level, g/dL	12.56±2.26	13.56±1.87	0.011*
WBC count, $\times 10^3/\mu L$	8.37±3.36	8.09±2.83	0.876
Platelet count, $\times 10^3/\mu L$	192.71±73.24	206.89±78.61	0.591
Blood glucose, mg/dL	136.20±55.38	136.91±82.76	0.932
Total cholesterol, mg/dL	157.32±37.39	161.95±37.70	0.453
AST, U/L	23.03±8.46	28.23±15.55	0.013*
ALT, U/L	17.00±8.71	21.79±15.54	0.012*
Creatinine clearance, mL/min	50.04±24.18	63.16±28.09	0.002*

Data are presented as number (%), mean±standard deviation, or median [interquartile range] values.
*p<0.05.
AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate transaminase; CAD, coronary artery disease; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age (>65 years=1 point, >75 years=2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); CHF, congestive heart failure; ECAS, extracranial atherosclerosis; HAS-BLED, Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal liver and/or renal function, Stroke history, Bleeding history or predisposition, labile international normalized ratio, Elderly (>65 years), Drugs and/or alcohol concomitant usage; ICAS, intracranial atherosclerosis; ISTH, International Society on Thrombosis and Haemostasis; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack; WBC, white blood cell.

had critical organ bleeding as determined by ISTH criteria. Gastrointestinal bleeding (GIB) events occurred in 45 patients (3.18%), life-threatening bleeding in 2, critical organ bleeding in 1, and decreased hemoglobin or blood transfusion after overt bleeding in 18.

Baseline characteristics of eligible patients are listed in Table 1. The non-major bleeding group included all cases with no bleeding or with bleeding events that do not meet ISTH criteria. The median NIHSS scores in the major bleeding and non-major bleeding groups were 11 (IQR 6–17) and 6 (IQR 2–14), respectively. Compared with patients in the non-major bleeding group, those who experienced major bleeding (n=33) had higher median NIHSS, CHA_2DS_2-VASc, and HAS-BLED scores, and lower mean hemoglobin, AST, ALT, and creatinine clearance values. Those in the major bleeding group were also more likely to have ICAS, a history of hypertension, and/or persistent AF.

Clinical factors associated with major bleeding risk

More patients were discharged on a vitamin K antagonist (warfarin, n=1,155) than those taking non-vitamin K antagonist OACs (NOACs, n=259) (Table 1). On the other hand, the incidence rate of major bleeding was higher in the NOACs group (n=8, 3.09%) than in the warfarin group (n=26, 2.25%). However, the proportion of those that experienced major bleeding event was higher among those who received warfarin than among those who received NOACs.

The results of univariable and multivariable analyses of baseline clinical factors for major bleeding risk are listed in Table 2. The univariable analyses indicated that major bleeding risk was positively associated with age (HR 1.06, 95% CI 1.01–1.10, p=0.010), ICAS (HR 2.72, 95% CI 1.27–5.84, p=0.010), initial NIHSS score (HR 1.08, 95% CI 1.03–1.13, p<0.001), hypertension (HR 3.59, 95% CI 1.27–10.20, p=0.016), persistent AF (HR 2.67, 95% CI 1.28–5.59, p=0.009), CHA_2DS_2-VASc score (HR 1.42, 95% CI 1.10–1.83, p=0.007), and HAS-BLED score (HR 2.49, 95% CI 1.56–3.95, p<0.001). On the other hand, variables with negative associations were initial hemoglobin (HR 0.73, 95% CI 0.62–0.86, p<0.001), creatinine clearance (HR 0.97, 95% CI 0.96–0.99, p=0.001), AST (HR 0.94, 95% CI 0.90–0.99, p=0.013), and ALT (HR 0.94, 95% CI 0.90–0.99, p=0.012).

The multivariable analysis of model 1 (Table 2) indicated that initial NIHSS score (HR 1.07, 95% CI 1.02–1.11, p=0.006), hypertension (HR 3.18, 95% CI 1.12–9.03, p=0.030), and persistent AF (HR 2.51, 95% CI 1.19–5.28, p=0.016) were significant predictors of major bleeding risk, whereas the initial hemoglobin level (HR 0.74, 95% CI 0.63–0.88, p=0.001) was negatively associated with major bleeding risk.

The multivariable analysis of model 2 (Table 2) indicated that major bleeding risk was independently associated with NIHSS score (HR 1.06, 95% CI 1.01–1.11, p=0.024), persistent AF (HR 2.77, 95% CI 1.31–5.87, p=0.008), and initial hemoglobin level (HR 0.76, 95% CI 0.64–0.90, p=0.002) after adjusting for the HAS-BLED score. In other words, except for hypertension, these associations remained significant after adjusting for the HAS-BLED score. ICAS presented a trend of association without statistical significance (HR 2.21, 95% CI 1.00–4.90, p=0.050).

The standard multiple regression analysis of significant

Table 2. Independent predictors of major bleeding risk in the univariable and multivariable analyses

Parameter	Univariable model		Multivariable model 1		Multivariable model 2 (adjusted for HAS-BLED score)	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Age, years	0.010	1.06 (1.01–1.10)				
ICAS	0.010	2.72 (1.27–5.83)			0.050	2.21 (1.00–4.90)
Initial NIHSS score	0.001	1.08 (1.03–1.13)	0.006	1.07 (1.02–1.11)	0.024	1.06 (1.01–1.11)
Hypertension	0.017	3.58 (1.26–10.17)	0.030	3.18 (1.12–9.03)		
Persistent AF	0.010	2.65 (1.27–5.54)	0.016	2.51 (1.19–5.28)	0.008	2.77 (1.31–5.87)
CHA_2DS_2VASc score	0.007	1.42 (1.10–1.82)				
HAS-BLED score	<0.001	2.48 (1.56–3.95)			<0.001	2.60 (1.53–4.41)
Initial hemoglobin, g/dL	<0.001	0.73 (0.62–0.86)	0.001	0.74 (0.63–0.88)	0.002	0.76 (0.64–0.90)
AST, U/L	0.013	0.94 (0.90–0.99)				
ALT, U/L	0.012	0.94 (0.90–0.99)				
Creatinine clearance, mL/min	0.001	0.97 (0.96–0.99)				

AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate transaminase; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age (>65 years=1 point, >75 years=2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); CI, confidence interval; HAS-BLED, Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal liver and/or renal function, Stroke history, Bleeding history or predisposition, labile international normalized ratio, Elderly (>65 years), Drugs and/or alcohol concomitant usage; HR, hazard ratio; ICAS, intracranial atherosclerosis; NIHSS, National Institutes of Health Stroke Scale.

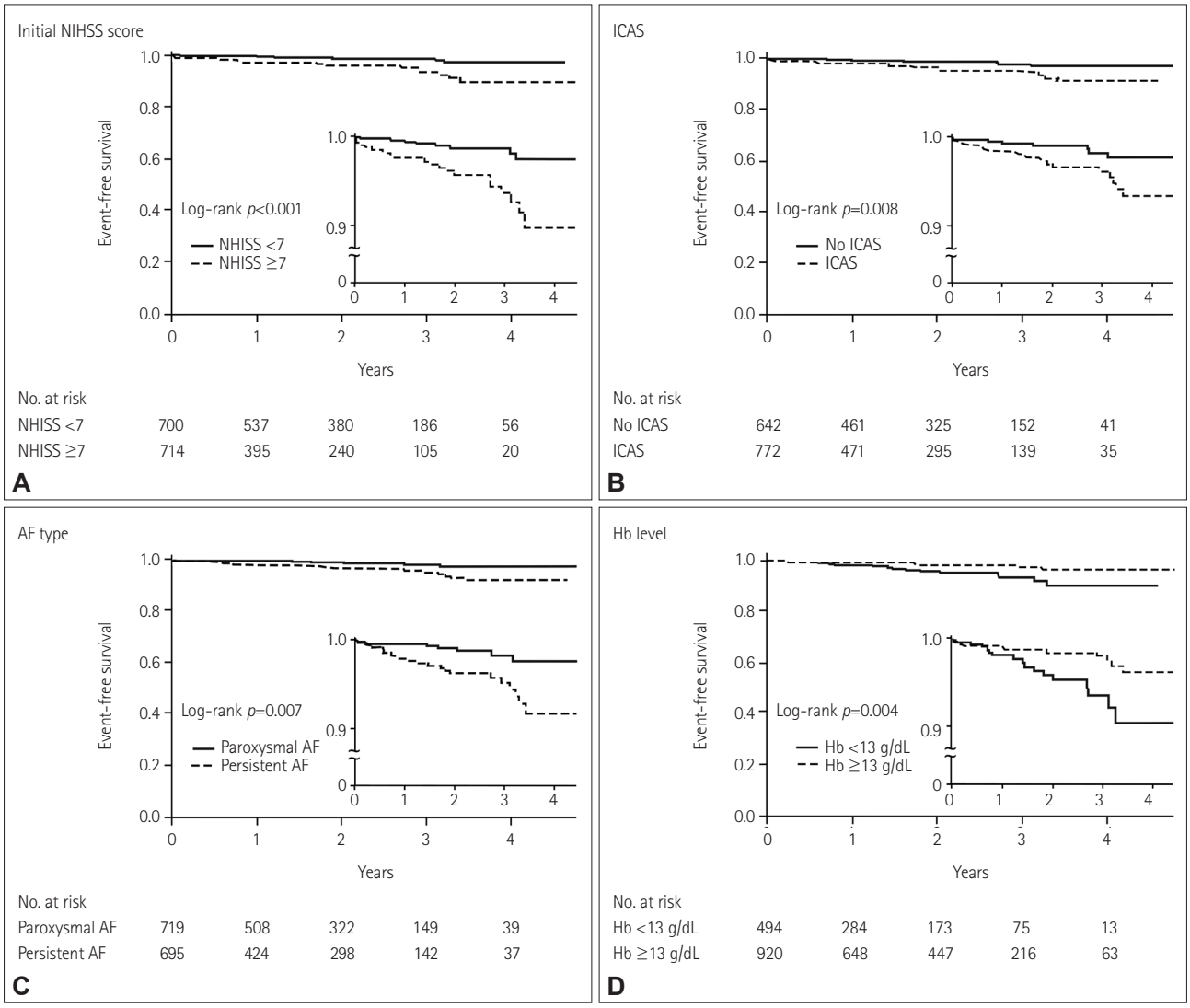

Fig. 2. Kaplan-Meier estimates of event-free survival for major bleeding according to significant predictors. Each predictor variable was dichotomized using the mean value as the cutoff (A-D). AF, atrial fibrillation; Hb, hemoglobin; ICAS, intracranial atherosclerosis; NIHSS, National Institutes of Health Stroke Scale.

variables in the univariable analysis without adjusting for the HAS-BLED score revealed that ICAS presented an insignificant trend of association (HR 2.13, 95% CI 0.97–4.71, p=0.061).

Event-free survival for major bleeding according to significant predictors

Cumulative event-free survival frequencies for each predictor significantly associated with major bleeding were calculated using the Kaplan-Meier method (Fig. 2). Each predictor variable was dichotomized using the mean value as the cutoff. The risk of major bleeding was approximately 1.1-fold higher in patients with NIHSS scores ≥7 than in those with scores <7 (p<0.001). Similarly, the incidence rate of major bleeding increased by more than 3-fold in the group with hypertension (p=0.01) and by 2.5-fold in the group with persistent AF (p=0.007). For the initial hemoglobin level, the incidence rate of major bleeding was 0.74 times lower in the group with an initial hemoglobin level of 13 g/dL or higher (p=0.001). There were distinct differences between the event-free survival probabilities of subgroups for each variable from the beginning of the study.

In explorative analyses that compared different AF groups, the NIHSS score was higher in the persistent AF group (9.63±7.61) than in the paroxysmal AF group (7.49±6.64). No significant interaction was identified between NIHSS score and AF type for major bleeding (p=0.564) (Supplementary Table 3 in the online-only Data Supplement).

A history of stroke, congestive heart failure, dyslipidemia, NIHSS score ≥7, and below-average creatinine clearance

were significantly more common in the persistent AF group (Supplementary Table 4 in the online-only Data Supplement).

DISCUSSION

This real-world study of patients with stroke and AF found that baseline neurological severity, AF type, and initial hemoglobin level were independent predictors of major bleeding. Moreover, each association with major bleeding (except for hypertension) remained significant after adjusting for HAS-BLED score. However, ICAS presented a trend of association without statistical significance.

Assessing the risk for bleeding is essential in treatment decisions for patients with stroke and AF taking OACs, which should be conducted on an individual basis. Several studies have found that the HAS-BLED score demonstrated better performance in predicting major bleeding compared with other contemporary tools for assessing the bleeding risk.[11,12] Given its simplicity, the HAS-BLED tool offers a clear advantage over previously mentioned bleeding risk stratification methods.[13] Indeed, HAS-BLED is recommended in the 2020 European Society of Cardiology Guidelines for AF as a simple, validated bleeding risk assessment tool.[9]

Risk factors for major bleeding during anticoagulation therapy in patients with AF have been identified in previous cohort studies and secondary analyses of clinical trial data. A previous study[14] that investigated the major bleeding risk in patients taking warfarin found that higher age, previous stroke, history of GIB, presence of serious comorbidities (e.g., recent myocardial infarction or renal dysfunction), and AF were important predictors. A recent systematic review[15] of the literature on anticoagulation-related bleeding complications in patients with AF found that higher age, uncontrolled hypertension, prior cardiovascular disease, prior stroke, anemia, history of bleeding, and concomitant use of other antithrombotic drugs were independent risk factors for bleeding. Diabetes, decreased hematocrit level, higher age, prior hemorrhage, prior stroke, and renal impairment were found to be independently associated with increased major bleeding risk in patients with AF taking OAC (warfarin or apixaban).[16]

The present study found that patients with AF-related stroke and high NIHSS scores were more likely to experience major bleeding events. A high NIHSS score typically indicates a severe stroke, and several studies have found that the severity of neurological deterioration is an important factor related to GIB occurrence.[17-19] Although the exact mechanism underlying GIB in patients with stroke has not been elucidated, pathophysiological mechanisms that increase gastrointestinal mucosal damage include interruption of the axis between the central nervous and digestive systems, antithrombotic or anticoagulant drugs use, and stress.[18] A previous study[19] suggested that the increased GIB risk in patients with stroke is due to vagal hyperactivity that results in increased gastric acid secretion.

The present study found that patients with stroke and persistent AF had a higher risk of major bleeding. A comparison of the NIHSS scores between patients with different AF types revealed a distinct difference between the mean values of the two groups, but there was no interaction between AF type and NIHSS score for major bleeding (Supplementary Table 3 in the online-only Data Supplement). The NIHSS scores, creatinine clearance and the frequencies of previous stroke, congestive heart failure, and dyslipidemia were significantly different between persistent AF and paroxysmal AF groups (Supplementary Table 4 in the online-only Data Supplement). The persistent AF group comprised a large proportion of patients with high stroke severity (NIHSS score ≥7) and with a history of stroke, or comorbidities, such as congestive heart failure, dyslipidemia, and renal impairment (Supplementary Table 5 in the online-only Data Supplement). Although the NIHSS score had no effect on major bleeding according to AF type, it is possible that patients with persistent AF have higher risk of bleeding because they have potential risk factors associated with major bleeding, including comorbidities.

The initial hemoglobin level was negatively associated with increased risk of major bleeding in this study. A previous study indicated that a low baseline hemoglobin level is an independent predictor of major bleeding risk in acute coronary syndrome.[20] In another study, a lower baseline hemoglobin level−even one within normal range−was correlated with higher long-term risks of major bleeding, ischemic stroke, and mortality after percutaneous coronary intervention.[21] However, the causal relationship between low initial hemoglobin level and a major bleeding event is unclear. A low hemoglobin level may be a marker of occult GIB, hemorrhagic diathesis, or propensity for bleeding in such situations. We therefore performed propensity score matching to determine whether the low baseline hemoglobin level in our study acted as a confounding variable affecting the results of our study due to selection bias. This analysis showed that no covariate exhibited a large imbalance, and so it can be concluded that a low baseline hemoglobin level did not serve as a confounder that led to selection bias, and hence is an independent predictor of major bleeding.

This study identified hypertension as a significant predictor of major bleeding in the univariable and multivariable regression analyses. Previous studies of patients with AF taking OACs found that uncontrolled hypertension, especially

a systolic blood pressure of 150 mm Hg or greater, was associated with an increased major bleeding risk.[22,23] Increased risks of bleeding complications were not found in those with or without a history of hypertension.

There is a previous report[24] on the importance of the optimal control of intracranial atherosclerotic disease to reduce major vascular events, and antiplatelet agents were administered to patients with ICAS in that study. However, the effect of ICAS on the occurrence of major bleeding due to the combined use of OACs and antiplatelet was not significant (p=0.885). The proportions of concomitant antiplatelet therapy were similar in patients with (n=127, 16.5%) and those without (n=103, 16.0%) ICAS. The effects of each medication type on major bleeding at hospital discharge were not significant (Supplementary Table 6 in the online-only Data Supplement). Another recent study[25] suggested that the burden of concomitant atherosclerotic vascular disease among patients with stroke and AF is associated with a higher risk of adverse vascular outcomes.

Our study had several limitations. First, the high dropout rate may have limited the reliability of the results due to a retrospective design of the study. Second, the incidence rate of major bleeding (1.35 per 100 patient-years, 95% CI 1.31−1.40 per 100 patient-years) was lower in our study than in a previous observational study that found that the median incidence rate of major bleeding in patients with AF who received a vitamin K antagonist was 2.0 per 100 patient-years (IQR 1.5−3.8 per 100 patient-years).[26] In the present study of real-world data, major bleeding risk was slightly underestimated for several reasons, including patients who were vulnerable to bleeding would not have been prescribed an OAC, and some at a high risk of bleeding might have died or dropped out. Third, only 34 patients among the sample experienced a major bleeding event, more than half of which were GIB (n=21). GIB generally has a broad spectrum, from relatively easy-to-correct to life-threatening bleeding, and is a common bleeding complication in the elderly such as the patients in our study. Among the study subjects, 19 had ICH, of which 4 were major bleeding according to ISTH criteria, and 2 were fatal. In other words, ICH is not necessarily fatal, and in some cases there may be minor or no sequelae. Fourth, 874 patients who did not take OACs after index stroke were excluded from this study. A previous K-ATTENTION study[2] found that there were differences between the baseline characteristics of patients who did and did not take OACs after stroke. Fifth, among all major bleeding events in our study, their proportion was higher in patients who received warfarin than in those who received NOACs. Several studies have found that non-vitamin K antagonist OACs are superior to warfarin in terms of the safety outcomes for major bleeding.[27,28] However, OAC type was not considered a confounding factor in the present study. A discrepancy in OAC use duration may have occurred because some patients switched between OAC types during the follow-up period. Sixth, there were no subsequent INR data other than baseline values, but data for time in the therapeutic range (TTR) were available (Supplementary Table 7 in the online-only Data Supplement). Therefore, there were no significant limitations in assessing the bleeding risk associated with warfarin use during the follow-up period. Seventh, since this study had a retrospective registry-based design, the modified HAS-BLED score was calculated.

In conclusion, this study identified independent associations between major bleeding and stroke-specific factors such as stroke severity and intracranial atherosclerosis in anticoagulated patients with stroke and AF.

The findings of this study have the clinical implication that baseline characteristics of patients with stroke and AF should be considered in secondary prevention for the net clinical benefit of balancing recurrent stroke prevention while minimizing bleeding complications.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0289.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Woo-Keun Seo received honoraria for lectures from Sanofi-Aventis, Otsuka Korea, Dong-A Pharmaceutical Co, Ltd; study grants from Daiichi Sankyo Korea Co, Ltd; a consulting fee from OBELAB, Inc; and a stock option from JLK Inspection. The other authors report no conflicts.

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