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Stroke and Systemic Thromboembolism according to CHA_2DS_2-VASc Score in Contemporary Korean Patients with Atrial Fibrillation

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Purpose: The incidence of stroke and/or systemic thromboembolism (SSE) has not been properly evaluated in well-anticoagulated atrial fibrillation (AF) patients. This study investigated the incidence of SSE according to CHA_2DS_2-VASc score in contemporary well-anticoagulated Korean AF patients.

Materials and Methods: From the prospective multicenter COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry, we identified 9503 patients with non-valvular AF (mean age, 68±8 years; female 35.5%) enrolled between June 2016 and May 2020 with eligible follow-up visits. Stroke incidence in the CODE-AF registry was compared with that in an oral anticoagulant (OAC)-naïve AF cohort from the Korean National Health Insurance database.

Results: The usage rates of OACs and antiplatelet agents were 73.5% (non-vitamin K OACs, 56.4%; warfarin, 17.1%) and 23.8%, respectively. During a mean follow-up period of 26.3±9.6 months, 163 (0.78 per 100 person-years) patients had SSE. The incidence rate (per 100 person-years) of SSE was 0.77 in the total population, 0.26 in low-risk patients [CHA_2DS_2-VASc score 0 (male) or 1 (female)], and 0.88 in high-risk patients (CHA_2DS_2-VASc score ≥2). Contemporary AF patients had a stroke rate that was about one-fifth the stroke rate reported in a Korean OAC-naïve AF cohort. In this cohort, most risk factors for CHA_2DS_2-VASc score showed significant associations with SSE. Female sex was not associated with an increased risk of stroke/SSE in well-anticoagulated AF patients.

Conclusion: Contemporary AF patients have a stroke rate about one-fifth that in OAC-naïve AF patients and exhibit different stroke risk factors.

Study Registration: ClinicalTrials.gov (NCT02786095).

Key Words: Atrial fibrillation, stroke, embolism, risk

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INTRODUCTION

As the most prevalent cardiac arrhythmia,[1-4] atrial fibrillation (AF) is associated with increased mortality rates due to stroke, congestive heart failure, and dementia, which have far-reaching socioeconomic burdens.[1-3,5,6] Although patients with AF should be prioritized for management of stroke prevention, use of oral anticoagulants (OACs) has been found to lead to a greater risk of bleeding, which may be fatal. Accordingly, OACs should be administered only when a net clinical benefit is anticipated. To help determine the need for OAC therapy, risk stratification for stroke is crucial.[7,8] CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) (doubled), vascular disease, age 65 to 74, female][9] is the most commonly used index for AF stroke prediction, and OACs are recommended by current stroke prevention guidelines for AF patients, with the exception of those who are classified as "low risk."[10-13] The point of net clinical benefit is defined as an annual stroke risk of 1%–2%.

The performance of CHA_2DS_2-VASc score in Asians has been validated and shown to be comparable to that seen in Western populations.[14,15] However, most data for stroke risk prediction according to this score have been derived in OAC-naïve populations, and although patients who receive OAC therapy are known to have 64% less risk of stroke relative to control/placebo patients,[16] the incidence of stroke/systemic thromboembolism (SSE) has not been properly evaluated in well-anticoagulated populations. The study aimed to examine the incidence of SSE based on CHA_2DS_2-VASc score in well-anticoagulated contemporary Korean AF patients. Furthermore, we compared stroke incidence in a contemporary AF registry with that in an OAC-naïve AF cohort from the Korean National Health Insurance Service database.

MATERIALS AND METHODS

Data source

The study design of the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) has been outlined elsewhere.[17] In brief, the CODE-AF registry is a prospective, observational, multicenter study at 18 tertiary hospitals from all regions in the Republic of Korea.[17] Patients who were >18 years old with non-valvular AF were enrolled in the study from June 2016 to May 2020. The CODE-AF registry's main objective was to evaluate the clinical outcomes of various medical treatments, such as OACs and rate or rhythm control therapy.[17] In addition, the study aimed to establish the clinical epidemiology of AF patients and to describe the course of diagnosis and therapy undertaken in patients.[17] The registry was coordinated and designed by the Korea Heart Rhythm Society.[17]

The data entered at each center were consistently audited, and data cleansing was conducted on the study's database. Cumulated data were enrolled in iCReaT (Internet-based Clinical Research and Trial management system, http://icreat.nih.go.kr), which is a web-based management system for clinical research provided by the Korean government. A follow-up visit was planned for every 6 months for each patient via an outpatient clinic or by telephone contact. The study complies to the ethical rules of the 1975 Declaration of Helsinki; each tertiary center ethics committee approved the study; and informed consent was given by all study patients. This study was registered at ClinicalTrials.gov (NCT02786095). The study was approved by the Yonsei University Severance Hospital Institutional Review Board (IRB Number: 4-2016-0105). All patients provided informed consent for inclusion in the study.

Study design and patients

Among the 11044 patients enrolled in the CODE-AF registry, patients with follow-up periods of at least 6 months (n=9503) were included. Patients without eligible follow up of at least 6 months (n=1541) were excluded (Fig. 1).

Baseline comorbidities and endpoints

Clinical history-taking was done for each patient at enrollment, and details on diagnosis of heart failure and OAC use were recorded. At the time of enrollment, CHA_2DS_2-VASc score for each subject was approximated.

The primary endpoint was incident ischemic stroke, which was defined as neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Central nervous system infarction was defined as brain, spinal cord, or retinal cell death caused by ischemia based on pathological, imaging, or other objective evidence of vascular injury.[18] Clinical evidence, such as symptoms related to cerebral, spinal cord, or retinal focal ischemic injury lasting more than 24 hours or until death, was also considered to indicate central nervous system infarction. The secondary outcome was a composite of primary endpoint and systemic embolism events, defined as sudden loss of end-organ perfusion based on clinical and objective evidence.

Statistical analysis

Baseline characteristics and comorbidities were characterized based on CHA_2DS_2-VASc score using descriptive statistics. Continuous variables are reported as means±standard deviations, and categorical variables are presented as frequencies (percentages). Event rates according to CHA_2DS_2-VASc score are presented as the number of events per 100 person-years. We used Cox proportional hazards regression analysis to examine stroke risk factors and determine the association between comorbidities and ischemic stroke incidence or the composite thromboembolism outcome. Conditional forward Cox regression analysis was conducted using factors associated with the endpoint after adjusting for sex and age. The entry and removal threshold were 0.05 and 0.10, respectively. The final model

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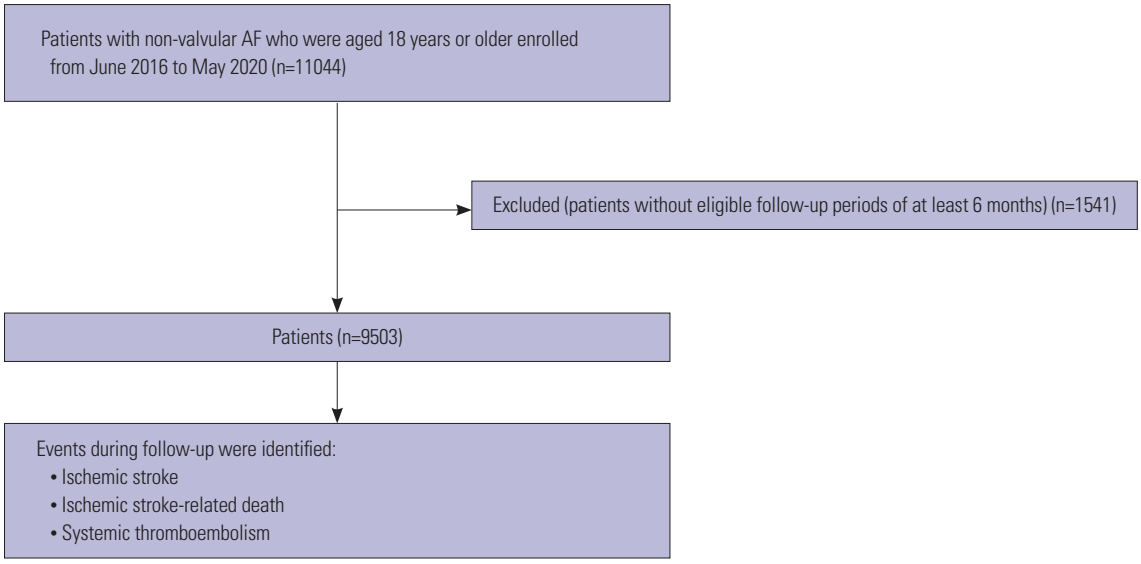

Fig. 1. Flowchart of study cohort enrollment. AF, atrial fibrillation.

included remaining factors associated with outcomes. None of the analyses performed made use of interdependent co-variables. Censoring occurred when patients reached ischemic stroke or composite endpoint events or death during the follow-up period and at the end of follow up.

c-statistic, which quantifies discriminant ability, was calculated to quantify the CHA_2DS_2-VASc score's capability to predict the primary and secondary endpoints and to test if the hypothesis schemes were superior to chance (c-statistic ≥0.5). All reported *p*-values were from tests that were two-tailed, and *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using R statistical software, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

This study included 9503 AF patients (mean age 68±8 years, female 35.5%). In this cohort of AF patients, the usage rates of OACs and antiplatelet agents were 73.5% [non-vitamin K oral anticoagulants (NOACs), 56.4%; warfarin, 17.1%] and 23.8%, respectively. Patients were classified according to CHA_2DS_2-VASc score into low-risk [0 or 1 point (female)], intermediate-risk (1 point, male), or high-risk (≥2 points) groups. Table 1 illustrates the distributions, demographics, and comorbidities of the groups based on CHA_2DS_2-VASc score. More than a quarter of the patient population (27.1%) was 75 years or older. The most prevalent comorbidity was hypertension (66.1%), followed by dyslipidemia (34.5%), diabetes mellitus (24.8%), and smoking history (ex-smoker) (23.8%). Table 1 lists the baseline characteristics of the OAC-naïve Korean National Health Insurance Service (NHIS) cohort[15] for illustrative purposes.

Risk of stroke

In total, 163 of 9503 patients (1.7%) experienced incident SSE throughout the mean follow-up period of 26.6±9.3 months. The ischemic stroke incidence rate (per 100 person-years) was 0.70 in the total study population, 0.26 in the low-risk group, 0.56 in the intermediate-risk group, and 0.80 in the high-risk group. Incidence rates of SSE in the Korean NHIS cohort study based on CHA_2DS_2-VASc score are also presented in Table 2 for illustrative purposes. The Korean NHIS study defined ischemic stroke as any diagnosis of stroke supported by computed tomography or magnetic resonance brain imaging. In the Korean NHIS cohort database, the incidence of SSE increased with an increase in CHA_2DS_2-VASc score. However, an increase in incidence rate (per 100 person-years) of SSE with increased CHA_2DS_2-VASc score was not evident in the well-anticoagulated CODE-AF registry (Table 2, Fig. 2).

Patients categorized as low risk (CHA_2DS_2-VASc score 0 in male or 1 in female) and intermediate risk (CHA_2DS_2-VASc score 1 in male) consistently had low SSE event rates of 0.26 and 0.65 per 100 person-years, respectively. Moreover, high-risk patients CHA_2DS_2-VASc score ≥2 had an SSE event rate ranging from 0.43 to 2.08. Incidence rates of SSE did not show a clear positive correlation with increasing CHA_2DS_2-VASc score, even in high-risk patients (Table 2). In comparison, ischemic stroke incidence rates (per 100 person-years) in the Korean NHIS Sample cohort were 3.32 in the total population, 0.23 in low-risk patients, and 4.59 in high-risk patients. Contemporary AF patients had a stroke rate approximately one-fifth of that of OAC-naïve AF patients (21.4%, $p<0.001$).

The median CHA_2DS_2-VASc score in this cohort was 2.6±1.7, and c-index values for ischemic stroke were 0.66 [95% confidence interval (CI) 0.59–0.73, $p<0.001$] at 1 year and 0.64 (95% CI 0.60–0.70, $p<0.001$) at 2 years. Therefore, the predictive value of CHA_2DS_2-VASc score for stroke was modest.

Risk factors for ischemic stroke and composite thromboembolism endpoints

A high CHA_2DS_2-VASc score predicted a high risk of SSE in this CODE-AF registry, and most of the individual CHA_2DS_2-VASc score components were associated with an increased risk of SSE, including older age (>75 years) [hazard ratio (HR) 1.55; 95%

Table 1. Patient Baseline Characteristics

Characteristics	CODE-AF registry				OAC-naïve Korea NHIS cohort
	Low risk (n=1264)	Intermediate risk (n=1378)	High risk (n=6861)	Total (n=9503)	Total (n=5855)
Age, yr	56±7	60±4	72±7	68±8	64±15
<65	1264 (100.0)	1042 (75.6)	1454 (21.2)	3760 (39.6)	2594 (44.3)
65–74	0 (0)	336 (24.4)	2829 (41.2)	3165 (33.3)	1700 (29.0)
>75	0 (0)	0 (0)	2578 (37.6)	2578 (27.1)	1561 (26.7)
Female sex	326 (25.8)	0 (0)	3050 (44.5)	3376 (35.5)	235 (48.4)
CHA_2DS_2-VASc score	0.3±0.4	1.0±0.0	3.3±1.3	2.6±1.7	3.3±2.1
History of TIA/ischemic stroke	0 (0)	0 (0)	1395 (20.3)	1395 (14.7)	1433 (24.5)
Myocardial infarction	0 (0)	5 (0.4)	260 (3.8)	265 (2.8)	764 (13.0)
Peripheral arterial disease	0 (0)	16 (1.2)	499 (7.3)	515 (5.4)	611 (10.4)
Heart failure	0 (0)	63 (4.6)	852 (12.4)	915 (9.6)	1869 (31.9)
Hypertension	0 (0)	862 (62.6)	5421 (79.0)	6283 (66.1)	4422 (75.5)
Diabetes mellitus	0 (0)	99 (7.2)	2256 (32.9)	2355 (24.8)	1168 (19.9)
ESRD	8 (0.6)	25 (1.8)	114 (1.7)	147 (1.5)	89 (1.5)
Cancer	74 (5.9)	80 (5.8)	767 (11.2)	921 (9.7)	N/A
Dyslipidemia	216 (17.1)	383 (27.8)	2677 (39.0)	3276 (34.5)	N/A
Bleeding history	31 (2.5)	69 (5.0)	650 (9.5)	750 (7.9)	N/A
Smoking history					
Current smoker	210 (16.6)	245 (17.8)	390 (5.7)	845 (8.9)	N/A
Ex-smoker	291 (23.0)	484 (35.1)	1484 (21.6)	2259 (23.8)	N/A
Non-smoker	763 (60.4)	649 (47.1)	4987 (72.7)	6399 (67.3)	N/A
Oral anticoagulation	431 (34.1)	641 (46.5)	5909 (86.1)	6981 (73.5)	
Non-vitamin K antagonist	257 (20.3)	368 (26.7)	4735 (69.0)	5360 (56.4)	N/A
Vitamin K antagonist	174 (13.8)	273 (19.8)	1174 (17.1)	1621 (17.1)	N/A
Antiplatelet agents	329 (26.0)	516 (37.4)	1422 (20.7)	2267 (23.8)	
Aspirin use	276 (21.8)	432 (31.3)	928 (13.5)	1636 (17.2)	2636 (45.0)
P_2Y_{12} inhibitor	53 (4.2)	84 (6.1)	494 (7.2)	631 (6.6)	N/A

CODE-AF, the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; ESRD, end-stage renal disease; N/A, not available; NHIS, National Health Insurance Service; OAC, oral anticoagulant; TIA, transient ischemic attack.
Values are expressed as numbers (%) or mean±standard deviation.

Table 2. Risk for Ischemic Stroke and Composite Thromboembolism Endpoints Per 100 Person-Years in Relation to CHA_2DS_2-VASc Score

CHA_2DS_2-VASc score	CODE-AF registry (n=9503)			OAC-naïve Korea NHIS cohort (n=5855)	
	Number of events	Ischemic stroke	Ischemic stroke/ systemic embolism	Ischemic stroke	Ischemic stroke/ systemic embolism
0 (male) or 1 (female)	7/1264	0.26	0.26	0.23	0.26
1 (male)	20/1378	0.56	0.65	1.04	1.20
2	21/2208	0.39	0.43	1.91	2.04
3	37/2016	0.71	0.83	2.54	2.67
4	37/1378	1.11	1.21	4.72	5.10
5	18/780	1.03	1.03	5.79	5.98
6	14/317	1.93	2.08	8.36	8.61
≥7	7/162	1.64	1.92	8.82	9.03
Total	163/9503	0.70	0.77	3.32	3.49

CODE-AF, the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; NHIS, National Health Insurance Service; OAC, oral anticoagulant.

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CI 1.12–2.14], history of TIA/ischemic stroke (HR 2.86; 95% CI 2.06–3.98), peripheral arterial disease (HR 1.97; 95% CI 1.19–3.26), heart failure (HR 1.71; 95% CI 1.11–2.64), and hypertension (HR 1.48; 95% CI 1.04–2.12). On multivariable analysis, an association between CHA_2DS_2-VASc score and SSE was consistently observed in patients with a previous history of ischemic stroke/TIA (HR 2.56; 95% CI 1.81–3.61), heart failure (HR 1.59; 95% CI 1.02–2.47), cancer (HR 1.72; 95% CI 1.13–2.62), and current smoking history (HR 2.63, 95% CI 1.03–6.73) (Table 3). There were no differences in stroke risk between males and females (Table 4).

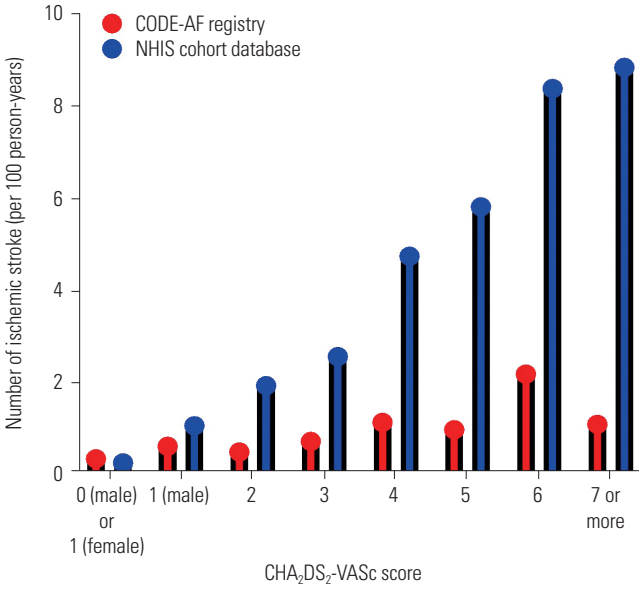

Fig. 2. Ischemic stroke endpoint per 100 person-years at risk in relation to CHA_2DS_2-VASc score. CODE-AF, the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; NHIS, National Health Insurance Service.

On multivariable analysis of the Korea NHIS cohort database, an association between CHA_2DS_2-VASc score and SSE was consistently observed in patients older than 75 years (HR 3.11; 95% CI 2.52–3.82) and those with a previous history of ischemic stroke/TIA (HR 2.44; 95% CI 2.12–2.80), heart failure (HR 1.26; 95% CI 1.09–1.45), hypertension (HR 1.69; 95% CI 1.32–2.15), and end-stage renal disease (HR 2.73, 95% CI 1.88–3.97) (Table 3, Fig. 3).

DISCUSSION

The main finding of this study is that contemporary AF patients have a stroke rate about one-fifth that of OAC-naïve AF patients. In this cohort, most risk factors included in the CHA_2DS_2-VASc scoring system showed significant associations with SSE. Female sex, a traditional risk factor for stroke and a component of the CHA_2DS_2-VASc score, was not associated with an increased

Table 3. Associations between Baseline Factors and Ischemic Stroke and Composite Thromboembolism Endpoints

	CODE-AF registry Ischemic stroke/systemic embolism			OAC-naïve Korea NHIS cohort database Ischemic stroke/systemic thromboembolism		
	Number of events	Univariable HR (95% CI)	Multivariable HR (95% CI)	Number of events	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, yr (mean age)						
65–74	57/3227	1.10 (0.80–1.52)	1.32 (0.88–1.98)	334/1700	3.34 (2.78–4.02)	2.10 (1.73–2.55)
>75	60/2618	1.55 (1.12–2.14)	1.48 (0.97–2.26)	352/1561	4.55 (3.79–5.47)	3.11 (2.52–3.82)
Female sex	58/3425	1.01 (0.73–1.39)	1.21 (0.84–1.74)	398/2835	0.91 (0.80–1.04)	0.73 (0.64–0.84)
History of TIA/Ischemic stroke	53/1422	2.86 (2.06–3.98)	2.56 (1.81–3.61)	420/1433	3.61 (3.16–4.13)	2.44 (2.12–2.80)
Myocardial infarction	7/269	1.52 (0.71–3.25)	1.05 (0.45–2.49)	143/764	1.46 (1.22–1.75)	0.95 (0.79–1.14)
Peripheral arterial disease	17/526	1.97 (1.19–3.26)	1.48 (0.83–2.65)	119/611	1.46 (1.20–1.77)	0.96 (0.79–1.17)
Heart failure	26/933	1.71 (1.11–2.64)	1.59 (1.02–2.47)	403/1869	2.21 (1.93–2.52)	1.26 (1.09–1.45)
Hypertension	122/6369	1.48 (1.04–2.12)	1.24 (0.85–1.79)	781/4422	3.72 (2.95–4.70)	1.69 (1.32–2.15)
Diabetes mellitus	48/2394	1.29 (0.92–1.80)	1.10 (0.78–1.55)	228/1168	1.55 (1.33–1.80)	1.14 (0.98–1.33)
ESRD	3/150	1.20 (0.38–3.76)	0.96 (0.30–3.03)	30/89	3.12 (2.17–4.49)	2.73 (1.88–3.97)
Cancer	28/938	1.85 (1.22–2.79)	1.72 (1.13–2.62)	-	-	-
Dyslipidemia	64/3315	1.15 (0.84–1.58)	0.90 (0.65–1.26)	-	-	-
Bleeding history	21/760	1.57 (0.99–2.49)	1.23 (0.77–1.96)	-	-	-
Smoking history				-	-	-
Current smoker	14/852	0.97 (0.56–1.68)	2.63 (1.03–6.73)	-	-	-
Ex-smoker	32/2300	0.67 (0.45–1.01)	0.62 (0.40–0.97)	-	-	-
Non-smoker	119/6501	1.38 (0.98–1.96)	-	-	-	-
Aspirin use	30/1640	0.97 (0.65–1.45)	1.11 (0.74–1.68)	526/2636	1.90 (1.66-2.18)	1.28 (1.11-1.47)

CI, confidence interval; CODE-AF, the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; ESRD, end-stage renal disease; HR, hazard ratio; NHIS, National Health Insurance Service; OAC, oral anticoagulant; TIA, transient ischemic attack.

Table 4. Ischemic Stroke and/or Systemic Thromboembolism Event Rates Per 100 Person-Years according to Sex, Stratified by CHA_2DS_2-VASc Scores

CHA_2DS_2-VASc score	Males			Females		
	Number of events	Ischemic stroke	Ischemic stroke/ systemic embolism	Number of events	Ischemic stroke	Ischemic stroke/ systemic embolism
0 (male) or 1 (female)	5/938	0.25	0.25	2/326	0.28	0.28
1 (male) or 2 (female)	20/1378	0.56	0.65	3/649	0.21	0.21
2 (male) or 3 (female)	18/1559	0.46	0.52	11/815	0.49	0.60
3 (male) or 4 (female)	26/1201	0.87	0.99	18/779	0.98	1.04
4 (male) or 5 (female)	19/599	1.28	1.44	9/475	0.85	0.85
≥5 (male) or ≥6 (female)	15/452	1.50	1.50	15/332	1.82	2.10
Total	103/6127	0.69	0.77	58/3376	0.71	0.77

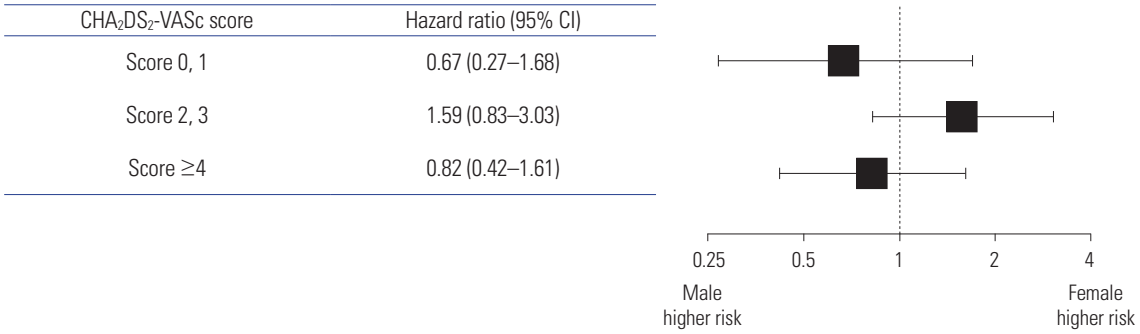

Fig. 3. Hazard ratios of interaction terms per risk score level. Model for calculating the risk for thromboembolism: Prob (thromboembolism)=$\beta_0+\beta_1$ (male)+β_2 (i.Score)+β_3 (i.Score×male). CI, confidence interval.

risk of stroke/SSE.

It is well established that OAC therapy has a net clinical benefit in AF patients with one or more stroke risk factors, and thus, OAC based on a patient's CHA_2DS_2-VASc score is recommended by many guidelines, as this score evaluates the risk of stroke.[10-13,18-20] However, stroke rates based on CHA_2DS_2-VASc score seem to vary based on study setting, population cohort, study methodology, and/or ethnicity.[21,22] In particular, higher stroke rates have been reported for Chinese cohorts compared to other ethnicities. Asians are also known to be at a higher risk of warfarin-related bleeding in comparison to other ethnic groups.[23,24] Thus, caution should be exercised when defining stroke rates and appropriate OAC treatment plans in Asian patients. In the current study, we demonstrated that contemporary AF patients, most of whom used OACs, had about one-fifth the stroke rate of that of a previous Korean OAC-naïve cohort study and a stroke rate lower than those of several OAC-naïve Western population-based cohorts.

When anticoagulated with warfarin, bleeding events, especially intracranial hemorrhage, have been found to be significantly more frequent in Asians than in non-Asians, even though Asians are traditionally less intensely anticoagulated with warfarin.[23] Although the annual risk of SSE is generally higher in Asians than in non-Asians, Asian AF patients are less likely to receive OAC therapy than non-Asian patients.[24] However, the benefit of NOACs, compared to warfarin, seems to be much larger in Asian patients than in non-Asian patients in terms of bleeding risk.[23] In Korea, the OAC prescription rate in the pre-NOAC era was below 30% in previous studies and below 50% in other Asian cohort studies.[23] The current study demonstrates that NOACs have been widely adopted in contemporary clinical practice with an OAC prescription rate above 80%.

In this cohort, history of TIA/ischemic stroke and heart failure were independent predictors of the incidence of stroke/SSE. Although several Western population-based cohort studies have demonstrated that female sex is a stroke risk factor, Asian cohort studies have shown otherwise.[25-29] In the present study, female sex was not associated with an increased risk of stroke/SSE in well-anticoagulated AF patients. Because CHA_2DS_2-VASc score was derived from OAC-naïve cohorts, stroke risk factors in fully anticoagulated populations may be different from OAC-naïve cohorts, and further studies for better risk stratification in these populations are warranted.

This study has a few limitations. First, as this was a prospective observational study, explanatory power was restricted relative to randomized control trials. Second, because all enrolled patients were from tertiary hospitals, this registry is subject to referral bias. However, this prospective cohort study has a strength in that it comprised 10000 patients with AF, which is sufficiently large enough to accurately reflect real-world stroke incidence and risk factors in an adequately anticoagulated AF population.

In conclusion, contemporary AF patients appear to have a stroke rate about one-fifth that of OAC-naïve AF patients. In this

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cohort, most risk factors included in the CHA_2DS_2-VASc scoring system showed significant associations with SSE. Female sex, a traditional risk factor for stroke and a component of the CHA_2DS_2-VASc score, was not associated with an increased risk of stroke/SSE in well-anticoagulated AF patients.

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AUTHOR CONTRIBUTIONS

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