ORIGINAL RESEARCH

Identification of Markers Associated With Development of Stroke in "Clinically Low-Risk" Atrial Fibrillation Patients

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***Background*—**Stroke and thromboembolic events may still occur in "clinically low-risk" atrial fibrillation (AF) patients as categorized by CHA_2DS_2-VASc score. Our aim was to assess the proportion of "clinically low-risk" patients using a nongender CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score of 0 to 1 among patients who experienced AF-associated stroke and to identify markers associated with stroke in "clinically low-risk" patients.

***Methods and Results*—**We retrospectively recruited nonvalvular AF patients who experienced embolic stroke between 2013 and 2016 from 9 institutes in Korea. AF patients with CHA_2DS_2-VA score of 0 to 1 at the time of stroke were analyzed and compared with "clinically low-risk" AF patients without stroke. A total of 3033 subjects with AF-associated stroke were recruited. Of these, 583 patients (19.2%) had CHA_2DS_2-VA score of 0 to 1. On multivariate analysis, age (≥60 years), N-terminal pro B-type natriuretic peptide (≥300 pg/mL), creatinine clearance (<50 mL/min), and left atrial dimension (≥45 mm) were independently associated with stroke. With the combined application of these 4 factors (collectively, ABCD score) to the "clinically low-risk" patients, the c-index was 0.858 (95% CI 0.838–0.877; P<0.001).

***Conclusions*—**The present study suggests a new insight into how additional use of markers can further refine stroke risk differentiation among AF patients initially classified as "clinically low-risk."

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT03147911. **(*J Am Heart Assoc*. 2019;8: e012697. DOI: 10.1161/JAHA.119.012697.)**

Key Words: ABCD score • atrial fibrillation • risk score • risk stratification • stroke, ischemic

Patients with atrial fibrillation (AF) have a 5-fold increased risk of stroke compared with matched individuals without AF, and strokes associated with AF are more likely to be fatal and disabling.[1] Effective stroke prevention requires oral anticoagulation (OAC),[2] but this should be counterbalanced by the potential risk of OAC-related bleeding events.[1] As a consequence, decision-making on whether OAC therapy should be prescribed requires careful risk stratification.[3]

The CHA_2DS_2-VASc score is now used in many guidelines for risk stratification and has a good performance in identifying nonvalvular AF patients at low stroke risk.[4] Nevertheless, stroke and thromboembolic events still occur

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Clinical Perspective

What Is New?

- Among patients who had been classified as low risk by the CHA_2DS_2-VASc scheme, the characteristics of patients who experienced ischemic stroke were investigated.

What Are the Clinical Implications?

- Considering the improved risk–benefit ratio of non-vitamin K oral anticoagulants, an updated or adjuvant scheme should be required in order to identify patients who are at a truly low risk for stroke.
- Although the ABCD (age [≥60 years], NT-proBNP (N-terminal pro B-type natriuretic peptide) [≥300 pg/mL], creatinine clearance [<50 mL/min], and left atrial dimension [≥45 mm]) scheme was derived from the retrospective, cross-sectional assessment, it is worth examining in a prospective way.

in such "low-risk" AF patients as categorized by the CHA_2DS_2-VASc score.[3,5] Recently, the introduction of the non-vitamin K oral anticoagulants (NOACs) has changed the landscape for stroke prevention in AF, although regional differences are apparent.[6] The availability of NOAC has shifted the stroke treatment threshold down to ≈0.9 event per 100-person years; indeed, NOACs can be considered even for AF patients with a nongender CHA_2DS_2-VASc score of 1.[7,8]

The incidence of stroke among AF patients, especially in a CHA_2DS_2-VASc score of 0 or 1, varies among different cohort populations.[5] Previous studies have suggested that the application of a modified CHA_2DS_2-VASc score might be more appropriate for stroke prevention in Asian populations.[9,10] In addition, the influence of female sex (the Sc criterion in CHA_2DS_2-VASc) on stroke risk in "low-risk" AF patients is debatable because female sex may be a *risk modifier* rather than a risk factor.[11,12] In such low-risk patients, use of the CHA_2DS_2-VA score (ie, female sex is excluded, or nongender CHA_2DS_2-VASc score) would suffice for risk stratification of such AF patients.[12]

Given that stroke events still occur in nonvalvular AF patients who are considered clinically "low risk" with a CHA_2DS_2-VA score of 0 or 1, further refinement of stroke risk stratification would be helpful in identifying those AF patients who may or may not get benefit from OAC therapy. Biomarkers have been proposed to be useful for this purpose.[13]

Our aim was to assess the proportion of embolic stroke in "low-risk" AF patients using a nongender CHA_2DS_2-VASc score (ie, CHA_2DS_2-VA) of 0 to 1 and to identify markers associated with stroke. Second, we used these data to derive a novel risk stratification schema that includes biomarkers, for refining stroke risk stratification among this "low-risk" cohort.

Methods

Study Population and Design

This study is composed of 2 separate cohorts. First, we retrospectively reviewed data of nonvalvular AF patients with cardioembolic stroke between January 2013 and December 2016 from the nationwide stroke registry including 9 institutes in Korea. Of these, consecutive patients with a CHA_2DS_2-VA score of 0 or 1 at the time of stroke event were enrolled. Second, we defined a control group as subjects who were matched by the nearest-neighbor method with type of AF and CHA_2DS_2-VASc score among nonvalvular AF patients without stroke from a consortium AF registry from 3 Korea University Hospitals from 2015 to 2016.[14]

The CHA_2DS_2-VA score was calculated by adding 2 points for age ≥75 years old and prior stroke or transient ischemic attack, and 1 point for congestive heart failure (or left ventricular ejection fraction ≤40%), hypertension, age 65 to 74 years, diabetes mellitus, and vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) with a maximum 8 points.[12,15]

Medical records of all subjects were comprehensively reviewed for demographic data, cardiovascular risk factors, parameters of transthoracic echocardiography, and laboratory data (complete blood counts, red blood cell distribution width, NT-proBNP [N-terminal pro B-type natriuretic peptide], blood urea nitrogen, creatinine, uric acid, and low-density cholesterol). Left ventricular ejection fraction was calculated using Simpson's biplane method and dimension of the left atrium (LA) was measured using M-mode of transthoracic echocardiography.

This study was conducted with approval of the Institutional Review Board at each institution. The authors declare that all supporting data are available within the article. The board waived the need for patient consent because of the retrospective, cross-sectional analysis design of the present study. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. This study was registered with ClinicalTrials.gov, unique identifier NCT03147911.

AF Diagnosis and Cardioembolic Stroke

Diagnosis of AF was made on ECG showing the typical pattern of AF with >30 s AF episode duration. AF was defined as paroxysmal AF if its duration was <7 days and persistent AF if its duration was ≥7 days. Nonvalvular AF was defined as the absence of mitral stenosis (>mild) and prosthetic mechanical mitral valve. Diagnosis of cardioembolic stroke was confirmed by the neurologists of each institute according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[16]

Statistical Analysis

Normally distributed continuous variables were expressed as mean and SD, and categorical data were expressed as numbers and percentages. Nonparametrically distributed data were reported as median values with interquartile ranges. For comparison across groups, continuous variables were compared using the Student *t* test or analysis of variance, as appropriate, and categorical variables were analyzed using the χ^2 test or Fisher exact test, as appropriate. Univariate logistic regression analysis was performed to identify the variables that were significantly related to stroke event. A multivariate logistic regression model was used to investigate the independent risk factors of stroke events. Variables that showed *P* value of <0.1 from the univariate logistic regression model were entered into the multivariate regression models. To assess the performance of the proposed risk differentiation scheme, receiver operating characteristic analysis was performed and the result of the receiver operating characteristic analysis was internally validated and calibrated using the bootstrapping technique to correct bias of the model. To compare the performance of different models, 2 receiver operating characteristic curves were compared according to the method as described by DeLong et al.[17] In order to quantitatively compare the ability to differentiate patients at risk according to each scheme, the integrated discrimination improvement and the net reclassification index (NRI) with a category-free option were calculated.[18] A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed by R version 3.2.1 (Foundation for Statistical Computing, Vienna, Austria) and STATA version 13.0 (Stata Corp, College Station, TX).

Results

A total of 3033 nonvalvular AF subjects with cardioembolic stroke were recruited. In Table 1, 583 patients (19.2%) had a CHA_2DS_2-VA score of 0 or 1 (198 patients [6.5%] in CHA_2DS_2-VA score of 0, 385 patients [12.7%] in CHA_2DS_2-VA score of 1). As a control group, 598 subjects were extracted from the nonvalvular AF registry consortium by nearest-neighbor propensity matching. Stroke patients were significantly older, with a female predominance, and had significantly lower estimated creatinine clearance rate (CCr), larger LA dimension, and higher uric acid and NT-proBNP levels, as compared with controls. When compared with the stroke group, control subjects had a significantly higher prevalence of hypertension and diabetes mellitus. There was no significant difference in mean CHA_2DS_2-VA score between the 2 groups.

Based on the CHA_2DS_2-VASc score, 462 patients with stroke (15.2%) had a CHA_2DS_2-VASc score of 0 or 1 (136 patients [4.5%] in CHA_2DS_2-VASc score of 0, 326 patients [10.7%] in a CHA_2DS_2-VASc score of 1). Baseline characteristics of subjects with CHA_2DS_2-VASc score of 0 or 1 are described in Table 2.

Biomarkers Associated With Stroke

On univariate analysis, older age (≥60 years), being female, hypertension, diabetes mellitus, LA dimension (≥45 mm), red blood cell distribution width, CCr (<50 mL/min), uric acid (>7 mg/dL), and NT-proBNP (≥300 pg/mL) were significantly associated with stroke events (Table 3). Type of AF and left ventricular ejection fraction were not significantly related with stroke events. Eleven variables (older age, being female, hypertension, diabetes mellitus, vascular disease, CHA_2DS_2-VA score, LA dimension [≥45 mm], red blood cell distribution width, CCr [<50 mL/min], uric acid [>7 mg/dL], and NT-proBNP [≥300 pg/mL]) were included in the multivariate logistic regression analysis.

On the multivariate regression model, age (≥60), NT-proBNP (≥300 pg/mL), CCr (<50 mL/min), and LA dimension (≥45 mm) were independently associated with stroke events. These were used to derive a simple score, *ABCD* (*A*ge, NT-pro*B*NP, *C*Cr, and *D*imension of the LA) score, based on the independent associated factors for stroke events. The β coefficient of each independent risk factor was assigned to a score number and each selected factor was assigned 1 point.

Performance of ABCD Score in Differentiating in "Clinically Low-Risk" Patients

The distribution of the CHA_2DS_2-VA score of 0 to 1 patients by the ABCD score is shown in Figure 1. There was a significant increase in stroke events according to increase in the ABCD score points (*P*<0.001) in patients with a CHA_2DS_2-VA score of 0 to 1 and those with a CHA_2DS_2-VASc score of 0 to 1.

Figure 2 shows the area under the resulting c-indexes (based on receiver operating characteristic curves) of the ABCD score. The c-index of the ABCD score was 0.858 (95% CI 0.838–0.877; *P*<0.001) in patients with a CHA_2DS_2-VA score of 0 to 1, and 0.850 (95% CI 0.827–0.873; *P*<0.001) in those with a CHA_2DS_2-VASc score of 0 to 1. The internally validated c-index of ABCD score was 0.780 (95% CI 0.752–0.808) using a bootstrapping procedure. With Hosmer–Lemeshow test, model calibration of ABCD score showed good agreements between observed stroke event and expected stroke event (*P*=0.077, Figure 3).

ABCD Score Versus CHA_2DS_2-VA or CHA_2DS_2-VASc Score

The c-indexes of the CHA_2DS_2-VA and CHA_2DS_2-VASc score were 0.527 (95% CI 0.499–0.554; *P*<0.001) and 0.548

Table 1. Baseline Characteristics of Subjects

	Stroke (N=583)	Control (N=598)	*P* Value
Age, y	60.9±8.4	52.3±9.5	<0.001
Age ≥65 y	176 (30.2%)	41 (6.9%)	<0.001
Female sex	183 (31.4%)	146 (24.4%)	0.009
Persistent AF	318 (55.1%)	306 (51.2%)	0.195
CHF	27 (4.6%)	41 (6.9%)	0.129
HTN	158 (27.1%)	228 (38.1%)	<0.001
DM	20 (3.4%)	41 (6.9%)	0.011
Vascular disease	4 (0.7%)	12 (2.0%)	0.087
CHA_2DS_2-VA score			0.065
0	198 (34.0%)	235 (39.3%)	
1	385 (66.0%)	363 (60.7%)	
Sex with CHA_2DS_2-VA score			
Male with 0	136 (23.3%)	179 (29.9%)	0.012
Male with 1	264 (45.3%)	273 (45.7%)	0.945
Female with 0	62 (10.6%)	56 (9.4%)	0.528
Female with 1	121 (20.8%)	90 (15.1%)	0.013
Male with 0 or 1 and female with 0	462 (79.2%)	508 (84.9%)	0.013
LVEF, %	60.0 (10.2)	62.5 (5.0)	0.144
LA dimension, mL	43.1 (9.0)	39.5 (7.5)	<0.001
Hb, g/dL	14.2 (2.2)	14.1 (2.6)	0.703
RDW, %	13.2 (1.2)	13.1 (0.9)	0.142
LDL, mg/dL	101.7±33.4	104.6±28.7	0.149
CCr, mL/min	78.2 (31.6)	98.9 (32.6)	<0.001
Uric acid, mg/mL	5.3 (2.2)	4.8 (2.2)	<0.001
NT-proBNP pg/mL	524.5 (608.5)	80.3 (172.9)	<0.001

Data are presented as mean±SD or median (interquartile range). AF indicates atrial fibrillation; CCr, creatinine clearance rate; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years; CHF, congestive heart failure; DM, diabetes mellitus; vascular disease, peripheral artery disease, myocardial infarction or aortic plaque; Hb, hemoglobin; HTN, hypertension; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; RDW, red blood cell distribution width.

Table 2. Baseline Characteristics of Subjects With CHA_2DS_2-VASc Score of 0 or 1

	Stroke (N=462)	Control (N=508)	*P* Value
Age, y	59.8±8.3	51.3±9.6	<0.001
Age ≥65 y	114 (24.7%)	28 (5.5%)	<0.001
Female sex	62 (13.4%)	56 (11.0%)	0.297
Persistent AF	246 (53.7%)	264 (52.0%)	0.633
CHF	18 (3.9%)	30 (5.9%)	0.196
HTN	112 (24.2%)	173 (34.1%)	0.001
DM	17 (3.7%)	30 (5.9%)	0.144
Vascular disease	3 (0.6%)	12 (2.4%)	0.058
CHA_2DS_2-VASc score			0.317
0	136 (29.4%)	179 (35.2%)	
1	326 (70.6%)	329 (64.8%)	
Sex with CHA_2DS_2-VASc score			
Male with 0	136 (29.4%)	179 (35.2%)	0.063
Male with 1	264 (57.1%)	273 (53.7%)	0.317
Female with 0	62 (13.4%)	56 (11.0%)	0.297
LVEF, %	59.0 (11.0)	62.5 (7.5)	0.123
LA dimension, mL	43.1 (9.0)	39.5 (7.5)	<0.001
Hb, g/dL	14.4 (2.2)	14.4 (2.6)	0.864
RDW, %	13.2 (1.2)	13.1 (0.9)	0.096
LDL, mg/dL	102.0 (44.5)	100.0 (39.0)	0.239
CCr, mL/min	80.8 (31.9)	100.0 (32.3)	<0.001
Uric acid, mg/mL	5.6 (2.1)	5.1 (2.2)	<0.001
NT-proBNP pg/mL	480.0 (574.0)	76.8 (171.6)	<0.001

Data are presented as mean±SD or median (interquartile range). AF indicates atrial fibrillation; CCr, creatinine clearance rate; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years; CHF, congestive heart failure; DM, diabetes mellitus; vascular disease, peripheral artery disease, myocardial infarction or aortic plaque; Hb, hemoglobin; HTN, hypertension; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; RDW, red blood cell distribution width.

(0.519–0.577; *P*<0.001), respectively (Figure 2). Corrected c-indexes from 1000 bootstrap samples for ABCD, CHA_2DS_2-VA, and CHA_2DS_2-VASc score were 0.870 (95% CI 0.848–0.891), 0.632 (95% CI 0.606–0.656), and 0.649 (95% CI 0.621–0.677), respectively. The c-index of the ABCD score was higher than those of the CHA_2DS_2-VA or CHA_2DS_2-VASc score (Table 4; DeLong test z=21.53; *P*<0.001, z=19.08; *P*<0.001, respectively).

The integrated discrimination improvement of the ABCD score was significantly improved as compared with CHA_2DS_2-VA and CHA_2DS_2-VASc score (Table 4; integrated discrimination improvement=0.339; *P*<0.001, integrated discrimination improvement=0.334; *P*<0.001, respectively). Significant NRIs were present with the ABCD score as compared with CHA_2DS_2-VA and CHA_2DS_2-VASc score, respectively (Table 4).

Discussion

The present study has several noteworthy findings: (1) among AF patients who developed a stroke, 19.2% had a CHA_2DS_2-VA score of 0 or 1; (2) clinical, biomarker, and imaging factors (ie, age [≥60], NT-proBNP [≥300 pg/mL], CCr [<50 mL/min], dimension of LA [≥45 mm], incorporated in the ABCD score) were independently associated with stroke events even in AF

Table 3. Univariate and Multivariate Logistic Regression Analysis for Factors Associated With Stroke in Patients With AF

CHA_2DS_2-VA Score of 0 or 1							
	Univariate Analysis			Multivariate Analysis			
	ß	OR (95% CI)	*P* Value	ß	OR (95% CI)	*P* Value	Pt.
Age ≥60 y	1.75	5.78 (4.5–7.45)	<0.001	1.623	5.06 (3.38–7.56)	<0.001	1
Female sex	0.348	1.42 (1.10–1.83)	0.008	0.047	1.05 (0.69–1.59)	0.823	
Persist AF	0.158	1.17 (0.93–1.47)	0.176				
CHF	−0.416	0.66 (0.40–1.09)	0.103				
HTN	−0.505	0.60 (0.47–0.77)	<0.001	−0.197	0.82 (0.49–1.37)	0.448	
DM	−0.729	0.48 (0.28–0.83)	0.009	−0.360	0.70 (0.28–1.75)	0.442	
Vascular disease	−1.087	0.34 (0.11–1.05)	0.061	−0.564	0.57 (0.11–2.89)	0.496	
CHA_2DS_2-VA score	0.230	1.26 (0.98–1.60)	0.057	−0.375	0.69 (0.41–1.16)	0.163	
LVEF, %	−0.010	0.99 (0.98–1.0)	0.138				
LA diameter ≥45 mm	1.312	3.71 (2.83–4.87)	<0.001	1.39	4.01 (2.70–5.97)	<0.001	1
RDW	0.172	1.19 (1.07–1.32)	0.001	−0.035	0.97 (0.86–1.09)	0.561	
LDL, mg/dL	−0.003	1.00 (0.99–1.00)	0.143				
CCr (<50 mL/min)	2.483	11.98 (5.13–27.97)	<0.001	1.933	6.91 (2.06–23.22)	0.002	1
Uric acid (>7 mg/dL)	0.658	1.93 (1.32–2.83)	0.008	0.186	1.20 (0.68–2.14)	0.527	
NT-proBNP (≥300 pg/mL)	2.759	15.78 (11.81–21.08)	<0.001	2.005	7.42 (5.15–10.70)	<0.001	1

AF indicates atrial fibrillation; CCr, creatinine clearance rate; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74; CHF, congestive heart failure; DM, diabetes mellitus; vascular disease, peripheral artery disease, myocardial infarction or aortic plaque; HTN, hypertension; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; OR, odds ratio; Pt, point; RDW, red blood cell distribution width.

patients with a CHA_2DS_2-VA score of 0 to 1 and CHA_2DS_2-VASc score of 0 to 1; and (3) the ABCD score was significantly superior to those of the CHA_2DS_2-VA or CHA_2DS_2-VASc score in differentiating "truly low-risk" patients.

The present study provides new insights into how addition of biomarkers can further refine stroke risk stratification among AF patients initially defined as "clinically low risk" based on the CHA_2DS_2-VA criteria. Major guidelines have

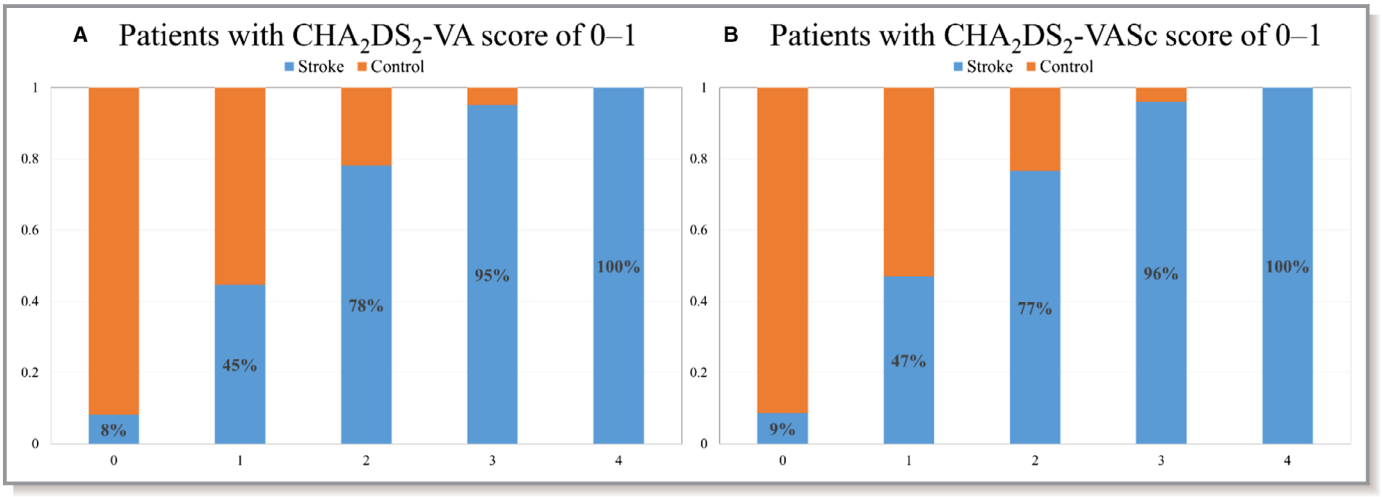

Figure 1. Distribution of AF patients with stroke event according to the ABCD score. **A**, Distribution of ABCD score in patients with CHA_2DS_2-VA score 0 or 1 is shown. **B**, Distribution of ABCD score in patients with CHA_2DS_2-VASc score 0 or 1 is shown. ABCD indicates age, NT-proBNP, CCr, and dimension of the LA; AF, atrial fibrillation; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and age 65 to 74; and CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, and sex category; CCr, creatinine clearance rate; LA, left atrium; NT-proBNP, N-terminal pro B-type natriuretic peptide.

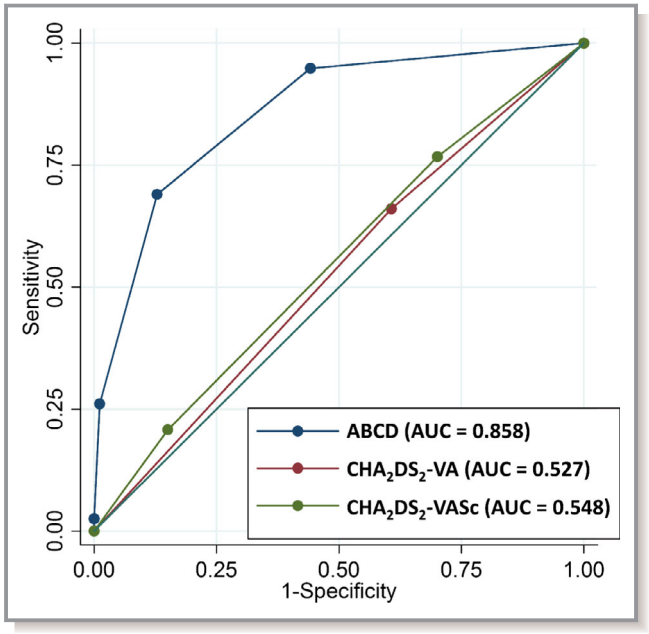

Figure 2. Receiver operating characteristic curve of the ABCD score for identifying a population with a truly low risk of stroke in AF patients. C-index of ABCD score was 0.858 (95% CI 0.838–0.877) and its risk stratification in low-risk group was superior to that of CHA_2DS_2-VA or CHA_2DS_2-VASc score. ABCD indicates age, NT-proBNP, CCr, and dimension of the LA; AF, atrial fibrillation; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and age 65 to 74 years; AUC, area under the curve; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, and sex category.

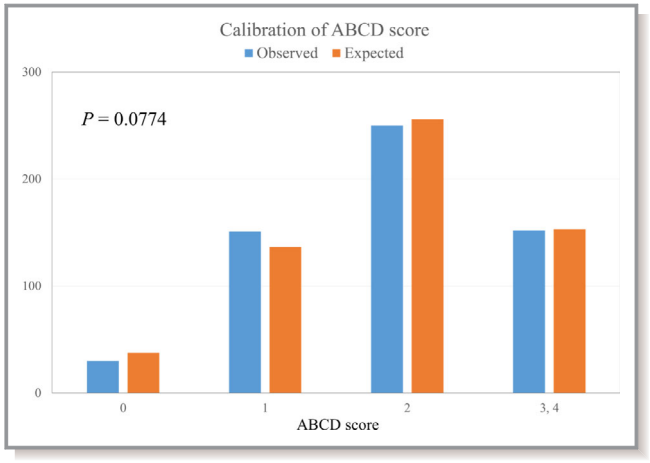

Figure 3. Calibration of ABCD score. ABCD score categories were defined as low risk (score=0), moderate risk (score 1, 2), and high risk (score 3, 4). There were no significant differences between observed stroke event number (blue) and expected stroke event number (red). ABCD indicates age, NT-proBNP, CCr, and dimension of the LA; AF, atrial fibrillation; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and age 65 to 74 years; CCr, creatinine clearance rate; LA, left atrium; NT-proBNP, N-terminal pro B-type natriuretic peptide.

recommended OAC treatment for prevention of thromboembolic events in patients with AF and CHA_2DS_2-VA and CHA_2DS_2-VASc score of ≥2.[19,20] Nevertheless, AF patients with 1 nongender CHA_2DS_2-VASc risk factor still have an elevated risk of stroke compared with patients with a CHA_2DS_2-VASc score of 0 and the clinical benefit of OAC may be positive in these patients.[5,7] However, the risk contribution of each component of the CHA_2DS_2-VASc score is not homogeneous.[21] As a consequence, decision-making for OAC in patients with AF and a CHA_2DS_2-VASc score of 1 requires consideration of bleeding risk and an individual weighing of stroke risk.[19,21] In this regard, adjuvant risk stratification using biomarkers may provide additional information to aid OAC treatment decision-making in these patients.[19]

The incidence of stroke in risk stratification scheme according to the CHA_2DS_2-VASc score also varies among different cohorts because of the characteristics of subjects, such as the proportions of different ethnicity, prevalence of chronic kidney disease, degree of LA remodeling, etc.[10] Furthermore, the impact of female sex on stroke among low-risk patients with AF is controversial,[11,12,22,23] and 1 recent study revealed that female sex was a "risk modifier" for stroke rather than a risk factor.[12] Of note, the incidence of stroke in

Table 4. C-Indexes, IDI, and NRI of the ABCD Score in Comparison With CHA_2DS_2-VA and CHA_2DS_2-VASc Score

	C-Index	95% CI	*P* Value	z Statistics*	*P* Value*	IDI*	*P* Value*	NRI*	*P* Value*
ABCD	0.858	0.838–0.877	<0.001						
CHA_2DS_2-VA	0.527	0.499–0.554	<0.001	21.53	<0.001	0.339	<0.001	0.769	<0.001
CHA_2DS_2-VASc	0.548	0.519–0.577	<0.001	19.08	<0.001	0.334	<0.001	0.787	<0.001

ABCD indicates age ≥60 years, NT-proBNP ≥300 pg/mL, CCr <50 mL/min, and dimension of LA ≥45 mm; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; CCr, creatinine clearance rate; IDI, integrated discriminatory improvement; NRI, net reclassification index; NT-proBNP, N-terminal pro B-type natriuretic peptide.
*For comparison with ABCD score.

Asian people may be higher compared with the white population, especially in patients with AF and a CHA_2DS_2-VASc score of 0 in whom OAC therapy is not indicated.[10,24]

Therefore, identifying "truly low-risk" patients using an adjuvant risk stratification scheme would be of clinical value in patients with AF and a low-risk CHA_2DS_2-VA or CHA_2DS_2-VASc profile (score of 0 or 1). Indeed, the approach to stroke prevention in AF has moved towards the default being OAC use unless the patient was deemed low risk, so relying on clinical risk stratification alone has limitations. As shown in this study, one fifth of patients with cardioembolic stroke were defined as clinically "low risk" based on the CHA_2DS_2-VA criteria, showing that further improvement in refining risk stratification is still needed in this group. Biomarkers have been proposed to have such a role.

Biomarkers ("biological markers"), whether blood, urine, or imaging based, will always improve on stroke risk stratification based on clinical factors.[25] Nevertheless, the use of multiple biomarkers has to be balanced against simplicity and practicality (and costs) of decision-making for OAC use, for stroke prevention in AF. In the present study, the ABCD score, which includes 2 blood biomarkers (NT-proBNP, creatinine clearance) and 1 imaging marker (LA dimension), showed good discriminatory value in both AF patients with a CHA_2DS_2-VA score of 0 to 1 or a CHA_2DS_2-VASc score of 0 to 1. Our results would suggest that the ABCD score can help physicians discriminate patients who have a truly low risk among AF patients with a CHA_2DS_2-VA or CHA_2DS_2-VASc score of 0 to 1 and would not require OAC treatment.

Consistent with our study, previous reports have demonstrated that elevated biomarkers such as NT-proBNP level, red blood cell distribution width, and uric acid level were significantly associated with stroke in patients with AF.[26–28] In the present study, red blood cell distribution width, uric acid levels (>7 mg/dL), and NT-proBNP level (≥300 pg/mL) were positively associated with stroke events on univariate analysis; however, only NT-proBNP level (≥300 pg/mL) was an independent predictor for stroke on multivariate analysis. Indeed, NT-proBNP levels have been positively associated with the incidence of stroke.[26,29]

In the present study, CCr (<50 mL/min) was another independent risk factor of stroke and this corresponds with prior studies.[30,31] Age is also a powerful driver of stroke risk in AF,[32] and also contributes 1 point to the ABCD score. Finally, LA enlargement contributes to blood stasis into the LA, and endothelial dysfunction of the LA may lead to thrombus formation.[33] LA enlargement may be a marker of atrial cardiomyopathy, which may cause thromboembolic events given atrial tissue abnormalities, such as fibrosis, endothelial cell dysfunction, and myocyte apoptosis.[33–35] Some studies have also shown that a dilated LA (≥45 mm) is associated with increased risk of stroke, consistent with our results.[36,37]

Limitations

Several limitations should be acknowledged. First, we were unable to estimate the annual stroke rate based on the ABCD score because of the retrospective nature and cross-sectional design of the present study. Second, since our study included only a Korean population, these results cannot be extrapolated to subjects of other ethnicities. Third, although the internal bootstrapping approach was conducted to supplement the absence of an external validation cohort, further studies on cohorts with different ethnicity will be needed to validate the ABCD score.

Conclusions

The present study provides new insights into how addition of biomarkers can further refine stroke risk stratification among AF patients initially defined as clinically "low risk." Almost one fifth of AF patients initially defined as "low risk" based on nongender clinical CHA_2DS_2-VASc criteria experienced embolic stroke. The ABCD score that applies biomarkers (NT-proBNP, creatinine clearance) and imaging (LA dimension) can further refine stroke risk stratification in this "clinically low-risk" patient group, and can help discriminate the AF population who are a "truly low-risk" group.

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