CHA_2DS_2-VASc Score (Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) for Stroke in Asian Patients With Atrial Fibrillation

A Korean Nationwide Sample Cohort Study

Tae-Hoon Kim, MD*; Pil-Sung Yang, MD*; Jae-Sun Uhm, MD; Jong-Youn Kim, MD; Hui-Nam Pak, MD; Moon-Hyoung Lee, MD; Boyoung Joung, MD†; Gregory Y.H. Lip, MD†

Background and Purpose—The CHA_2DS_2-VASc stroke score (congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female) is used in most guidelines for risk stratification in atrial fibrillation (AF), but most data for this score have been derived in Western populations. Ethnic differences in stroke risk may be present. Our objective was to investigate risk factors for stroke in AF and application of the CHA_2DS_2-VASc score in an Asian AF population from Korea.

Methods—A total of 5855 oral anticoagulant–naive nonvalvular AF patients aged ≥20 years were enrolled from Korea National Health Insurance Service Sample cohort from 2002 to 2008 and were followed up until December 2013.

Results—The incidence rates (per 100 person-years) of ischemic stroke were 3.32 in the total population, being 0.23 in low-risk (CHA_2DS_2-VASc score 0 [male] or 1 [female]) and 4.59 in high-risk patients (CHA_2DS_2-VASc ≥2). Incidence rates of ischemic stroke or the composite thromboembolism end point showed a clear increase with increasing CHA_2DS_2-VASc score. On multivariable analysis, significant associations between CHA_2DS_2-VASc risk factors and ischemic stroke were observed; however, the significance of vascular disease or diabetes mellitus was attenuated after multivariate adjustment, and female sex (hazard ratio, 0.73; 95% confidence interval, 0.64–0.84) had a lower risk of ischemic stroke than males. Patients who were categorized as low risk consistently had an event rate <1% per year.

Conclusions—The performance of CHA_2DS_2-VASc score in Asians is comparable with that in Western populations. The score shows good performance in defining the truly-low-risk AF patients for stroke/thromboembolism. **(*Stroke*. 2017;48:1524-1530. DOI: 10.1161/STROKEAHA.117.016926.)**

Key Words: atrial fibrillation ■ death ■ Korea ■ stroke ■ thromboembolism

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

Atrial fibrillation (AF) is associated with a ≈5-fold increased risk of ischemic stroke,[1] and stroke prevention is a major priority in the clinical management of AF. When compared with control/placebo, oral anticoagulation (OAC) therapy reduces the risk of stroke by 64% and the risk of death by 26%.[2] Hence, current guidelines recommend OAC for stroke prevention of AF patients unless they are deemed to be at low risk of stroke.[3–6] Given that OAC also increases bleeding risk (which can be fatal), OAC therapy should be decided on the basis of the expected net clinical benefit of OAC therapy. Therefore, stroke risk stratification is a critical step, and an annual stroke risk of 1% to 2% is considered as the threshold at which OAC therapy yields a net clinical benefit.[7,8]

The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, female)[9] is now used in most guidelines for stroke prevention in AF, with OAC being generally recommended

Received February 1, 2017; final revision received March 7, 2017; accepted March 20, 2017.

From the Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea (T.-H.K., P.-S.Y., J.-S.U., J.-Y.K., H.-N.P., M.-H.L., B.J.); and Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom (G.Y.H.L.).

*Drs T.-H. Kim and Yang contributed equally.

†Drs Joung and Lip are joint senior authors.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.016926/-/DC1.

Correspondence to Boyoung Joung, MD, Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50 Yonseiro, Seodaemun-gu, Seoul, 03722, Republic of Korea, E-mail cby6908@yuhs.ac, or Gregory Y.H. Lip, MD, Institute of Cardiovascular Sciences, City Hospital, University of Birmingham, Birmingham B18 7QH, England, United Kingdom, E-mail g.y.h.lip@bham.ac.uk

© 2017 American Heart Association, Inc.

for ≥2 CHA$_2$DS$_2$-VASc stroke risk factors.[3–6] However, these guideline recommendations were derived from the assumption that each score corresponds to fixed stroke rates, and most data for the CHA$_2$DS$_2$-VASc score were derived and validated in Western cohorts.[9,10] Indeed, the application of CHA$_2$DS$_2$-VASc score to Asian populations has been debated because the annual stroke risk of some cohorts in Asian populations seems to vary from that reported from Western populations.[11–15] Ethnic differences may also be evident, with higher event rates in Chinese cohorts[15] compared with (for example) Japanese cohorts.[16]

Using a nationwide cohort database, our objective was to investigate risk factors for stroke in AF and application of the CHA$_2$DS$_2$-VASc score in an Asian AF population from Korea.

Methods

National Health Insurance Service (NHIS) is the single insurer managed by the Korean government, and the majority of Korean population (97.1%) is mandatory subscribers, with the remaining 3% of the population being medical aid subjects. The database is open to researchers, whose study protocols are approved by the official review committee. Korean National Health Insurance Service - Sample Cohort (K-NHIS Sample Cohort) was created and released by NHIS in 2014 and contains 1 025 340 individuals representing the total Korean population from the beginning in 2002, amounting to 2.2% of the entire population in the Korean National Health Insurance Service, and followed by 2013. The database contains patients' sociodemographic information, their use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data.

Study Population

A total of 7529 patients with AF who were aged ≥20 years were identified from Korea NHIS sample cohort database during the screening period from January 2002 to December 2008; 482 patients with valvular AF (mitral stenosis, any mechanical or bioprosthetic heart valve, or mitral valve repair) and 1192 patients receiving OACs at baseline were excluded. A final total of 5855 OAC-naive AF patients were enrolled in the study cohort and were followed up until December 2013 (Figure 1). AF was identified with *International Classification of Disease, Tenth Revision (ICD-10)* codes; I48 (AF and atrial flutter), I48.0 (AF), and I48.1 (atrial flutter). To ensure accuracy, diagnosis was established based on 1 inpatient or 2 outpatient records of *ICD-10* codes in the database.[17,18]

To evaluate the accuracy of our definition of AF, we conducted a validation study in two hospitals with 628 randomly chosen patients with the *ICD-10* code I48. Their ECGs were reviewed by 2 physicians (Daehoon Kim and Junbeom Park). The patients were ascertained to have AF if it was documented by ECG examinations. The positive predictive value was found to be 94.1%.

Baseline Comorbidities and End Points

Baseline comorbidities were evaluated during the 7-year screening period (January 2002 to December 2008) and identified from the medical claims according to the *ICD-10* codes and prescription codes, and all comorbidities were established based on 1 inpatient or 2 or more outpatient records of *ICD-10* codes in the database, which was similar to previous studies with NHIS sample cohort.[19,20] Hypertension, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, end-stage renal disease, peripheral arterial disease, a history of myocardial infarction, and a history of stroke and transient ischemic attack were assessed. The CHA$_2$DS$_2$-VASc score for each subject was estimated at the end of the screening period. The use of aspirin was also assessed at the start of the follow-up period, and only prescriptions >3 months were counted. To avoid the underestimation of aspirin utilization because of over-the-counter purchase in the study population, we additionally analyzed the over-the-counter aspirin purchase data during the 5-year follow-up period. Definitions of comorbidities are presented in Table I in the online-only Data Supplement.

The primary end point was incident ischemic stroke (including ischemic stroke–related death) during the 5-year follow-up period (from January 2009 to December 2013). Any diagnosis of ischemic stroke with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging was defined as incident ischemic stroke. The secondary end point was the composite of primary end point and systemic embolism events (the composite thromboembolism end point), which was defined as having *ICD-10* codes of atrial embolism (*ICD-10*: I74) or renal infarction (*ICD-10*: N280) as inpatient records. The accuracy of the diagnosis of an ischemic stroke in the NHIS claim data was previously validated.[21]

Statistical Analysis

Descriptive statistics were used to characterize baseline characteristics and comorbidities according to the CHA$_2$DS$_2$-VASc score. Continuous variables were expressed as the mean±SD, and categorical variables were reported as frequencies (percentage). The incidence rates of end points according to the CHA$_2$DS$_2$-VASc score are presented as 100 person-years and adjusted for exposure to aspirin treatment assuming that aspirin provides a 19% reduction in TE risk,[2] to give an indication

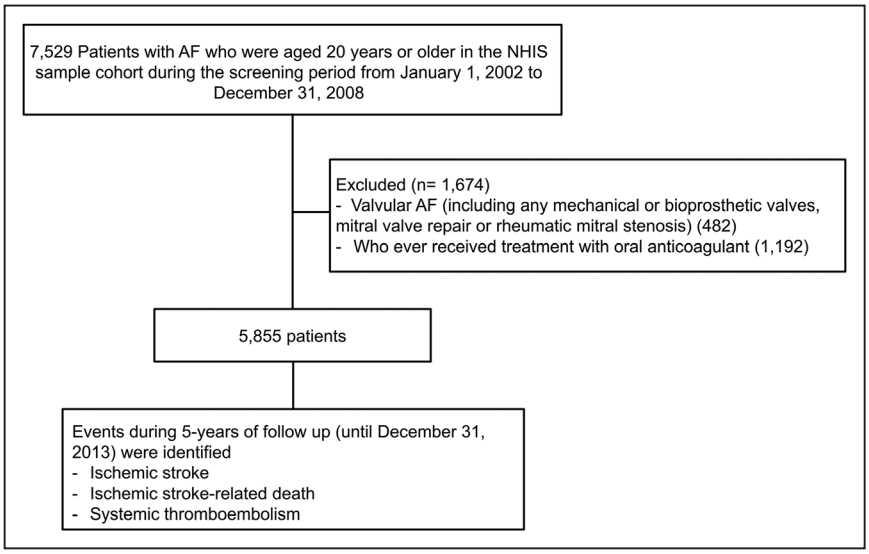

Figure 1. Flowchart of study cohort enrollment. AF indicates atrial fibrillation; and NHIS, National Health Insurance Service.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

of untreated rate. To provide perspective, we also show event rates according to the CHA_2DS_2-VASc score in the non-AF population from this data set. The cumulative incidence of AF and differences according to the CHA_2DS_2-VASc score were displayed and estimated by the Kaplan–Meier analysis using the log-rank test. To explore determinants for the risk of stroke, Cox proportional-hazards regression analysis was used to investigate the association between the comorbidities and the incidence of ischemic stroke or the composite thromboembolism end point. Factors associated with outcome after age and sex adjustment were used in a conditional forward Cox regression analysis. The threshold for entry was 0.05 and for removal was 0.10. Remaining factors significantly associated with outcomes were retained for the final model. Interdependent covariables were not used simultaneously in any of the analyses. The patients were censored at the date when the ischemic stroke or the composite end point events occurred, at the date of their death, at the date of OAC initiation during follow-up period, or at end of follow-up.

To quantify the predictive value for ischemic stroke and the composite thromboembolism end point, we calculated the C statistics, which quantifies discriminant ability and is a measure of the area under the receiver–operator characteristic curve, and tested the hypothesis that these schemes performed significantly better than chance (indicated by a C statistic ≥0.5). The odds ratio for the increased relative risk of the absence of ischemic stroke was assessed by logistic regression analysis. All tests were 2-tailed, with $P<0.05$ considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 23.0; SPSS, Inc, Chicago, IL).

Results

This study included 5855 OAC-naive nonvalvular AF patients (mean age: 43.9±11.5 years; female 48.4%) who had diagnosed AF during the 6-year screening period. Patients were classified according to CHA_2DS_2-VASc scores as low-risk (0 or 1 point [in female]), intermediate-risk (1 point in male), and high-risk (≥2 points) groups, respectively. Patients' distribution, demographic data, and comorbidities according to CHA_2DS_2-VASc scores are listed in Table 1. The proportion of patients aged ≥75 years was 26.7% in total population. Hypertension was the most prevalent comorbidity (75.5%), followed by heart failure (31.9%), vascular disease (20.6%), and diabetes mellitus (19.9%). Baseline characteristics of 2 primary source cohort populations from which the CHA_2DS_2-VASc score was derived[9,22] are also listed in Table 1, for illustrative purposes.

Risk of Stroke

During the mean follow-up period of 50.6±17.6 months, 819 of 5855 patients (14.0%) experienced incident ischemic stroke. The incidence rates (per 100 person-years) of ischemic stroke or the composite thromboembolism end point show a clear increase with increasing CHA_2DS_2-VASc score (Table 2; Figure 2). The incidence rates (per 100 person-years) of ischemic stroke were 3.32 in the total study population, being 0.23 in low-risk, 1.04 in intermediate-risk, and 4.59 in high-risk patients. The incidence rates of ischemic stroke/systemic embolism of 2 primary source cohort populations according to CHA_2DS_2-VASc score are also listed in Table 2, for illustrative purposes.

Patients who were categorized as low risk by the CHA_2DS_2-VASc score (ie, score 0 in males or 1 in females) consistently

Table 1. Patient Baseline Characteristics

	Korea NHIS Cohort Database				The Euro Heart Survey	Denmark Nationwide Cohort
	Low Risk (CHA_2DS_2-VASc 0 or 1 [Female])	Intermediate Risk (CHA_2DS_2-VASc 1 [Male])	High Risk (CHA_2DS_2-VASc ≥2)	Total (n=5855)	Total (n=1084)	Total (n=73 538)
Age, y	44±12	53±11	69±12	64±15	66±14	N/A
<65	0 (0)	0 (0)	1561 (35.1)	2594 (44.3)	N/A	15 130 (20.5)
65–74	0 (0)	76 (13.8)	1624 (36.5)	1700 (29.0)	N/A	14 544 (19.8)
>75	860 (100)	474 (86.2)	1260 (28.3)	1561 (26.7)	309 (28.5)	43 864 (59.7)
Women	446 (51.9)	0 (0)	2389 (53.7)	235 (48.4)	442 (40.8)	37 651 (51.2)
CHA_2DS_2-VASc score	0.52±0.50	1.00	4.09±1.69	3.28±2.08	N/A	N/A
History of TIA/ischemic stroke	0 (0)	0 (0)	1433 (32.2)	1433 (24.5)	97 (9.1)	13 368 (18.2)
Atherosclerotic disease						
Myocardial infarction	0 (0)	8 (1.5)	756 (17.0)	764 (13.0)	N/A	N/A
Peripheral arterial disease	0 (0)	7 (1.3)	604 (13.6)	611 (10.4)	62 (5.8)	N/A
Vascular disease	0 (0)	15 (2.7)	1191 (26.8)	1206 (20.6)	N/A	12 873 (17.5)
Heart failure	0 (0)	17 (3.1)	1852 (41.7)	1869 (31.9)	253 (23.5)	13 126 (17.9)
Hypertension	0 (0)	405 (73.6)	4017 (90.4)	4422 (75.5)	729 (67.3)	25 060 (34.1)
Diabetes mellitus	0 (0)	37 (6.7)	1131 (25.4)	1168 (19.9)	187 (17.3)	6496 (8.8)
ESRD	2 (0.2)	5 (0.9)	82 (1.8)	89 (1.5)	N/A	N/A
COPD	38 (4.4)	26 (4.7)	609 (13.7)	673 (11.5)	N/A	N/A
Aspirin use	86 (10.0)	225 (40.9)	2325 (52.3)	2636 (45.0)	802 (74.0)	25 503 (34.7)

Values are expressed in n (%) or mean±SD. Vascular disease is previous myocardial infarction, peripheral arterial disease, or aortic plaque. COPD indicates chronic obstructive pulmonary disease; ESRD, end-stage renal disease; N/A, not available; NHIS, National Health Insurance Service; and TIA, transient ischemic attack.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

Table 2. Ischemic Stroke or the Composite Thromboembolism End Point per 100 Person-Years at Risk in Relation to CHA$_2$DS$_2$-VASc Scores in 5855 Patients Without Anticoagulation Throughout Follow-Up

	Korea NHIS Cohort Database (n=5855)						The Euro Heart Survey (n=1084)	Denmark Nationwide Cohort (n=73 538)
		Ischemic Stroke		Ischemic Stroke/Systemic Embolism			Ischemic Stroke/Systemic Embolism	Ischemic Stroke/Systemic Embolism
CHA$_2$DS$_2$-VASc Score	No. of Patients	Unadjusted	Adjusted for Aspirin*	Unadjusted	Adjusted for Aspirin*	CHA$_2$DS$_2$-VASc Score	Adjusted for Aspirin	Unadjusted
0 (male) or 1 (female)	860	0.23	0.26	0.26	0.29	0	0	0.69
1 (male)	550	1.04	1.18	1.20	1.35	1	0.7	1.51
2	975	1.91	2.21	2.04	2.35	2	1.9	3.01
3	911	2.54	2.88	2.67	3.04	3	4.7	4.41
4	836	4.72	5.34	5.10	5.76	4	2.3	6.69
5	770	5.79	6.54	5.98	6.76	5	3.9	10.42
6	513	8.36	9.50	8.61	9.77	6	4.5	12.85
≥7	440	8.82	9.97	9.03	10.21	≥7	11.4	14.0
Total	5855	3.32	3.79	3.49	3.98	Total	2.3	5.29

NHIS indicates National Health Insurance Service.

*Adjustment made for exposure to aspirin treatment, assuming that aspirin provides a 19% reduction in thromboembolism risk, to give an indication of untreated rates.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

had an event rate <1% per year. The proportion of patients who remained in low risk gradually decreased from 14.7% at baseline to 11.4% at the end of follow-up (or within a year before stroke), and there were 6 thromboembolic events in these truly-low-risk patients during the entire follow-up period of 5 years (rate, 0.18 per 100 person-years; 95% confidence interval [CI], 0.14–0.25). A low-risk category in CHA$_2$DS$_2$-VASc score was predictive of the absence of ischemic stroke during the 5-year follow-up (odds ratio, 16.4; 95% CI, 8.8–30.8; P<0.001).

Median CHA$_2$DS$_2$-VASc score in this cohort was 3.28 (± 2.08), and the predictive value of the CHA$_2$DS$_2$-VASc score for stroke was good, as reflected by C indexes for ischemic stroke at 1 year and 5 years of 0.719 (95% CI, 0.71–0.73; P<0.001) and 0.714 (95% CI, 0.70–0.73; P<0.001), respectively.

Comparison With the Non-AF Population

The overall risk of stroke and systemic embolism in OAC-naive AF patients was increased ≈3-fold compared with age- and sex-matched non-AF subjects. Table II in the online-only Data Supplement provides details on event rates for each point of the CHA$_2$DS$_2$-VASc score, where AF patients had generally higher event rates compared with non-AF subjects. In the low-risk group (ie, CHA$_2$DS$_2$-VASc 0 in males or 1 in females), the incidence per 100 person-years of stroke and systemic embolism was similar to that seen in the non-AF population (0.26 versus 0.23, respectively; Figure I in the online-only Data Supplement).

Risk Factors for Ischemic Stroke and the Composite Thromboembolism End Point

All risk factors, except female sex (hazard ratio [HR], 0.94; 95% CI, 0.82–1.07), included in the CHA$_2$DS$_2$-VASc–scoring system showed significant associations with incident ischemic stroke on univariate analysis (Table 3). These associations with ischemic stroke events were greatest for age ≥75 years (HR, 4.70; 95% CI, 3.32–4.37), history of stroke or transient ischemic attack (HR, 3.81; 95% CI, 3.32–4.37), end-stage renal disease (HR, 2.36; 95% CI, 1.56–3.57), and chronic obstructive pulmonary disease (HR, 1.72; 95% CI, 1.43–2.07).

On multivariable analysis, the significance of vascular disease (HR, 0.98; 95% CI, 0.84–1.15) or diabetes mellitus (95% CI, 1.13; 95% CI, 0.96–1.32) were attenuated after multivariate adjustment, and female sex (HR, 0.75; 95% CI, 0.63–0.86) had a lower risk of ischemic stroke than males. The risk factors with significant associations were virtually the same irrespective of whether the end point was ischemic stroke or composite thromboembolism event.

Discussion

In this nationwide study using a large real-world cohort of OAC-naive AF patients, we demonstrate that the CHA$_2$DS$_2$-VASc score shows good performance in the South Korean

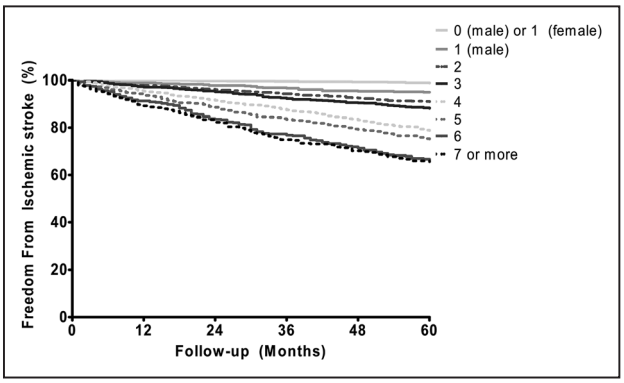

Figure 2. The rate of ischemic stroke among patients with CHA$_2$DS$_2$-VASc scores of 0 to ≥7.

Table 3. Associations Between Baseline Factors and Ischemic Stroke and the Composite Thromboembolism End Point in Patients Without Anticoagulant Treatment

	Ischemic Stroke					Ischemic Stroke/Systemic Embolism				
	Number With Event	Univariable		Multivariable		Number With Event	Univariable		Multivariable	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Age, y										
<65	161/2594	Ref	…	Ref	…	173/2594	Ref	…	Ref	…
65–74	320/1700	3.44	2.84–4.16	2.11	1.73–2.58	334/1700	3.34	2.78–4.02	2.10	1.73–2.55
>75	338/1561	4.70	3.90–5.68	3.11	2.51–3.85	352/1561	4.55	3.79–5.47	3.11	2.52–3.82
Women	385/2835	0.94	0.82–1.07	0.75	0.63–0.86	398/2835	0.91	0.80–1.04	0.73	0.64–0.84
Ischemic stroke/TIA	411/1433	3.81	3.32–4.37	2.58	2.23–2.97	420/1433	3.61	3.16–4.13	2.44	2.12–2.80
Atherosclerotic disease										
Myocardial infarction	139/764	1.49	1.24–1.79	0.97	0.81–1.17	143/764	1.46	1.22–1.75	0.95	0.79–1.14
Peripheral arterial disease	113/611	1.45	1.19–1.76	0.95	0.78–1.17	119/611	1.46	1.20–1.77	0.96	0.79–1.17
Vascular disease	221/1206	1.54	1.32–1.80	0.98	0.84–1.15	231/1206	1.54	1.32–1.79	0.95	0.84–1.14
Heart failure	380/1869	2.16	1.88–2.48	1.23	1.06–1.42	403/1869	2.21	1.93–2.52	1.26	1.09–1.45
Hypertension	750/4422	4.04	3.16–5.17	1.85	1.43–2.40	781/4422	3.72	2.95–4.70	1.69	1.32–2.15
Diabetes mellitus	216/1168	1.53	1.31–1.79	1.13	0.96–1.32	228/1168	1.55	1.33–1.80	1.14	0.98–1.33
ESRD	23/89	2.36	1.56–3.57	2.03	1.33–3.09	30/89	3.12	2.17–4.49	2.73	1.88–3.97
COPD	134/673	1.72	1.43–2.07	1.13	0.94–1.37	143/673	1.76	1.47–2.10	1.16	0.97–1.40
Aspirin use	505/2636	1.93	1.68–2.23	1.30	1.12–1.50	526/2636	1.90	1.66–2.18	1.28	1.11–1.47

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HR, hazard ratio; and TIA, transient ischemic attack.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

population, particularly in defining the truly-low-risk AF patients for stroke. Almost all risk factors included in CHA_2DS_2-VASc–scoring system showed significant associations with ischemic stroke and the composite thromboembolism end point, although female sex was not an independent risk factor for ischemic stroke or the composite end point after multivariate adjustment.

Discrepancies in Reported Stroke Rates

Several studies have demonstrated that the net clinical benefit of OAC is evident in AF patients with one or more stroke risk factors.[23,24] Various guidelines recommend OAC use based on the patients' risk of stroke by the CHA_2DS_2-VASc score.[3–6] Unsurprisingly, there are variations in reported CHA_2DS_2-VASc point score stratum-specific stroke rates, reflecting different study settings, population cohorts, study methodology, or ethnic groups.[25,26] Indeed, significant differences in reported event rates are evident in Asian studies, with higher event rates in Chinese cohorts.[16] One US study suggested that African-Americans with AF merited one extra point for ethnicity on the CHA_2DS_2-VASc score,[27] whereas Chao et al[15] proposed a recalibration of the CHA_2DS_2-VASc score for Asians, with one point given for the age 50 to 64 years criteria.

Hence, additional studies are clearly needed to carefully define stroke rates in different ethnic groups. In this study, we have now demonstrated for the first time in a large Korean Asian population that there are comparable CHA_2DS_2-VASc point score stratum–specific stroke rates compared with that seen in several Western cohorts cited in guidelines.[22,28]

Also, AF patients had generally higher event rates for each point of the CHA_2DS_2-VASc score compared with non-AF subjects in our cohort. In the low-risk group (ie, CHA_2DS_2-VASc 0 in males or 1 in females), the incidence per 100 person-years of stroke and systemic embolism in AF patients was low and similar to rates seen in the non-AF population.

Defining the Truly-Low-Risk Patients

The suggested threshold of annual ischemic stroke risk for a favorable net clinical benefit from OAC for patients with AF is between 1% and 2%.[7] The introduction of non–vitamin K antagonist OACs with improved efficacy and safety compared with warfarin has lowered the threshold for OAC therapy for AF patients from an annual stroke rate of 1.7% with vitamin K antagonists to 0.9% with non–vitamin K antagonist OACs.[7] Indeed, the 1.7% per year annual risk treatment threshold with warfarin may even be lower with good-quality anticoagulation control, as reflected by a time in therapeutic range >70%.[29] Therefore, the focus has now shifted away from predicting high-risk patients toward identifying patients with a truly low risk of ischemic stroke in whom OAC has no net clinical benefit.[30]

In this study, the incidence rates (per 100 person-years) of ischemic stroke were 0.23 in low-risk patients (CHA_2DS_2-VASc score 0 [male] or 1 [female]), 1.04 in intermediate-risk patients (CHA_2DS_2-VASc=1 in male), and 4.59 in high-risk patients (CHA_2DS_2-VASc ≥2). Although some recent studies have shown higher reported stroke rates in Asian populations than those of other cohort studies in Western populations,[11,31,32]

the CHA$_2$DS$_2$-VASc score seems to have a good performance in defining the truly-low-risk AF patient for stroke in the Korean population, as reflected by a large odds ratio for the low-risk CHA$_2$DS$_2$-VASc score category for predicting the absence of ischemic stroke.

Stroke Risk Factors

Several cohort studies have shown that female sex is a risk factor for stroke, albeit with an age dependency to this risk.[33–37] Several Asian cohort studies from Hong Kong,[11] China,[12] Taiwan,[38] and Japan[13] have suggested that female sex was not an independent risk factor for ischemic stroke, again suggesting some potential ethnic differences in the risk of stroke between Asian and non-Asian populations. Consistent with previous Asian studies, female sex was not a risk factor for stroke in our cohort and instead had a lower stroke risk of ischemic stroke than males. Beyond the biological difference between males and females, other sex differences in lifestyle patterns, social responsibility, and behaviors can make a different impact on the sex differences according to ethnicity. However, we are not able to identify these complicated factors within our cohort database. Further prospective studies are needed to evaluate this sex effect on stroke risk in AF patients. Other risk factors in our population such as older age, history of stroke or transient ischemic attack, heart failure, and hypertension remained independent stroke risk factors, consistent with Western cohorts.

Limitations

To our knowledge, this is the first population-based investigation in the Korean population to assess the risk of ischemic stroke in OAC-naive AF patients. Our study should be interpreted in the context of the following limitations. First, baseline AF diagnosis and estimation of incidence of ischemic stroke or systemic embolism were on diagnostic codes registered by the physicians; therefore, the diagnosis of AF and ischemic stroke could be inaccurate although the method for the diagnosis has been validated in previous studies, and our internal validation found a high correlation with actual AF diagnosis. Second, patients who received aspirin were enrolled in the present study; therefore, the stroke rate could be slightly affected by aspirin use, despite some adjustment for aspirin use in analyses.

Conclusions

The performance of CHA$_2$DS$_2$-VASc score in Asians is comparable with that seen in Western populations. The score shows good performance in defining the truly-low-risk AF patients for stroke/TE.

Source of Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF-2012R1A2A2A02045367 and 2010-0021993) and grants from the Korean Healthcare Technology R&D project funded by the Ministry of Health and Welfare (HI12C1552, HI16C0058, and HI15C1200).

Disclosures

Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. He is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No fees are received personally. The other authors report no conflicts.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18:1609–1678. doi: 10.1093/europace/euw295.
4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–76. doi: 10.1016/j.jacc.2014.03.022.
5. Interventions to prevent stroke. Recommendations. Atrial fibrillation: management [Clinical guideline 180]. National-Institute-for-Health-and-Care-Excellence. https://www.nice.org.uk/guidance/cg180/chapter/1-Recommendations#interventions-to-prevent-stroke-2. Accessed March 1, 2017.
6. Chiang CE, Wang TD, Li YH, Lin TH, Chien KL, Yeh HI, et al; Hypertension Committee of the Taiwan Society of Cardiology. 2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension. *J Formos Med Assoc*. 2010;109:740–773. doi: 10.1016/S0929-6646(10)60120-9.
7. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011;4:14–21. doi: 10.1161/CIRCOUTCOMES.110.958108.
8. Overvad TF, Nielsen PB, Lip GY. Treatment thresholds for stroke prevention in atrial fibrillation: observations on the CHA2DS2-VASc score. *Eur Heart J Cardiovasc Pharmacother*. 2017;3:37–41. doi: 10.1093/ehjcvp/pvw022.
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584.
10. Nielsen PB, Lip GY. Adding rigor to stroke rate investigations in patients with atrial fibrillation. *Circulation*. 2017;135:220–223. doi: 10.1161/CIRCULATIONAHA.116.025944.
11. Siu CW, Lip GY, Lam KF, Tse HF. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm*. 2014;11:1401–1408. doi: 10.1016/j.hrthm.2014.04.021.
12. Guo Y, Apostolakis S, Blann AD, Wang H, Zhao X, Zhang Y, et al. Validation of contemporary stroke and bleeding risk stratification scores in non-anticoagulated Chinese patients with atrial fibrillation. *Int J Cardiol*. 2013;168:904–909. doi: 10.1016/j.ijcard.2012.10.052.
13. Tomita H, Okumura K, Inoue H, Atarashi H, Yamashita T, Origasa H, et al; J-RHYTHM Registry Investigators. Validation of risk scoring system excluding female sex from CHA2DS2-VASc in Japanese patients with nonvalvular atrial fibrillation – subanalysis of the J-RHYTHM registry. *Circ J*. 2015;79:1719–1726. doi: 10.1253/circj.CJ-15-0095.
14. Hung Y, Chao TF, Liu CJ, Tuan TC, Lin YJ, Chang SL, et al. Is an oral anticoagulant necessary for young atrial fibrillation patients with a cha2ds2-vasc score of 1 (men) or 2 (women)? *J Am Heart Assoc*. 2016;5:e003839.
15. Chao TF, Lip GY, Liu CJ, Tuan TC, Chen SJ, Wang KL, et al. Validation of a modified CHA2DS2-VASc score for stroke risk stratification in Asian patients with atrial fibrillation: a nationwide cohort study. *Stroke*. 2016;47:2462–2469. doi: 10.1161/STROKEAHA.116.013880.
16. Bai Y, Shantsila A, Lip GY. Ischemic stroke risk in East Asian patients with CHA2DS2-VASc score of 1: systematic review and meta-analysis. *Expert Rev Cardiovasc Ther*. 2017;15:145–150. doi: 10.1080/14779072.2017.1281742.
17. Chen SJ, Liu CJ, Chao TF, Wang KL, Chen TJ, Chou P, et al. Dental scaling and atrial fibrillation: a nationwide cohort study. *Int J Cardiol*. 2013;168:2300–2303. doi: 10.1016/j.ijcard.2013.01.192.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

18. Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, et al. Rate-control treatment and mortality in atrial fibrillation. *Circulation*. 2015;132:1604–1612. doi: 10.1161/CIRCULATIONAHA.114.013709.
19. Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Underweight is a risk factor for atrial fibrillation: a nationwide population-based study. *Int J Cardiol*. 2016;215:449–456. doi: 10.1016/j.ijcard.2016.04.036.
20. Lee SR, Choi EK, Rhee TM, Lee HJ, Lim WH, Kang SH, et al. Evaluation of the association between diabetic retinopathy and the incidence of atrial fibrillation: a nationwide population-based study. *Int J Cardiol*. 2016;223:953–957. doi: 10.1016/j.ijcard.2016.08.296.
21. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the national health insurance service-national sample cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2016:dyv319.
22. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
23. Lip GY, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost*. 2015;114:826–834. doi: 10.1160/TH15-07-0565.
24. Fauchier L, Clementy N, Bisson A, Ivanes F, Angoulvant D, Babuty D, et al. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated? *Stroke*. 2016;47:1831–1836. doi: 10.1161/STROKEAHA.116.013253.
25. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation*. 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057.
26. Nielsen PB, Larsen TB, Skjøth F, Overvad TF, Lip GY. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. *Sci Rep*. 2016;6:27410. doi: 10.1038/srep27410.
27. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. *J Am Coll Cardiol*. 2016;68:461–470. doi: 10.1016/j.jacc.2016.05.044.
28. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510. doi: 10.1093/eurheartj/ehr488.
29. Proietti M, Lip GY. Major outcomes in atrial fibrillation patients with one risk factor: impact of time in therapeutic range observations from the SPORTIF trials. *Am J Med*. 2016;129:1110–1116. doi: 10.1016/j.amjmed.2016.03.024.
30. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet*. 2016;388:806–817. doi: 10.1016/S0140-6736(16)31257-0.
31. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;64:1658–1665. doi: 10.1016/j.jacc.2014.06.1203.
32. Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. *J Am Coll Cardiol*. 2015;66:1339–1347. doi: 10.1016/j.jacc.2015.07.026.
33. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290:1049–1056. doi: 10.1001/jama.290.8.1049.
34. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–1691. doi: 10.1161/CIRCULATIONAHA.105.553438.
35. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307:1952–1958. doi: 10.1001/jama.2012.3490.
36. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ*. 2012;344:e3522.
37. Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost*. 2012;10:1745–1751. doi: 10.1111/j.1538-7836.2012.04853.x.
38. Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, et al. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation– a nation wide database analysis. *Atherosclerosis*. 2011;217:292–295. doi: 10.1016/j.atherosclerosis.2011.03.033.

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

CHA_2DS_2-VASc Score (Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) for Stroke in Asian Patients With Atrial Fibrillation: A Korean Nationwide Sample Cohort Study

Tae-Hoon Kim, Pil-Sung Yang, Jae-Sun Uhm, Jong-Youn Kim, Hui-Nam Pak, Moon-Hyoung Lee, Boyoung Joung and Gregory Y.H. Lip

Stroke. 2017;48:1524-1530; originally published online April 28, 2017;
doi: 10.1161/STROKEAHA.117.016926
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/6/1524

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2017/04/28/STROKEAHA.117.016926.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/

Downloaded from http://stroke.ahajournals.org/ by guest on July 2, 2018

Supplementary Table 1. Definitions and ICD-10 codes used for defining the comorbidities

Comorbidities	Definitions	ICD-10 codes or conditions
Heart failure	Defined from diagnosis*	ICD10: I11.0, I50, I97.1
Hypertension	Defined from diagnosis*	ICD10: I10, I11, I12, I13, I15
Diabetes mellitus	Defined from diagnosis* plus treatment	ICD10: E10, E11, E12, E13, E14 Treatment: all kinds of oral antidiabetics and insulin
Ischemic stroke	Defined from diagnosis*	ICD10: I63, I64
TIA	Defined from diagnosis*	ICD10: G45
Previous MI	Defined from diagnosis*	I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis*	ICD10: I70.0, I70.1, I70.2, I70.8, I70.9

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.

Supplementary Table II. Ischemic stroke, systemic embolism, or the composite thromboembolism endpoint /100 person-years at risk in relation to CHA_2DS_2-VASc scores in 5,855 OAC naïve AF population and age/sex matched non-AF population.

CHA_2DS_2-VASc score	OAC naïve AF Korean population (n=5,855)			*Age and sex matched Non-AF Korean population (n=115,896)		
	Ischemic stroke	Systemic embolism	Ischemic stroke/systemic embolism	Ischemic stroke	Systemic embolism	Ischemic stroke/systemic embolism
0 (male) or 1 (female)	0.23	0.02	0.26	0.23	0.02	0.23
1 (male)	1.04	0.15	1.18	0.93	0.07	0.97
2	1.91	0.17	2.21	1.24	0.10	1.30
3	2.54	0.19	2.88	1.82	0.12	1.94
4	4.72	0.42	5.34	2.51	0.20	2.74
5	5.79	0.35	6.54	3.53	0.22	3.91
6	8.36	0.60	9.50	4.25	0.25	4.70
7 or more	8.82	0.61	9.97	5.12	0.40	5.67
Total	3.32	0.27	3.79	1.32	0.10	1.39

*Age and sex matched with Propensity-score matching with propensity scores estimated using a non-parsimonious multiple logistic regression model between OAC naïve AF group and non-AF group (1:20 matching). The matching procedure was performed using R packages, including Matchit, RItools, and CEM (Ho DE et al. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Political Analysis 2007; 15: 199-236.).

Supplementary Figure I. Incidence rates of ischemic stroke/systemic embolism according to each CHA2DS2-VASc scores (A) and risk categories as stratified by low (score 0 or 1 in female), intermediate (1 in male), and high risk (≥2) (B).