Validation of Conventional Thromboembolic Risk Factors in a Korean Atrial Fibrillation Population — Suggestion for a Novel Scoring System, CHA₂DS₂-VAK —

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Background: There is little evidence that focuses on the ethnic variability of clinical risk factors for thromboembolism (TE) in atrial fibrillation (AF). We aimed to investigate the effect of each traditional risk factor in the Korean AF population.

Methods and Results: Medical records of 12,876 consecutive patients (aged >18 years) newly diagnosed and followed up with non-valvular AF from 2000 to 2013 were reviewed. TE events, including ischemic stroke and systemic embolism, were investigated for risk factor validation. Among the total of 12,876 patients, 1,390 (10.8%) had TE events. In univariate/multivariate analysis adjusting for clinical factors and antithrombotic medications, traditional risk factors included in the CHA₂DS₂-VAsC scheme showed statistical significance, except for female sex, which was not a predictor of events. Additionally, chronic kidney disease (CKD; hazard ratio 1.62, $P<0.001$) was shown to be an independent predictor of TE events. Based on the analysis, we developed a novel stratification system, CHA₂DS₂-VAK, omitting the female sex category and adding CKD. The new scoring system showed greater discrimination in event rates between score 0 and 1 patients.

Conclusions: Female sex was not associated with TE events in a Korean non-valvular AF population. The novel CHA₂DS₂-VAK scoring system, with substitution of CKD for female sex, might be more appropriate for the Korean population.

Key Words: Atrial fibrillation; CHA₂DS₂-VAK; Chronic kidney disease; Females; Thromboembolism

Current risk stratification schemes for atrial fibrillation (AF) have shown modest predictive power for thromboembolic (TE) events (C-statistics approximately 0.6).^{1,2} However, many potential factors have not been fully assessed, because of a lack of systemic reviews in large populations. Chronic kidney disease (CKD) is one such potential factor considered as a predictor for TE events in AF patients.^{3,4} Recent findings suggest that a creatinine clearance of ≤ 60 mL/min or less may even be an independent predictor of stroke and systemic embolism.⁵

There is little evidence supporting ethnic variability of TE risk evaluation for AF. Traditional risk stratification systems have been developed based on Western population cohorts,⁶ the most popular being the CHA₂DS₂-VAsC system, which was also based on the Birmingham scheme and refined using European cohorts.⁷ Recently, Japanese investigators reported that female sex is not a risk factor for TE events among Japanese non-valvular AF patients mostly treated with warfarin.⁸ In the current AF guidelines, CHA₂DS₂-VAsC score of 1 with female factor is not considered as an anticoagulation indication.

The objective of this study was to create a novel scheme

for use in Asian AF patients by refining and incorporating traditional and potential risk factors. The new scoring system was then compared with existing systems.

Methods

Our study protocol was approved by the institutional review boards in Seoul National University Hospital and was in accordance with the Declaration of Helsinki.

Study Population

The study population was from a real-world, retrospective single-center cohort. Consecutive patients aged >18 years, who were newly diagnosed with non-valvular AF and followed up from 2000 to 2013 were systemically analyzed. Patients whose renal function was not assessed at the time of AF diagnosis or who did not visit the clinic more than twice were excluded from the analysis. Patients with follow-up duration <30 days were also excluded from the analysis. The study patients visited the cardiovascular center every 3 or 4 months. Follow-up data were obtained from medical record review. Because the patients included

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in this cohort (including patients from 2000 to 2013) were treated prior to the release of non-vitamin K antagonist oral anticoagulant in Korea, all patients with anticoagulants were prescribed warfarin.

Definition and Validation of TE Risk Factors

Risk factors were defined according to previous AF guidelines.^{7,9} Hypertension was defined as resting blood pressure ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic on at least 2 occasions, or being on antihypertensive pharmacologic therapy. Diabetes was defined as fasting glucose ≥ 126 mg/dL, hemoglobin A1c $\geq 6.5\%$, or use of diabetes medications. Vascular disease included myocardial infarction, peripheral artery disease and presence of complex aortic plaque. Heart failure (HF) was defined as signs/symptoms of HF or objective evidence of reduced left ventricular ejection fraction ($<40\%$). CKD was defined as presence of kidney damage or pathologically reduced glomerular filtration rate (MDRD estimated GFR <60 mL/min/1.73 m²) for more than 3 months, irrespective of the cause, according to KDIGO guidelines.¹⁰ When a diagnosis of any risk factor was unclear, we referred to the medical records of the responsible physician. TE events were defined as ischemic stroke, transient ischemic attack (TIA) and systemic embolism. Ischemic stroke included all types of stroke with an ischemic cause, and hemorrhagic stroke was classified as bleeding.⁹

CHA₂DS₂-VAK: a Novel Stratification System

CHA₂DS₂-VAsC was renamed CHA₂DS₂-VAK because the “S”ex “c” category was replaced with “K”idney disease (Table 1). This new system was based on the validation results described here.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation. The risk of ischemic stroke was analyzed by univariate and multivariate Cox proportional-hazards method. A 95% confidence interval (CI) is reported with predictive values. The means were compared using Student's t-test. Categorical variables were compared by Fisher's

Table 1. Novel Thromboembolic Risk Stratification System (CHA₂DS₂-VAK)

Risk factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65–74 years	1
Chronic Kidney disease	1
Total	9

TIA, transient ischemic attack.

Table 2. Baseline Characteristics of Korean AF Patients

	Total (n=12,876)	Thromboembolic event		P value
		Yes (n=1,390)	No (n=11,486)	
Age (years)	64.9 $\pm$ 12.0	68.4 $\pm$ 9.6	64.5 $\pm$ 12.2	<0.001
65–74	4,746 (36.9%)	573 (41.2%)	4,173 (36.3%)	<0.001
≥ 75	2,594 (20.1%)	377 (27.1%)	2,217 (19.3%)	<0.001
Female	4,700 (36.5%)	540 (38.8%)	4,160 (36.2%)	0.055
Hypertension	4,203 (32.6%)	726 (52.2%)	3,477 (30.3%)	<0.001
Diabetes	2,539 (19.7%)	404 (29.0%)	2,135 (18.6%)	<0.001
Previous TE event	481 (3.7%)	87 (6.3%)	394 (3.4%)	<0.001
Vascular disease	661 (5.1%)	121 (8.7%)	540 (4.7%)	<0.001
CKD	3,712 (28.8%)	536 (38.6%)	3,176 (27.7%)	<0.001
Heart failure	2,228 (17.3%)	318 (22.9%)	1,910 (16.6%)	<0.001
CHA ₂ DS ₂ -VAsC score	1.72 $\pm$ 1.22	2.26 $\pm$ 1.24	1.65 $\pm$ 1.20	<0.001
0	1,866 (14.5%)	67 (4.9%)	1,799 (15.7%)	
1	4,357 (33.8%)	335 (24.1%)	4,022 (35.0%)	
2	3,660 (28.4%)	445 (32.0%)	3,215 (28.0%)	
3	1,935 (15.0%)	331 (23.8%)	1,604 (14.0%)	
≥ 4	1,058 (8.2%)	212 (15.3%)	846 (7.4%)	
Hemoglobin (g/dL)	12.9 $\pm$ 1.9	12.7 $\pm$ 1.9	13.0 $\pm$ 2.0	<0.001
Creatinine	1.24 $\pm$ 1.06	1.30 $\pm$ 0.99	1.24 $\pm$ 1.07	0.036
GFR (mL/min/1.73 m ²)	68.4 $\pm$ 22.9	64.1 $\pm$ 22.1	68.9 $\pm$ 22.9	<0.001
Cholesterol	163.7 $\pm$ 32.9	158.4 $\pm$ 29.4	164.4 $\pm$ 33.3	<0.001
LDL (mg/dL)	99.2 $\pm$ 27.9	95.6 $\pm$ 24.3	99.8 $\pm$ 28.4	<0.001
HbA1c (%)	6.4 $\pm$ 1.0	6.3 $\pm$ 0.9	6.4 $\pm$ 1.1	0.017
Antiplatelets	4,705 (36.5%)	507 (36.4%)	4,198 (36.6%)	0.929
Anticoagulation	4,386 (34.1%)	80 (5.7%)	4,306 (37.5%)	<0.001
No anticoagulant	3,703 (28.8%)	782 (56.2%)	2,921 (25.4%)	<0.001
Follow-up duration (years)	4.67 $\pm$ 3.72	4.86 $\pm$ 3.68	4.46 $\pm$ 3.63	<0.001

CKD, chronic kidney disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; TE, thromboembolism.

Table 3. Univariate and Multivariate Analyses for Risk Factor Verification

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.05	1.04–1.05	<0.001	1.04	1.03–1.04	<0.001
Age ≥75 years	2.14	1.89–2.41	<0.001			
Female	1.06	0.95–1.17	0.325	0.96	0.86–1.07	0.411
Hypertension	1.95	1.76–2.17	<0.001	1.59	1.44–1.80	<0.001
Diabetes	1.49	1.33–1.68	<0.001	1.23	1.10–1.40	<0.001
Previous TE event	2.20	1.77–2.73	<0.001	1.57	1.26–1.96	<0.001
Vascular disease	1.76	1.46–2.12	<0.001	1.23	1.02–1.49	0.043
CKD	1.62	1.45–1.80	<0.001	1.17	1.04–1.31	0.007
Heart failure	1.25	1.11–1.42	<0.001	1.19	1.05–1.36	0.007
Anticoagulation	0.10	0.08–0.13	<0.001	0.11	0.09–0.14	<0.001

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; TE, thromboembolism.

Figure 1. Annual thromboembolic event rate according to CHA₂DS₂-VASc score and sex category. Female patients showed similar event rates with males, even though they have a lower CHA₂DS₂-VASc score.

exact test and the χ^2 test.

We validated each risk factor (age, sex, HF, hypertension, diabetes, previous stroke history, vascular disease and CKD) by univariate and multivariate Cox survival model. In multivariate survival analysis, TE prophylaxis (none/antiplatelet agent/ anticoagulant) was compensated as a covariate. The novel stratification system was derived from the above statistical analyses. Model comparison between the novel system and the CHA₂DS₂-VASc scheme was achieved using the area under curve (AUC) of receiver-operator curves (ROC). Subgroup analyses for the patients with CHA₂DS₂-VASc score of 1 and oral anticoagulant-naïve patients were done.

P<0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 21.0 software package (IBM SPSS, New York, USA).

Results

In total, 12,876 consecutive non-valvular AF patients were enrolled. There were 1,390 (10.8%) TE events during the study period. Baseline characteristics are described in **Table 2**. The prevalence of traditional risk factors was significantly different between patients with and without TE events, except for female sex.

TE Risk Factor Verification

In the univariate analysis, female sex did not show predictive power for TE events. Age over 75 years and a history of previous TE events, which are granted 2 points each in the CHA₂DS₂-VASc system, showed a higher hazard ratio

than other significant risk factors such as hypertension, diabetes, vascular disease and CKD. For age factor validation, we re-analyzed the stroke risk by dividing the age into 5-year groups and the results are described in **Figure S1**. In this analysis, the TE risk began to increase from age 60, and increased sharply at age 65, and overuse of anticoagulation was also a significant determinant for prediction. In the multivariate analysis, most risk factors retained their predictive power, although female sex was still not a significant predictor for TE events (**Table 3**). In the subgroup of patients not on anticoagulants (n=8,490, **Table S1**), females sex was not a predictor for TE events (P=0.539), but CKD was a significant predictor for outcome (P<0.001) (**Table S2**).

Female sex did not show significant predictive power for TE events among the study population (P=0.325, **Table 2**). The risk of patients with CHA₂DS₂-VASc=0 was not statistically different from those with score 1 for female sex. The risk of male patients with score 1 was not different from female patients with score 2 (**Figure 1**). There was a significant difference in the TE risk between sex category in the same CHA₂DS₂-VASc score (P<0.001 in score 1, P=0.001 in score 2, and P=0.044 in score ≥3 patients). The Kaplan-Meier curves for TE events according to sex and CHA₂DS₂-VASc score in anticoagulant-naïve patients are shown in **Figure S2**. The subgroup analysis of the female factor showed no prognostic power for TE events (**Figure S3**).

CKD was an important predictor for TE events (HR 1.62, P<0.001 in univariate analysis). The multivariate analysis correcting for conventional risk factors included in the CHA₂DS₂-VASc scoring system also showed that

CKD significantly predicted TE risk (Table 3). TE risk was shown to increase as GFR decreased (Figure 2).

CHA₂DS₂-VAK: a Novel Stratification System

In the traditional CHA₂DS₂-VASc scoring system, risk of TE events increased according to score. Compared with patients with score 0, risk for patients with score 1 showed a 2.10-fold increase (95% CI 1.64–2.77, P<0.001), score 2 patients had a 3.42-fold increase (95% CI 2.64–4.42, P<0.001), score 3 patients had a 4.69-fold increase (95% CI 3.61–6.12, P<0.001), and score >3 patients had a 5.86-fold increase (95% CI 4.46–7.72, P<0.001). The AUC of the CHA₂DS₂-VASc in the cohort was 0.639 (95% CI 0.62–0.65, P<0.001) by ROC curve.

To enhance the predictive and discriminative power of the CHA₂DS₂-VASc scheme, we substituted the female category with CKD and renamed. CHA₂DS₂-VASc as CHA₂DS₂-VAK (Table 1). Based on the relative risk in this study, age over 75 years and previous stroke history were given 2 points each as in the CHA₂DS₂-VASc scoring system. The new CHA₂DS₂-VAK system had an AUC of 0.650 (95% CI 0.64–0.66, P<0.001). Compared to patients with CHA₂DS₂-VAK score 0, patients with score 1 had a 2.43-fold increase in risk (95% CI 1.94–3.05, P<0.001), score 2 patients had a 3.40-fold increase (95% CI 2.72–4.25, P<0.001), score 3 patients had a 5.43-fold increase (95% CI 4.33–6.81, P<0.001), and patients with score over 3 had a 5.91-fold increase in risk (95% CI 4.66–7.51, P<0.001).

The annual TE event rate for both the CHA₂DS₂-VAK and CHA₂DS₂-VASc scheme are described in Table 4. The data for anticoagulant-naïve patients are shown in Table S3. Applying the new system, a total of 5,296 (41.1%) patients have changes in their risk stratification. There were 2,154 (16.7%) patients getting an additional point, and 3,142 (24.2%) patients lost 1 point from their CHA₂DS₂-VASc scores. Detailed data of patients with changes when converting to the CHA₂DS₂-VAK score are described in Table S4. The difference according to the CHA₂DS₂-VAK scores (0, 1, and 2) derived from a CHA₂DS₂-VASc score of 1 was further analyzed. The new system better discriminated intermediate-risk patients (Figure 3). In this analysis, CHA₂DS₂-VAK score 2 patients had a 3-fold increased risk of TE than score 0 patients (HR 3.35, 95% CI 2.29–4.92, P<0.001), even though their CHA₂DS₂-VASc scores were the same at 1.

Discussion

The main findings of the present study were as follows. (1) In this Korean AF cohort, female sex was not associated with increased risk of TE events. (2) CKD predicted TE

events similarly to CHA₂DS₂-VASc components, except for female sex. Based on these findings, we created a novel stratification system, CHA₂DS₂-VAK, which is an acronym for modified HF, hypertension, age, diabetes, stroke history, vascular disease, age 65–74 and kidney disease. This new system enhanced discrimination of low to intermediate TE risk in AF patients.

The trend of increasing age at AF diagnosis in the Korean population aligns with data gathered in Western studies.^{11,12} As the age at diagnosis increases, more patients have ≥1 points starting at diagnosis, and distinguishing AF patients with intermediate risk has become an important issue. Many potential TE risk factors for AF have been suggested, including clinical factors, biomarkers, and brain imaging.^{13,14} Although this facilitates a systematic approach to AF evaluation, there are concerns that newly incorporated factors will create score inflation as well. With the novel CHA₂DS₂-VAK system, the number of low- to intermediate-risk patients (scores 0 and 1) are increased, but the ability to predict risk is more powerful. The change in category has importance in these groups, because it could lead to changes in antithrombotic strategy.

In Western cohorts, women with AF have a moderately increased risk of stroke compared with men,^{15,16} but this finding has not had consistency in Asian studies. Recently,

Table 4. Annual Thromboembolic Event Rates (%/year) for CHA ₂ DS ₂ -VAK and CHA ₂ DS ₂ -VASc Systems								
	CHA ₂ DS ₂ -VAK				CHA ₂ DS ₂ -VASc			
	Total	Events	Annual incidence rate	HR (95% CI)	Total	Events	Annual incidence rate	HR (95% CI)
0	2,617	105	0.84%	1.00 (Ref.)	1,866	67	0.84%	1.00 (Ref.)
1	3,392	271	1.81%	2.43 (1.94–3.05)	4,357	335	1.78%	2.13 (1.64–2.78)
2	3,044	333	2.62%	3.40 (2.72–4.25)	3,660	445	2.84%	3.41 (2.64–4.42)
3	2,112	346	4.00%	5.43 (4.33–6.81)	1,935	331	3.88%	4.70 (3.61–6.11)
≥4	1,711	335	4.15%	5.91 (4.66–7.51)	1,058	212	4.94%	5.86 (4.46–7.72)

CI, confidence interval; HR, hazard ratio.

Japanese and Chinese investigators reported that female sex may not be a risk of TE at all, at least in Japanese AF patients.^{8,17,18} In our study, we demonstrated that women did not have an increased risk of TE compared with men. According to Western population studies, numerous possible mechanisms explaining the difference between the sexes have been proposed, such as differences in the structure and function of the left atrium,¹⁹ endothelial dysfunction, markers of platelet activation²⁰ and effect of hormone replacement therapy.²¹ However, there could also be a genetic difference among races affecting these factors, and further research is needed to verify and establish the reasons for these ethnic differences.

CKD is a well-known risk factor associated with increased risk of stroke, systemic TE and bleeding among patients with AF.^{3,22,23} This has been a consistent finding in Eastern population cohort studies.^{4,24} There have been numerous attempts to incorporate kidney disease into the risk stratification system, and this issue is still controversial.^{25,26} Previous studies have shown that anticoagulation was useful for AF patients with CKD, and CKD patients on anticoagulation showed the same risk as non-CKD patients in our cohort.

The current TE risk stratification systems such as CHA₂DS₂-VASc or CHADS₂ have a lot to be improved and refined. First of all, the ethnic difference has to be considered in AF management guidelines for stroke prevention. Ethnic differences in stroke incidence, severity or mortality are generally known.^{27,28} Each risk factor candidate currently attracting the attention of researchers should be carefully examined from an ethnic perspective. Second, to improve the current modest predictive power for TE events, each clinical factor (hypertension, diabetes, HF or vascular disease, etc.) might be refined in detail. For example, duration of diabetes is independently associated with ischemic stroke risk, adjusting for risk factors.²⁹ Among hypertensive patients, left ventricular hypertrophy

is an important risk factor for stroke.³⁰ In another study, HF with preserved left ventricular function was suggested to be a significant determinant of stroke in AF,³¹ based on which there was no difference in TE events between HF with and without left ventricular dysfunction.³² The prognostic importance of AF patients with HF has been previously analyzed in various settings, including clinical trials,³³ outpatient cohorts,³⁴ and within epidemiologic studies.³⁵ Those studies mainly evaluated the risks related to AF in patients with reduced left ventricular systolic function. However, there is evidence regarding an association between HF with preserved ejection fraction and stroke in patients with AF.³⁶

Recently, there has been increased interest in biomarkers to help refine the risk assessment in AF populations.¹³ We also believe that the future of TE prediction lies in the combination of clinical factors, biomarkers, genetic factors and imaging modalities. However, we think that personalized AF treatment essentially based on clinical risk factors is important.³⁷ Consequently, based on our study results, the novel CHA₂DS₂-VAK scheme could be a better prognostic model for predicting TE events in Asian AF patients, using clinical factors.

Study Limitations

Several should be considered in the interpretation of these real-world, retrospective single-center cohort results. There were inherent limitations in diagnostic accuracy and event ascertainment, particularly when a patient moved away or had an outcome event in another area. Another limitation was the diagnosis of clinical factors, which was largely dependent on responsible physicians' records, leading to under- or overdiagnosis. Third, several risk factors need further validation in future studies. For example, there is a lack of evidence for assigning 2 and 1 points each for age above 75 and 65 years, respectively. Lastly, considering the ethnic aspect of this study, the results might not be immediately applicable to the Western AF population, but we hope that it will help improve the current AF guidelines in the near future by embracing ethnic variability.

Acknowledgment

Our study protocol was approved by the institutional review board of Seoul National University Hospital, and was in accordance with the Declaration of Helsinki. Informed consent was waived because of the study being a retrospective review, and it was impractical to obtain consent from such a large number of patients. The data were analyzed anonymously.

Disclosures

None.

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Supplementary Files

Supplementary File 1

Figure S1. Hazard ratio for thromboembolic risk according to age group.

Figure S2. Kaplan-Meier curves for thromboembolic events according to sex and CHA₂DS₂-VASc score (oral anticoagulant-naïve patients).

Figure S3. The subgroup analysis of the female factor.

Table S1. Baseline characteristics of anticoagulant-naïve patients

Table S2. Univariate and multivariate analyses for risk factor verification (anticoagulant-naïve patients)

Table S3. Annual thromboembolic event rates (%/year) for CHA₂DS₂-VAK and CHA₂DS₂-VASc systems (anticoagulant-naïve patients)

Table S4. Numbers of patient with changed points in CHA₂DS₂-VAK score

Please find supplementary file(s);
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