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). 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. Recent findings suggest that a creatinine clearance of ≤60 mL/min or less may even be an independent predictor of stroke and systemic embolism.

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, the most popular being the CHA2DS2-VASc system, which was also based on the Birmingham scheme and refined using European cohorts. 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. 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...
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. 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 ≥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. 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.

**Statistical Analysis**

Continuous variables are presented as mean±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 | 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 |
|-------------------------|------------------|----------------------|---------|
| Age (years)             | 64.9±12.0        | 66.4±9.6             | 64.5±12.2 |          |
| 65–74                   | 4,746 (36.9%)    | 573 (41.2%)          | 4,173 (36.3%) |          |
| ≥75                     | 2,594 (20.1%)    | 377 (27.1%)          | 2,217 (19.3%) |          |
| Female                  | 4,700 (36.5%)    | 540 (38.8%)          | 4,160 (36.2%) |          |
| Hypertension            | 4,203 (32.6%)    | 726 (52.2%)          | 3,477 (30.3%) |          |
| Diabetes                | 2,539 (19.7%)    | 404 (29.0%)          | 2,135 (18.6%) |          |
| Previous TE event       | 481 (3.7%)       | 87 (6.3%)            | 394 (3.4%) |          |
| Vascular disease        | 661 (5.1%)       | 121 (8.7%)           | 540 (4.7%) |          |
| CKD                     | 3,712 (28.8%)    | 536 (38.6%)          | 3,176 (27.7%) |          |
| Heart failure           | 2,228 (17.3%)    | 318 (22.9%)          | 1,910 (16.6%) |          |
| CHA2DS2-VASc score      | 1.72±1.22        | 2.26±1.24            | 1.65±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±1.9         | 12.7±1.9             | 13.0±2.0 | <0.001  |
| Creatinine              | 1.24±1.06        | 1.30±0.99            | 1.24±1.07 | 0.036   |
| GFR (mL/min/1.73 m²)    | 68.4±22.9        | 64.1±22.1            | 68.9±22.9 | <0.001  |
| Cholesterol             | 163.7±32.9       | 158.4±29.4           | 164.4±33.3 | <0.001  |
| LDL (mg/dL)             | 99.2±27.9        | 95.6±24.3            | 99.8±28.4 | <0.001  |
| HbA1c (%)               | 6.4±1.0          | 6.3±0.9              | 6.4±1.1  | 0.017   |
| Antiplatelets           | 4,705 (36.5%)    | 507 (36.4%)          | 4,198 (36.6%) | 0.929   |
| Anticoagulation         | 4,386 (34.1%)    | 80 (6.7%)            | 4,306 (37.5%) | <0.001  |
| No anticoagulant        | 3,703 (28.6%)    | 782 (56.2%)          | 2,921 (25.4%) | 0.001   |
| Follow-up duration (years) | 4.67±3.72       | 4.86±3.68            | 4.4±3.63 | <0.001  |

CKD, chronic kidney disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; TE, thromboembolism.
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-naive patients are shown in Figure S2. The subgroup analysis of the female factor showed no prognostic power for TE events (Figure S3).

Exact test and the \( \chi^2 \) 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 system 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-naive 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).

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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).

**CHA:DS-VAK: a Novel Stratification System**

In the traditional CHA:DS-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 CHA:DS-VASc scheme, we substituted the female category with CKD and renamed CHA:DS-VASc as CHA:DS-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 CHA:DS-VASc scoring system. The new CHA:DS-VAK system had an AUC of 0.650 (95% CI 0.64–0.66, P<0.001). Compared to patients with CHA:DS-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 CHA:DS-VAK and CHA:DS-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 Table S3.

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 CHA:DS-VAK system, the number of low- to intermediate-risk patients (scores 0 and 1) is 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,

**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 CHA:DS-VASc components, except for female sex. Based on these findings, we created a novel stratification system, CHA:DS-VAK, which is an acronym for female sex. Based on these findings, we created a novel stratification system, CHA:DS-VAK, which is an acronym for female sex. Based on these findings, we created a novel stratification system, CHA:DS-VAK, which is an acronym for female sex.

**Table 4. Annual Thromboembolic Event Rates (%/year) for CHA:DS-VAK and CHA:DS-VASc Systems**

| CHA:DS-VAK | CHA:DS-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         | 1,771       | 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.
Among hypertensive patients, left ventricular hypertrophy
hormone replacement therapy.21
reasons for these ethnic differences.

Japanese and Chinese investigators reported that female
sex may not be a risk of TE at all, at least in Japanese AF
patients.8 Previous studies have shown that anticoagulation
was useful for AF patients with CKD, and CKD patients
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 imme-
diately 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.

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 imme-
diately 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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Go AS, et al. Renal dysfunction as a predictor of stroke and
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 associa-
tion 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.3 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 personal-
ized 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 prognos-
tic model for predicting TE events in Asian AF patients,
using clinical factors.

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 controver-
sial.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

Figure 3. Difference in thromboembolic event rates according
to CHA2DS2-VAK score among patients with the same
CHA2DS2-VASc score of 1. Patients with CHA2DS2-VASc of 1
were differentiated into a CHA2DS2-VAK score of 0 (n=907), 1
(n=2700), and 2 (n=750). Patients with CHA2DS2-VAK score
of 2 had a more than 3-fold higher risk of thromboembolism
than those with a score of 0, even though their CHA2DS2-VASc
scores were the same.
systemic embolism in patients with nonvalvular atrial fibrillation: Validation of the R(2)CHA2DS2V(2) index in the ROCKET AF (Rivaroxaban once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (Anticoagulation and Risk Factors In Atrial fibrillation) study cohorts. Circulation 2013; 127: 224 – 232.

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