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Risk of Ischemic Stroke in Patients With Non-Valvular Atrial Fibrillation Not Receiving Oral Anticoagulants

— Korean Nationwide Population-Based Study —

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Background: Atrial fibrillation, the most common cardiac arrhythmia, is associated with an elevated thromboembolic risk, including ischemic stroke. Guidelines recommend the stratification of individual stroke risk and tailored antithrombotic therapy. This study investigated the demographics, comorbidities, and prognosis of non-valvular AF (NVAF) in Korean patients.

Methods and Results: We extracted data on 10,846 patients with newly diagnosed NVAF who were naïve to oral anticoagulants from the National Health Insurance Service-National Sample Cohort. $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for each subject using claims data. The study endpoints were ischemic stroke, thromboembolism, and mortality. Mean age was 63.7 years, and 46.8% of the patients were women. Women were older and had higher $CHADS_2$ and CHA_2DS_2-VASc scores. During 30,138 person-years of follow-up, ischemic stroke occurred at a rate of 2.95/100 person-years. $CHADS_2$ and CHA_2DS_2-VASc scores showed good performance in risk prediction. CHA_2DS_2-VASc score performed better at discriminating stroke risk in patients with low-risk profiles. The presence of female sex and vascular disease added little improvement in risk prediction.

Conclusions: Korean NVAF patients had high risk of stroke and mortality, and had multiple comorbidities. While both $CHADS_2$ and CHA_2DS_2-VASc schema had good performance in risk prediction, CHA_2DS_2-VASc score was superior in identifying truly low-risk patients. Given that Asian ethnicity is associated with bleeding events, individualized accurate risk prediction is necessary to improve patient outcomes.

Key Words: Atrial fibrillation; Epidemiology; Ischemic stroke

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia.[1] Its incidence and prevalence continue to increase with aging of the population.[2] AF is known to affect approximately 1% of the general population, and recent studies suggest that the prevalence of AF in the USA and Europe will double in the next 50 years.[2,3] The prevalence and incidence of AF in Korea is similar to that of Western countries.[4–6] The incidence of AF increases with advancing age, and hypertension is an important contributing factor.[7]

AF is associated with a substantial health-care and economic burden, and is associated with a high risk of cardiovascular mortality and hospitalization.[8] Most importantly, AF increases the risk of thromboembolic events, such as ischemic stroke, by 3–5-fold.[9,10] The risk of stroke in patients with AF increases with increasing number of comorbidities.[11] Current guidelines recommend anti-thrombotic therapy for stroke prevention in AF patients according to stroke risk stratification.[6,12,13] The $CHADS_2$ and CHA_2DS_2-VASc scoring systems are the most popular tools to estimate individual stroke risk.[11,14,15]

Global multicenter randomized controlled trials previously showed that Asian AF patients have different risk and prognosis profiles compared with subjects from other parts of the world.[16–18] A comprehensive evaluation of Asian patients with AF, however, has not been reported. The aim of this study was therefore to utilize population-based claims data to identify the demographics, comorbidities, and prognosis of non-valvular AF (NVAF) in Korean patients not receiving oral anticoagulants (OAC). This information is fundamental to the development of strategies for stroke prevention and outcome improvement

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Table 1. Subject Clinical Characteristics

Clinical characteristics	Total (n=10,846)	Women (n=5,078)	Men (n=5,768)	P value
Age (years)	63.7±15.0	65.9±15.1	61.8±14.5	<0.001†
65–74	5,900 (54.4)	3,094 (60.9)	2,806 (48.6)	<0.001
≥75	2,760 (25.4)	1,637 (32.2)	1,123 (19.5)	<0.001
HTN	7,553 (69.6)	3,606 (71.0)	3,947 (68.4)	0.004
Diabetes	2,299 (21.2)	1,071 (21.1)	1,228 (21.3)	0.800
Stroke/TIA/TE	1,816 (16.7)	867 (17.1)	949 (16.5)	0.388
CHF	2,676 (24.7)	1,388 (27.3)	1,288 (22.3)	<0.001
VD	1,963 (18.1)	920 (18.1)	1,043 (18.1)	0.962
MI	983 (9.1)	421 (8.3)	562 (9.7)	0.009
Ischemic heart disease	4,080 (37.6)	1,859 (36.6)	2,221 (38.5)	0.042
Chronic lung disease	2,653 (24.5)	1,147 (22.6)	1,506 (26.1)	<0.001
Thyroid disorders	107 (1.0)	66 (1.3)	41 (0.7)	0.002
End-stage renal disease	171 (1.6)	74 (1.5)	97 (1.7)	0.349
$CHADS_2$ score				<0.001
0	1,747 (16.1)	832 (16.4)	915 (15.9)	
1	2,473 (22.8)	956 (18.8)	1,517 (26.3)	
2	2,852 (26.3)	1,316 (25.9)	1,536 (26.6)	
3	2,011 (18.5)	1,022 (20.1)	989 (17.1)	
≥4	1,763 (16.3)	952 (18.7)	811 (14.1)	
CHA_2DS_2-VASc score				<0.001
0	871 (8.0)	0 (0.0)	871 (15.1)	
1	2,016 (18.6)	788 (15.5)	1,228 (21.3)	
2	2,005 (18.5)	772 (15.2)	1,233 (21.4)	
3	1,949 (18.0)	880 (17.3)	1,069 (18.5)	
4	1,666 (15.4)	935 (18.4)	731 (12.7)	
5	1,239 (11.4)	852 (16.8)	387 (6.7)	
≥6	1,100 (10.1)	851 (16.8)	249 (4.3)	

Data given as mean±SD or n (%). †Mann-Whitney U-test. CHF, congestive heart failure; HTN, hypertension; MI, myocardial infarction; TE, thromboembolism; TIA, transient ischemic attack; VD, vascular disease.

in Korean patients with NVAF.

Methods

Subjects

We extracted data on patients with newly-diagnosed NVAF ≥20 years old from the sample cohort provided by the Korean National Health Insurance Service (NHIS). The cohort profile is described elsewhere.[7,19] In brief, the NHIS is a mandatory universal health insurance system that covers approximately 97% of Korean residents. Data in the NHIS database include demographic information, medical treatment, and disease diagnoses according to the International Classification of Diseases-10 (ICD-10). The sample cohort released by the NHIS is a dynamic retrospective cohort with data from a random sample of 1,025,340 individuals, equivalent to approximately 2% of the Korean population. The database is open to any researchers whose study protocols have been approved by the official review committee. This study was carried out from November 2015 to July 2016.

NVAF was defined as AF in the absence of rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, or mitral valve repair.[20,21] AF was identified using the ICD-10 codes (I48.0–I48.4, I48.9) registered by the physicians responsible for treatment.[22,23] To minimize selection bias, a patient was defined as having AF when 1 or more AF diagnoses were made during hospitalization or when 2 or more AF diagnoses were made at outpatient clinics. We excluded patients with any AF diagnosis during the first year following the inception of the database in order to ensure a washout period >1 year. Those with a diagnosis of mitral stenosis (I050, I52, I059) or the presence of mechanical heart valves (Z952–Z954) were also excluded from analysis. We also excluded subjects who had been prescribed OAC within 1 month after the initial diagnosis of AF and who had experienced any of the study outcomes (listed in the next section) with the diagnosis of AF. Finally, a total of 10,846 NVAF patients were enrolled. The study protocol was exempt from review by the Seoul National University Hospital Institutional Review Board (1505-009-667).

Definitions

The primary endpoint of this study was ischemic stroke. Secondary endpoints included thromboembolism, cardiovascular mortality, and all-cause mortality. Stroke was defined according to ICD-10 codes (I63-64) for diagnoses made during hospitalization and according to brain imaging such as computed tomography and magnetic resonance imaging. Thromboembolism was a composite of ischemic stroke, transient ischemic attack (TIA; ICD-10 code G45), and systemic (ICD-10 code I74) or pulmonary embolic events (ICD-10 code I26). Patients were censored when they were prescribed oral vitamin K antagonists.

Table 2. Clinical Events According to Risk Scoring System and Sex

Score	No. subjects	Rate of ischemic stroke (95% CI) per 100 person-years		
		Total	Women	Men
$CHADS_2$				
0	1,747	0.27 (–1.90~2.45)	0.16 (–2.83~3.15)	0.39 (–2.77~3.56)
1	2,473	1.14 (–1.02~3.31)	0.87 (–2.40~4.13)	1.36 (–1.52~4.25)
2	2,852	2.77 (0.41~5.14)	2.21 (–1.03~5.44)	3.43 (–0.03~6.90)
3	2,011	4.64 (1.56~7.71)	3.87 (–0.28~8.01)	5.59 (1.02~10.2)
≥4	1,763	15.2 (11.7~18.7)	14.0 (9.31~18.6)	16.9 (11.7~22.2)
CHA_2DS_2-VASc				
0	871	0.33 (–2.92~3.58)	–	0.33 (–2.92~3.58)
1	2,016	0.80 (–1.40~2.99)	0.17 (–2.89~3.23)	1.47 (–1.68~4.62)
2	2,005	1.61 (–0.91~4.13)	0.77 (–2.72~4.25)	2.55 (–1.09~6.19)
3	1,949	2.80 (–0.04~5.63)	1.16 (–2.61~4.93)	5.01 (0.71~9.31)
4	1,666	4.87 (1.66~8.07)	3.84 (–0.17~7.86)	6.73 (1.40~12.1)
5	1,239	7.84 (3.83~11.9)	5.28 (0.53~10.0)	14.9 (7.41~22.4)
≥6	1,100	15.4 (10.8~19.9)	13.5 (8.46~18.5)	25.7 (14.9~36.5)
Total	10,846	3.01 (2.82~3.21)	2.74 (2.48~3.00)	3.31 (3.01~3.60)

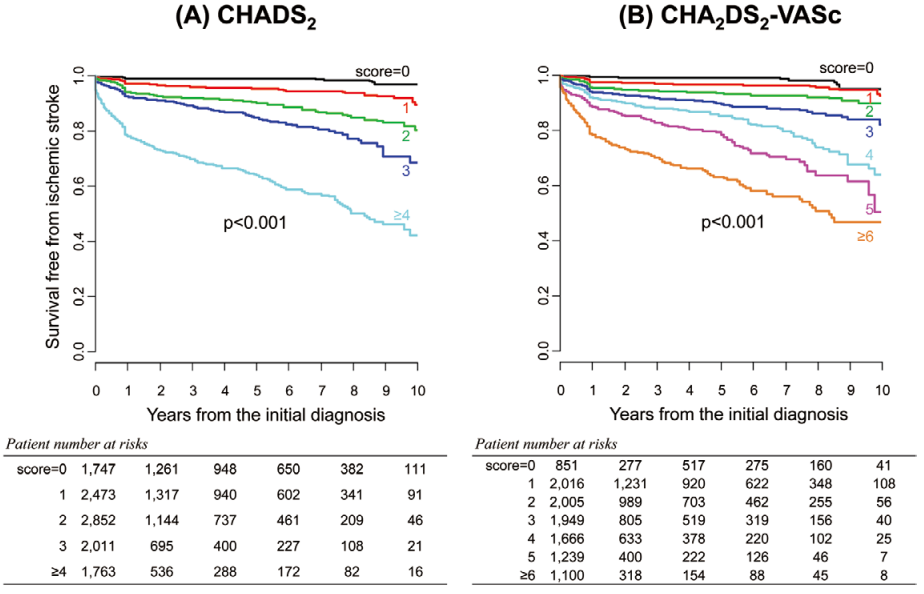

Figure 1. Kaplan-Meier survival curves for freedom from ischemic stroke according to (**A**) $CHADS_2$ and (**B**) CHA_2DS_2-VASc score.

The stroke risk of individual patients was stratified according to the $CHADS_2$ and CHA_2DS_2-VASc schemas. $CHADS_2$ score was calculated by assigning 1 point each for congestive heart failure (CHF), hypertension, age ≥75 years, and diabetes, and 2 points for prior stroke or TIA.[12,13] The CHA_2DS_2-VASc score was calculated by assigning 1 point each for CHF/left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] ≤40%), hypertension, diabetes, peripheral vascular disease (including prior myocardial infarction [MI] or complex aortic plaque), age 65–74 years, and female gender, and 2 points for prior stroke or TIA and for age ≥75 years.[12,13] Risk factors were defined using the registered diagnosis codes prior to the initial diagnosis of NVAF.

Statistical Analysis

Continuous variables were given as mean±SD, and dichotomous variables as numbers and percentages. Categorical variables were compared using chi-squared test. Kolmogorov-Smirnov goodness-of-fit test was done for continuous variables. Mann-Whitney U-test or Student's t-test was used according to the distribution of the variables.

Annual event rates were described as the number of events per 100 person-years and the corresponding 95% CI. Person-time was censored at the time when OAC were prescribed during follow-up. Survival curves were plotted using the Kaplan-Meier method, and compared using log-rank test. Cox proportional hazards models were used to evaluate the risk of time-dependent variables. Harrell's c-index was used to estimate the predictive value of each

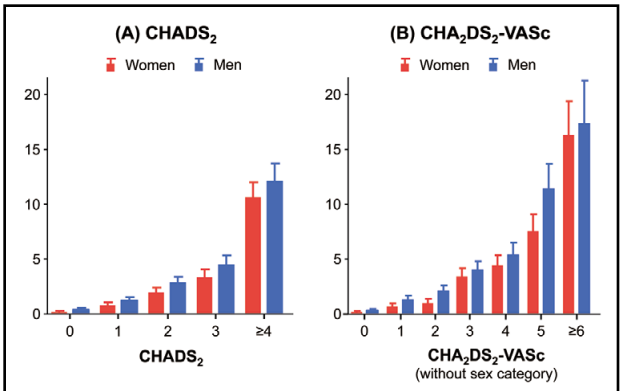

Figure 2. Annual risk of ischemic stroke (per 100 person-years) in (blue) men and (red) women according to (**A**) $CHADS_2$ and (**B**) CHA_2DS_2-VASc scores without the female sex category. Box, median; whiskers, range.

risk scoring system on the risk of ischemic stroke. The area under the receiver operating characteristic curve (AUC) was also calculated. Integrated discrimination improvement and the net reclassification improvement (NRI) were calculated to compare the performance of the scoring schemas.[24]

Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and R programming version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). Two-sided P<0.05 was considered statistically significant.

Results

Baseline Subject Characteristics

Table 1 lists the baseline characteristics of the 10,846 study patients. Mean age was 63.7±15.0 years (range, 20–95 years). Women accounted for 46.8% of the patients. While hypertension was the most common comorbidity (69.6%), 37.6% of the patients had ischemic heart disease, and 16.7% had a history of stroke, TIA, and systemic thromboembolism. Mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.0±1.4 and 2.9±1.9, respectively. The percentages of patients with $CHADS_2$ and CHA_2DS_2-VASc score zero were 16.1% and 8.0%, respectively. The number of patients with CHA_2DS_2-VASc score ≥2 was 73.4%. Female patients with NVAF differed from the male patients in many ways. Women were older by 4 years (65.9±15.1 years vs. 61.8±14.5 years, P<0.001) and had higher rates of hypertension, CHF, and thyroid disease. MI, ischemic heart disease, and chronic lung disease were more common in men than in women. Female patients had higher $CHADS_2$ and CHA_2DS_2-VASc scores the male patients.

Risk of Stroke and Risk-Scoring System

The patients were followed up for a median of 1.17 years (IQR, 0.33–4.83 years). The risk of ischemic stroke according to the risk scoring systems and gender is given in **Table 2**. During a total of 29,466 person-years at risk in patients naïve to OAC, ischemic stroke occurred in 888 patients (3.01 per 100 person-years): 2.74 per 100 person-years for women, and 3.31 per 100 person-years for men. The 2 scoring systems were shown to be useful in discriminating the risk of ischemic stroke (AUC, 0.74; 95% confidence intervals [CI]: 0.72–0.75 for $CHADS_2$; AUC, 0.71; 95% CI: 0.69-0.73, for CHA_2DS_2-VASc; Harrell's c-index, 0.79 for $CHADS_2$ and 0.78 for CHA_2DS_2-VASc). The CHA_2DS_2-VASc score had a lower NRI than the $CHADS_2$ score (−1.7%; 95% CI: −4.2 to 0%; P=0.03). Survival free from stroke according to $CHADS_2$ and CHA_2DS_2-VASc is shown in **Figure 1**. Higher $CHADS_2$ and CHA_2DS_2-VASc score were associated with a higher risk of ischemic stroke. Event rates for thromboembolism and mortality are given in **Table S1**.

Sex as a Risk Factor for Stroke

Table 3 lists univariable and multivariable analysis for the risk of ischemic stroke for each component of the CHA_2DS_2-VASc schema. On univariable analysis each component significantly increased the risk of thromboembolism except female sex, which showed a trend toward a lower risk of stroke with borderline significance. On multivariable analysis, female sex and vascular disease were not associated with an increased risk of stroke.

When stratified by $CHADS_2$ score, men and women had a similar risk of stroke (**Table 2**; **Figure 2A**). The CHA_2DS_2-VASc system, however, overestimated the stroke risk in women (**Table 2**): the observed risk of stroke was actually lower than that expected from the CHA_2DS_2-VASc score (**Figure S1**), and CHA_2DS_2-VASc score better discriminated the stroke risk when the sex category was not considered (**Figure 2B**).

Risk of Stroke and $CHADS_2$ Score 0 or 1

A $CHADS_2$ score of 0 and a CHA_2DS_2-VASc score of 0–1

Table 3. Significant Indicators of Ischemic Stroke

	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age 65–74 years	3.28 (2.77~3.88)	<0.001	2.14 (1.80~2.54)	<0.001
Age ≥75 years	3.95 (3.31~4.70)	<0.001	2.33 (1.93~2.80)	<0.001
Female sex	0.89 (0.78~1.01)	0.079	0.75 (0.66~0.86)	<0.001
HTN	3.61 (2.98~4.37)	<0.001	1.82 (1.49~2.23)	<0.001
Diabetes	1.64 (1.42~1.90)	<0.001	1.21 (1.04~1.41)	0.012
Stroke/TIA/TE	7.21 (6.32~8.23)	<0.001	5.17 (4.50~5.93)	<0.001
CHF	2.30 (2.00~2.65)	<0.001	1.54 (1.33~1.78)	<0.001
VD	1.50 (1.28~1.75)	<0.001	0.95 (0.81~1.11)	0.517

Abbreviations as in Table 1.

Table 4. Annual Risk of Thromboembolic Events vs. 0/1 $CHADS_2$ and CHA_2DS_2-VASc Score

$CHADS_2$	CHA_2DS_2-VASc (1 point for female sex)			CHA_2DS_2-VASc (no points for female sex)		
	CHA_2DS_2-VASc	n	Ischemic stroke Event rates (95% CI) per 100 person-years	CHA_2DS_2-VASc	n	Ischemic stroke Event rates (95% CI) per 100 person-years
0	Total	1,747	0.27 (–1.90~2.44)	Total	1,747	0.27 (–1.90~2.44)
	0	871	0.33 (0.14~0.51)	0	1,659	0.25 (0.14~0.36)
	1	876	0.22 (0.09~0.36)	1	88	0.78 (–0.10~1.66)
1	Total	2,473	1.13 (–1.02~3.28)	Total	2,473	1.13 (–1.02~3.28)
	1	1,184	1.44 (1.05~1.82)	1	1,912	1.16 (0.90~1.42)
	2	1,049	0.86 (0.56~1.15)	2	534	0.98 (0.49~1.48)
	3	240	1.05 (0.28~1.82)	3	27	2.00 (–1.88~5.88)

Table 5. Reported Risk of Stroke According to $CHADS_2$ and CHA_2DS_2-VASc Score

	Event rates (95% CI) per 100 person-years				
$CHADS_2$	Korea (present study)	Taiwan[26]	Japan[27]	US medicare[14]	
0	0.27 (–1.90~2.45)	1.80 (1.74~1.87)	0.54 (0.28~1.02)	1.9 (1.2~3.0)	
1	1.14 (–1.02~3.31)	3.08 (2.99~3.16)	0.93 (0.57~1.50)	2.8 (2.0~3.8)	
2	2.77 (0.41~5.14)	4.49 (4.38~4.61)	1.54 (0.95~2.50)	4.0 (3.1~5.1)	
3	4.64 (1.56~7.71)	5.33 (5.17~5.48)	2.66 (1.52~4.64)	5.9 (4.6~7.3)	
4	11.1 (0.96~12.5)	4.86 (4.67~5.05)	6.05 (3.46~10.57)	8.5 (6.3~11.1)	
5	22.8 (19.8~25.8)	5.80 (5.54~6.07)	3.89 (1.32~11.43)	12.5 (8.2~17.5)	
6	36.2 (26.6~45.8)	7.10 (6.59~7.65)	7.24 (1.28~41.01)	18.2 (10.5~27.4)	
	Event rates (95% CI) per 100 person-years				
CHA_2DS_2-VASc	Korea (present study)	Taiwan[26]	Japan[27]	Euro Heart Survey[11]	Denmark[15]
0	0.61 (0.39~0.83)	1.15 (1.24~1.07)	0.53 (0.23~1.24)	0 (0~0)	0.66 (0.57~0.76)
1	0.92 (0.74~1.10)	2.11 (2.03~2.20)	0.55 (0.25~1.19)	0.6 (0.0~3.4)	1.45 (1.32~1.58)
2	2.10 (1.81~2.39)	3.39 (3.29~3.50)	1.11 (0.62~2.00)	1.6 (0.3~4.7)	2.92 (2.76~3.09)
3	3.49 (3.08~3.91)	3.89 (3.78~4.01)	1.38 (0.81~2.37)	3.9 (1.7~7.6)	4.28 (4.10~4.47)
4	5.14 (4.54~5.73)	4.61 (4.47~4.75)	1.52 (0.83~2.80)	1.9 (0.5~4.9)	6.46 (6.20~6.74)
5	9.53 (8.51~10.5)	5.12 (4.95~5.30)	4.43 (2.68~7.30)	3.2 (0.7~9.0)	9.97 (9.53~10.43)
6	17.35 (15.25~19.45)	5.18 (4.96~5.40)	4.07 (1.87~8.89)	3.6 (0.4~12.3)	12.52 (11.78~13.31)
7	41.44 (36.40~46.48)	6.22 (5.90~6.54)	1.56 (0.28~8.86)	8.0 (1.0~26.0)	13.96 (12.57~15.51)
8	37.48 (29.43~45.54)	7.98 (7.41~8.60)	6.95 (1.23~39.35)	11.1 (0.3~48.3)	14.10 (10.90~18.23)
9	48.17 (24.14~72.20)	10.50 (9.02~12.15)	>100	100 (2.5~100)	15.89 (7.95~31.78)

were associated with a truly low risk of stroke (<1%/year; **Table 4**). CHA_2DS_2-VASc score was superior in identifying truly low-risk patients when the sex category was not taken into account. Rates of stroke among patients with CHA_2DS_2-VASc score 0, 1, and 2 are described in detail according to the presence of each risk factor in **Table S2**.

Discussion

In this study, >10,000 NVAF patients with up to 30,000 person-years of follow-up were analyzed using population-based data in Korea. We found that (1) Korean NVAF patients had a high risk of stroke and mortality; (2) both the $CHADS_2$ and CHA_2DS_2-VASc schemas showed good risk stratification for stroke; (3) CHA_2DS_2-VASc score better discriminated stroke risk in those with low-intermediate risk according to $CHADS_2$ score; and (4) female sex had little impact on risk stratification in the Korean NVAF population.

AF predisposes patients to thromboembolic events including ischemic stroke, and is associated with an increased risk of cardiovascular mortality and morbidity.[9,25] A recent study reported that the prevalence and incidence of AF in Korea is similar to that of Western countries.[6] The risks of stroke and mortality stratified by $CHADS_2$ and CHA_2DS_2-VASc scores in this study were similar to those of previous studies (**Table 5**).[11,14,15,26,27]

The CHA_2DS_2-VASc schema has replaced the older $CHADS_2$ schema in current guidelines as studies have demonstrated its superior performance in risk stratification for low-intermediate-risk patients.[12,13] Additional studies have also shown better risk stratification with CHA_2DS_2-VASc than with $CHADS_2$.[11,15,26] The present study also demonstrated that CHA_2DS_2-VASc is superior in identifying patients with a truly low risk of stroke, but sex had little impact on risk prediction with the CHA_2DS_2-VASc schema. Women have been shown to be at an increased risk of stroke compared with men in several previous studies, mostly

from Western countries.[28–30] A recent study from Japan, however, produced results similar to the present study: women had higher $CHADS_2$ scores than men, and female sex was not shown to be a risk factor for thromboembolic events.[31] One of the limitations of that study was that the majority of patients were receiving warfarin.

There may be several explanations for these conflicting results. First, there may be racial differences. The occurrence of ischemic stroke in the general population is more frequent in women than in men in the USA, but is less frequent in women than in men in Korea.[32,33] In addition, Asian AF patients have been shown to have several distinctive features in major randomized controlled trials, including a high risk of bleeding.[17,18] Second, there may be cultural factors. The use of oral contraceptives and dependence on tobacco or alcohol, which are well-known risk factors of ischemic stroke, are less prevalent in Asian women than in women in other parts of the world.[34] Last, we cannot exclude the possibility that women have a low stroke awareness and have poorer access to medical care. The present finding, that women have a similar risk of stroke as do men when stratified according to risk factors, needs to be validated in future studies.

This study has several limitations. The first was the observational nature of this study. The second was that the definitions were dependent on claims data. Misclassification is a potential source of bias when using administrative claims data.[35] For example, LV dysfunction (LVEF $\leq$40%) without a history of CHF could not be detected using this database. In addition, we could not obtain detailed information on the specific types or the duration of NVAF. Also, the diagnosis of ischemic stroke was not adjudicated, and reasons for not prescribing OAC could not be identified. And third, lifestyle habits such as smoking, drinking, diet pattern and exercise were not available from the claims database.

Conclusions

Korean NVAF patients were at high risk of ischemic stroke and death. Both the $CHADS_2$ and CHA_2DS_2-VASc scoring systems performed well in predicting stroke risk, but female sex contributed little improvement in risk prediction in Korean NVAF patients. More data are required on anti-thrombotic therapy in female NVAF patients with low-risk profiles.

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Disclosures

The authors declare no conflict of interest.

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Supplementary Files

Supplementary File 1

Figure S1. Annual risk of ischemic stroke (per 100 person-years) in (blue) men and (red) women according to CHA_2DS_2-VASc score, including the female sex category.

Table S1. Clinical events and mortality according to risk scoring system

Table S2. Risk of ischemic stroke vs. CHA_2DS_2-VASc score and risk factors

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