Original Contribution

Age Threshold for Ischemic Stroke Risk in Atrial Fibrillation

Cohort Data Covering the Entire Korean Population

Tae-Hoon Kim, MD*; Pil-Sung Yang, MD*; Hee Tae Yu, MD; Eunsun Jang, MS; 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—Although older age is one of the most important risk factor for stroke in atrial fibrillation (AF), the appropriate age threshold (eg, CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years, female], 1 point for age 65–74 years, 2 points for age ≥75 years) for increased risk is controversial because actual age thresholds may differ between countries and ethnic groups. We investigated the age threshold for ischemic stroke risk among Asian AF patients.

Methods—Using National Health Insurance Service database, including 426 650 oral anticoagulant–naive nonvalvular AF patients from 2005 to 2015, with ≤2 nongender-related CHA_2DS_2-VASc risk scores (CHA_2DS_2-VASc score 0–2 in males, 1–3 in females), we assessed the risk of ischemic stroke in AF patients according to the age.

Results—Patients who fulfill the age risk criterion (age, 65–74 years) without other risk factors showed a significantly higher risk of stroke (4.76 per 100 person-years [100PY]; adjusted hazard ratio, 2.25; 95% confidence interval [CI], 2.17–2.36) compared with patients with 1 risk score other than age (1.87/100PY). Patients aged 55 to 59 years with no risk factors showed similar risk of stroke (1.94/100PY; adjusted hazard ratio, 0.95; 95% confidence interval, 0.90–1.00) than patients with 1 risk score (2.06/100PY). Patients aged 65 to 69 years and no other risk factors had similar stroke risk (4.08/100PY; adjusted hazard ratio, 0.93; 95% confidence interval, 0.90–0.97) than patients with 2 nongender-related risk scores (4.42/100PY).

Conclusions—Older age is the most important predictor of ischemic stroke in AF, particularly for patients with low to intermediate risk of stroke. These nationwide data suggest lowering the current age threshold (age, ≥65 years) in the CHA_2DS_2-VASc score to age ≥55 years might be appropriate among Asian patients with AF. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021047.)**

Key Words: age threshold ■ atrial fibrillation ■ patients ■ risk factor ■ stroke

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population, and stroke prevention is the principal management priority in patients with AF given its association with a 5-fold increase in stroke risk.[1–4] However, the risk of stroke in AF is not identical for all patients groups and depends on patients' age and comorbidities, which have resulted in the development of clinical scores to aid stroke risk stratification for AF patients. Currently, the congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years, female score (CHA_2DS_2-VASc)[5] is widely used in most guidelines for stroke prevention in AF, with oral anticoagulant (OAC) being generally recommended for those with ≥2 CHA_2DS_2-VASc stroke risk factors.[6–10] OAC therapy should be decided on the basis of the expected net clinical benefit, and an annual stroke risk of 1% to 2% is considered as the treatment threshold at which OAC therapy yields a net clinical benefit.[11,12] The predictive ability of the CHA_2DS_2-VASc was validated in Korean AF population from a nationwide health insurance data[3] and also was shown to help identify truly low risk of stroke in Korean AF.[13]

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

*Drs Kim and Yang contributed equally.

†Drs Joung and Lip shared senior and corresponding authorship.

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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, Republic of Korea 120–752, E-mail cby6908@yuhs.ac or Gregory Y.H. Lip, MD, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom, E-mail g.y.h.lip@bham.ac.uk

Older age is the most important risk factor for ischemic stroke in AF among individual risk factors which were included in the CHA_2DS_2-VASc score, particularly for low to intermediate risk patients.[14,15] However, the appropriate age threshold (eg, CHA_2DS_2-VASc score, 1 point for age 65–74 years, 2 points for age ≥75 years) is still controversial because actual age thresholds may differ between countries and ethnic groups. Moreover, the ability of a risk scoring scheme to identify AF patients who are at truly low-risk of stroke is an even more important in Asians because stroke risk among Asians may be much higher than that among Western populations.[16–21] In this respect, recent Asian data[22,23] have demonstrated that the age threshold of 65 years in Asian patients may be too high and may need to be reset lower, perhaps to 50 years for the initial identification of truly low-risk of stroke AF patients in whom OAC therapy are not needed, especially in the era of non–vitamin K antagonist OAC (NOAC).[11]

Our objective was to investigate the appropriate age threshold for ischemic stroke risk by (1) comparing the estimated annual risk of ischemic stroke in the different age group strata to the suggested annual stroke risk threshold for a favorable net clinical benefit from OAC, and (2) comparing the hazard ratios (HRs) for ischemic stroke in the different age group strata in low (no risk factors) or intermediate (1 non-gender-related (NGR) risk factor) risk groups with patients who were categorized as higher risk group (+1 risk score) by the CHA_2DS_2-VASc score, among Asian AF patients in Korea from a nationwide health insurance data.

Methods

This study is based on the national health claims database (National Health Insurance Service [NHIS]-2018-4-028) established by the NHIS of Republic of Korea,[24,25] and the authors have no conflict of interest with NHIS. Because the intellectual property right of this database belongs to the National Health Insurance Corporation, we are not authorized to open the data, analytical methods, and study materials to other researchers for purposes of reproducing the results or replicating the procedure. However, any investigator can apply for the use of the database because it has been open to the public for research purpose (https://nhiss.nhis.or.kr/). The NHIS is the single insurer managed by the Korean government, and the majority (97.1%) of Korean population are mandatory subscribers, with the remaining 3% of the population being medical aid subjects. The NHIS database contains the information of medical aid subjects; therefore, it is based on the entire Korean population.[2] The following medical information is provided: patients' sociodemographic information, their use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. Every population in the NHIS database was linked by the Korean social security numbers, and all social security numbers were deleted after constructing the cohort by giving serial numbers to prevent leakage of personal information. These databases are open to researchers, whose study protocols are approved by the official review committee. This study was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0179), and informed consent was waived.

Study Population

In the Korean NHIS data, 426 650 patients with prevalent AF who were aged ≥18 years with ≤2 NGR CHA_2DS_2-VASc risk scores (CHA_2DS_2-VASc score, 0–2 in males, 1–3 in females) were identified during the period from January 1, 2005 to December 31, 2015. The following were exclusion criteria: (1) those with valvular AF, such as mitral valve stenosis and prosthetic valve disease (*International Classification of Diseases, Tenth Revision*-I050, I052, I342; n=51 389), (2) those who ever received treatment with OAC before enrollment (n=76 365), and (3) those with ≥3 NGR risk scores (n=391 571; Figure 1).

AF was diagnosed using the *International Classification of Diseases, Tenth Revision* codes, I48 (AF and atrial flutter), I48.0 (AF), and I48.1 (atrial flutter). Moreover, patients were defined as AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department to ensure diagnostic accuracy.[26] The AF diagnosis has previously been validated in the NHIS database with a positive predictive value of 94.1%.[2,27–30]

Baseline Comorbidities and Ischemic Stroke

Comorbidities were defined using the medical claims according to *International Classification of Diseases, Tenth Revision* codes and prescription medication use. Diabetes mellitus was defined when patients had a diabetes mellitus diagnosis and used of at least 1 antidiabetic drug. To ensure diagnostic accuracy, we defined patients with comorbidities, including hypertension, heart failure, transient ischemic attack, systemic embolism, myocardial infarction, peripheral arterial disease, chronic kidney disease, and dyslipidemia, when it was a discharge diagnosis or was confirmed more than twice in an outpatient setting, which was similar to previous studies with NHIS.[2,3,31] Ischemic stroke was defined with any admission diagnosis of ischemic stroke with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging.[3] The definitions of comorbidities and main diagnosis of hospitalization are presented in Table I in the online-only Data Supplement. The comorbidities were defined at the time of AF diagnosis and assessed annually during the follow period.

Statistical Analysis

Descriptive statistics were used to characterize baseline characteristics and comorbidities. Continuous variables were expressed as the mean±SD, and categorical variables were reported as frequencies (percentage). We assessed the risk of ischemic stroke in according to the number of NGR risk score (0, 1, or 2) and according to the category of risk factors the patient has (whether age risk criterion was included or not). The incidence rates of ischemic stroke are presented as the number of event per 100 person-years (100PY), with the 95% confidence interval (CI) estimated by exact binomial probabilities. Cox proportional hazards regression was used to estimate the unadjusted and adjusted HR the ischemic stroke according to the number of NGR risk scores stratified by age. To control for confounding, we added gender, chronic kidney disease, dyslipidemia, and income status and age (only among patients who do not fulfil the age risk criterion) to our multivariable models. For Cox proportional hazards regression analysis, the patient's index date for these analyses was the first AF diagnosis date and 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. Furthermore, we attempted to minimize the effect of time-dependent changes in the patients' age and risk factors by assessing only 1-year outcome and by assessing the outcome during follow-up period before patients develop new NGR risk factors (before presenting with ischemic stroke). All tests were 2-tailed, with $P<0.05$ considered significant. Statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC) and SPSS version 23.0 statistical package (SPSS, Inc, Chicago, IL).

Results

Patient baseline characteristics were presented in Table 1. A total of 426 650 patients included in the analysis: 108 553 (25.4%) patients with no risk factors (CHA_2DS_2-VASc score 0 in males, 1 in females), 120 224 (28.2%) with 1 NGR risk score (CHA_2DS_2-VASc score 1 in males, 2 in females), and 197 873 (46.4%) with 2 NGR risk score (CHA_2DS_2-VASc score 2 in males, 3 in females) at baseline. Data (1 891 679 PY; mean, 4.4±3.8 years/patient) were included in the stroke

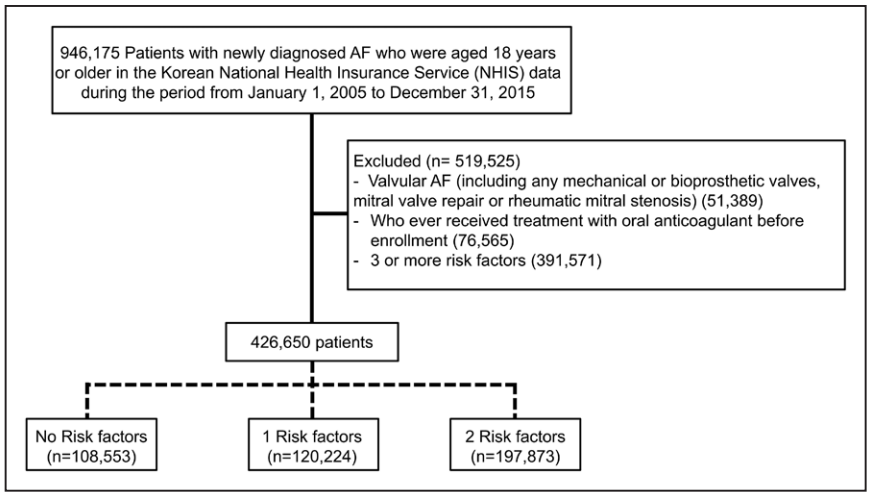

Figure 1. Flowchart of study population enrollment and analyses. AF indicates atrial fibrillation; and NHIS, National Health Insurance Service.

incidence analysis. The proportion of patients who fulfill the age risk criteria was 17.4% (age ≥65 years) in 1 risk score group, and 16.4% (age ≥65 years) and 19.8% (age ≥75 years) in 2 risk score group, respectively. Hypertension was the most prevalent risk factor (74.9%), followed by age (age ≥65 years, 17.4%), diabetes mellitus (4.4%), vascular disease (1.7%), and heart failure (1.6%) in 1 risk score group. Similar trends were seen in 2 NGR risk score group.

Comparisons Between Age Risk Criterion and Other Risk Factors

Table 2 shows the HRs for ischemic stroke according to the number and category of NGR risk factors. Patients with 1 NGR risk factor (CHA_2DS_2-VASc score 1 in male, 2 in female) had an increased risk of ischemic stroke (2.06/100PY; adjusted HR, 2.29; 95% CI, 2.21–2.37) than those with no risk factors (0.89/100PY). Among patients with 1 NGR risk score, patients with the age risk criterion (age, 65–74 years) showed a significantly higher risk of stroke (4.76 per 100PY; adjusted HR, 2.25; 95% CI, 2.17–2.36) compared with patients with 1 risk score other than age (heart failure, hypertension, diabetes mellitus, or vascular disease; 1.87/100PY).

Patients with 2 NGR risk scores (CHA_2DS_2-VASc score 2 in male, 3 in female) had an increased risk of ischemic stroke (4.42/100PY, adjusted hazard HR, 4.59; 95% CI, 4.16–4.42) than those with no risk factors. Among patients with 2 NGR risk scores, patients fulfilling the age risk criterion (ie, age 65–74 years and 1 other risk factor or age ≥75 years) had an increased risk of stroke (5.91/100PY; adjusted HR, 1.78; 95% CI, 1.73–1.82) compared with patients aged<65 years and 2 other nonage risk factors (2.75/100PY).

Table 1. Patient Baseline Characteristics by the Number and Categories of Nongender-Related Risk Factors

	No Risk Factors (CHA_2DS_2-VASc 0 or 1[Female]; n=108 553)	One Nongender-Related Risk Factor (CHA_2DS_2-VASc 1 in Male or 2 in Female; n=120 224)	Two Nongender-Related Risk Factors (CHA_2DS_2-VASc 2 in Male or 3 in Female; n=197 873)
Age, y	44±12	55±11	66±12
<65	108 553 (100)	99 355 (82.6)	124 173 (62.8)
65–74	NA	20 869 (17.4)	34 476 (16.4)
>75	NA	NA	39 224 (19.8)
Women	46 484 (42.8)	46 128 (38.4)	72 170 (36.5)
Heart failure	NA	1940 (1.6)	39 201 (19.8)
Hypertension	NA	90 046 (74.9)	169 903 (85.9)
Diabetes mellitus	NA	5311 (4.4)	41 312 (20.9)
TIA/ischemic stroke history	NA	NA	10 874 (5.5)
Vascular disease	NA	2058 (1.7)	24 523 (12.4)
Myocardial infarction	NA	1117 (0.9)	12 616 (6.4)
Peripheral arterial disease	NA	970 (0.8)	13 586 (6.9)
CKD	743 (0.7)	3435 (2.9)	9312 (4.7)
Dyslipidemia	25 339 (23.3)	59 463 (49.5)	111 970 (56.6)

Values are expressed in n (%) or mean±SD. Vascular disease denotes previous myocardial infarction, peripheral arterial disease, or aortic plaque. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years, female; CKD, chronic kidney disease; NA, ; and TIA, transient ischemic attack.

Table 2. The Number of Nongender-Related Risk Factors and HRs for Ischemic Stroke During the Entire Follow-Up Period

		1 Nongender-Related Risk Factor (CHA_2DS_2-VASc 1 in Male or 2 in Female)			2 Nongender-Related Risk Factors (CHA_2DS_2-VASc $_2$ in Male or 3 in Female)		
	No Risk Factors (n=108 553)	All (n=120 224)	Age <65 and 1 Other Risk Factors* (n=99 355)	Age 65-74 (n=20 869)	All (n=197 873)	Age <65 and 2 Other Risk Factors* (124 173)	Age ≥Ag† (n=73 700)
Ischemic stroke events, n	5128	11 871	8639	3232	32 812	9611	23 201
Person-years	572 255	577 306	509 360	67 946	742 164	349 279	392 885
Crude stroke incidence rate, per 100 person-years	0.89	2.06	1.70	4.76	4.42	2.75	5.91
Among all patients							
HR (unadjusted) [95% CI]	Ref	2.20 [2.13–2.27]	1.87 [1.81–1.94]	3.99 [3.82–4.17]	4.29 [4.16–4.42]	2.94 [2.84–3.04]	5.27 [5.11–5.43]
HR (adjusted‡) [95% CI]	Ref	2.29 [2.21–2.37]	1.86 [1.80–1.93]	3.95 [3.78–4.13]	4.59 [4.45–4.73]	2.85 [2.75–2.96]	5.46 [5.29–5.63]
HR (adjusted§;) [95% CI]	Ref	NA	1.22 [1.18–1.26]	NA	NA	1.73 [1.67–1.80]	NA
Among 1 risk factors							
HR (unadjusted) [95% CI]	…	…	Ref	2.31 [2.22–2.41]	…	…	…
HR (adjusted‡) [95% CI]	…	…	Ref	2.25 [2.17–2.36]	…	…	…
Among 2 risk factors							
HR (unadjusted) [95% CI]	…	…	…	…	…	Ref	1.83 [1.79–1.87]
HR (adjusted‡) [95% CI]	…	…	…	…	…	Ref	1.78 [1.73–1.82]

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years, female; CI, confidence interval; HR, hazard ratio; and NA, .

*Other risk factor risk factors include heart failure, hypertension, diabetes mellitus, and vascular disease.

†Patients aged 65 to 74 y and 1 other risk factor (among heart failure, hypertension, diabetes mellitus, and vascular disease) or patients aged ≥75 y.

‡Adjusted for sex, dyslipidemia, chronic kidney disease, and income status.

§Adjusted for sex, dyslipidemia, chronic kidney disease, income status, and age (continuous variables).

Age Threshold and Risk of Ischemic Stroke

The crude incidence of ischemic stroke according to the number(s) and the category of NGR risk scores are displayed in Figure 2. In patients without risk factors (CHA_2DS_2-VASc score of 0 [males] or 1 [females]), the incidence rate of ischemic stroke continuously increased from younger to older age group strata, and the stroke incidence rate in patients aged 60 to 64 years (2.87 per 100PY; 95% CI, 2.72–3.03) exceeded that of the 1 NGR risk score group (CHA_2DS_2-VASc score of 1 [males] or 2 [females]; 2.06 per 100PY; 95% CI, 2.02–2.09).

In patients with 1 NGR risk score, the incidence rate of ischemic stroke in patients aged 70 to 74 years (5.71 per 100PY; 95% CI, 5.44–6.00) exceeded that of the 2 NGR risk score group (CHA_2DS_2-VASc score of 2 [males] or 3 [females]; 4.42 per 100PY; 95% CI, 4.37–4.47).

The relative risk of ischemic stroke for AF patients without risk factors in different age groups compared with patients with 1 NGR risk score was expressed using adjusted HRs, which continuously increased from younger to older age group strata (Figure 3). Patients aged 55 to 59 years with no risk factors had similar risk of ischemic stroke (adjusted HR, 0.95; 95% CI, 0.90–1.00) when compared with patients with 1 NGR risk score, and patients aged 60 to 64 years with no risk factors showed even higher risk of stroke (adjusted HR, 1.20; 95% CI, 1.13–1.27) than patients with 1 NGR risk score. Similarly, the relative risk of ischemic stroke for AF patients with 1 NGR risk score compared with patients with 2 NGR risk score continuously increased from younger to older age group strata (Figure 3B). Patients aged 65 to 69 years (who fulfill the age risk criterion and no other risk factors) had similar risk of ischemic stroke (adjusted HR, 0.93; 95% CI, 0.90–0.97), and patients aged 70 to 74 years with no other risk factor had even higher risk of stroke (adjusted HR, 1.07; 95% CI, 1.02–1.12), when compared with patients with 2 NGR risk scores.

Several sensitivity analyses with different follow-up periods were performed to compare the HRs for ischemic stroke in the different age group strata by (1) assessing only 1-year outcome (Figure 3B), and (2) assessing the outcome during the period before patients develop new NGR risk factors (Figure I in the online-only Data Supplement). Similar results were found in these analyses. These results were consistent in further sensitivity analyses, excluding patients with aspirin use and patients who experienced intracranial hemorrhage, and including systemic embolic event as an outcome (data not shown).

Discussion

In this analysis of >400 000 OAC-naive AF patients with ≤2 NGR CHA_2DS_2-VASc risk scores using Nationwide cohort data covering the entire Korean population, the age risk criterion (age, 65–74 years for 1 point; age, ≥75 years for 2 point) was the most powerful risk factor for prediction of ischemic stroke compared with other risk factors included in

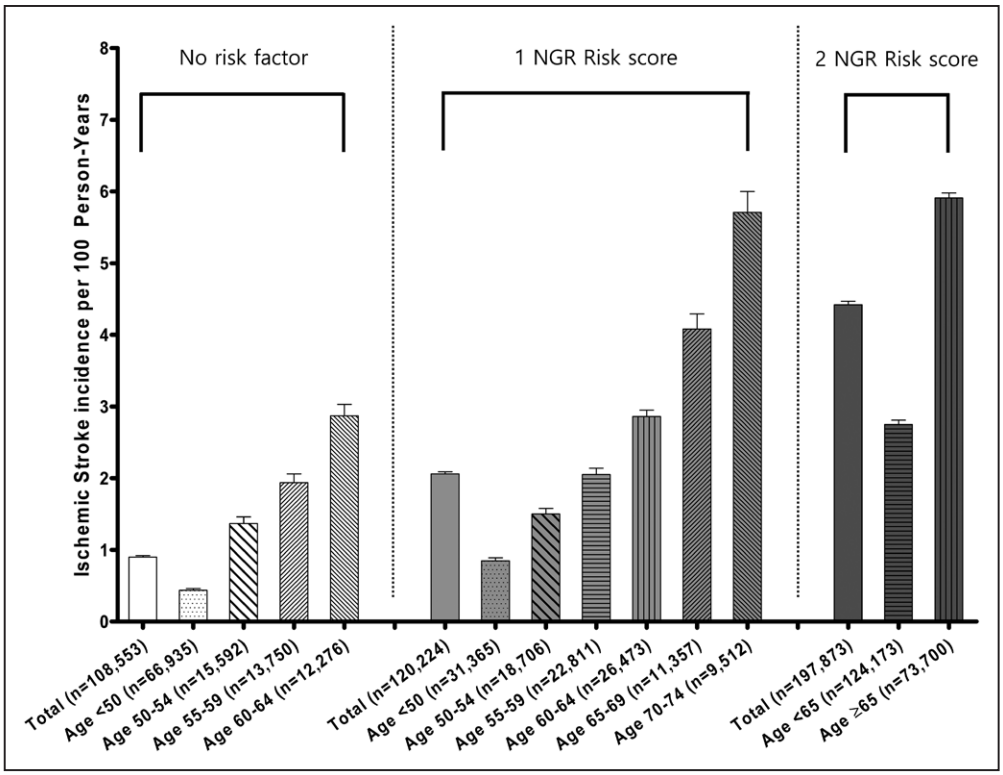

Figure 2. Crude incidence rates of ischemic stroke during the entire follow-up period in patients with no risk factors, 1 nongender-related (NGR) risk score, and 2 NGR risk score, stratified by age.

the CHA_2DS_2-VASc scoring system. When compared with AF patients with 1 NGR risk score, patients aged 55 to 59 years with no risk factor had a similar risk of stroke, which was assessed by both crude incidence rates of ischemic stroke and adjusted HRs. Moreover, patients aged 65 to 69 years and no other risk factor (NGR risk score 1 because of age risk criterion) showed a similar risk of stroke to AF patients with 2 NGR risk scores. These data support that lowering the current age threshold in Asian patients with AF should be considered given older age being the most powerful predictor of ischemic stroke in this population.

Because we excluded 391 571 patients who had ≥3 risk factors (eg, CHA_2DS_2-VASc ≥3 in males, ≥4 in females), actual number of OAC-naive NVAF patients was 818 221, and the proportion of lone AF among total OAC-naïve AF population was 13.3%, which is consistent with previous studies.[22,32] This proportion seems to be even lower if patients who ever received OAC treatment are included.

Difference in Age Threshold Between Different Ethnic Groups

Since the introduction of the NOAC with improved efficacy and safety, the threshold for initiating OACs has been lowered from an annual stroke rate of 1.7% with vitamin K antagonists to 0.9% with NOACs.[11] Thus, the focus has now shifted away from predicting high-risk patients toward initially identifying patients with a truly low risk of ischemic stroke in whom OAC has no net clinical benefit.[33] Moreover, identifying truly low-risk patients of stroke is an even more important in Asians. Many previous studies have consistently demonstrated that the risk of ischemic stroke in patients with AF was at least 2- to 3-fold higher in Asians than non-Asians, either for nonanticoagulated patients in registry studies[15,16,32,34,35] or for anticoagulated patients in the pivotal randomized trials for NOACs.[21,36] Indeed, a study by Chao et al[22] suggested that the age threshold for stroke prevention in Asian AF patients in Taiwan could perhaps be lowered from 65 to 50 years, and Chan et al[23] also reported similar result for AF patients in Hong Kong. However, some ethnic differences may be evident even among Asians, with higher event rates in Chinese cohorts[20] compared with (for example) Japanese cohorts, notwithstanding more methodological limitations in the latter studies.[37] The present study reports consistent results in the entire Korean population with previous studies in Chinese populations and may have implications for treatment guidelines in Asian AF patients.

Age Threshold in Korean Population

Lowering the current lower age threshold (65 years) to 55 years may be needed not only for identifying the truly low risk of stroke patients given the higher annual incidence rate of ischemic stroke in these patients aged 55 to 59 years (1.94/100PY) and 60 to 64 years (2.87/100PY) without other risk factors. This exceeds the suggested threshold of annual ischemic stroke risk for a favorable net clinical benefit from OAC (1% to 2%).[11] Because patients aged 55 to 64 without other risk factors had low HAS-BLED score at AF diagnosis and had low incidence rate of major bleeding (Table II in the online-only Data Supplement), they might have a positive net clinical benefit from anticoagulation. Moreover, our study demonstrates that lowering the upper age threshold (75 years)

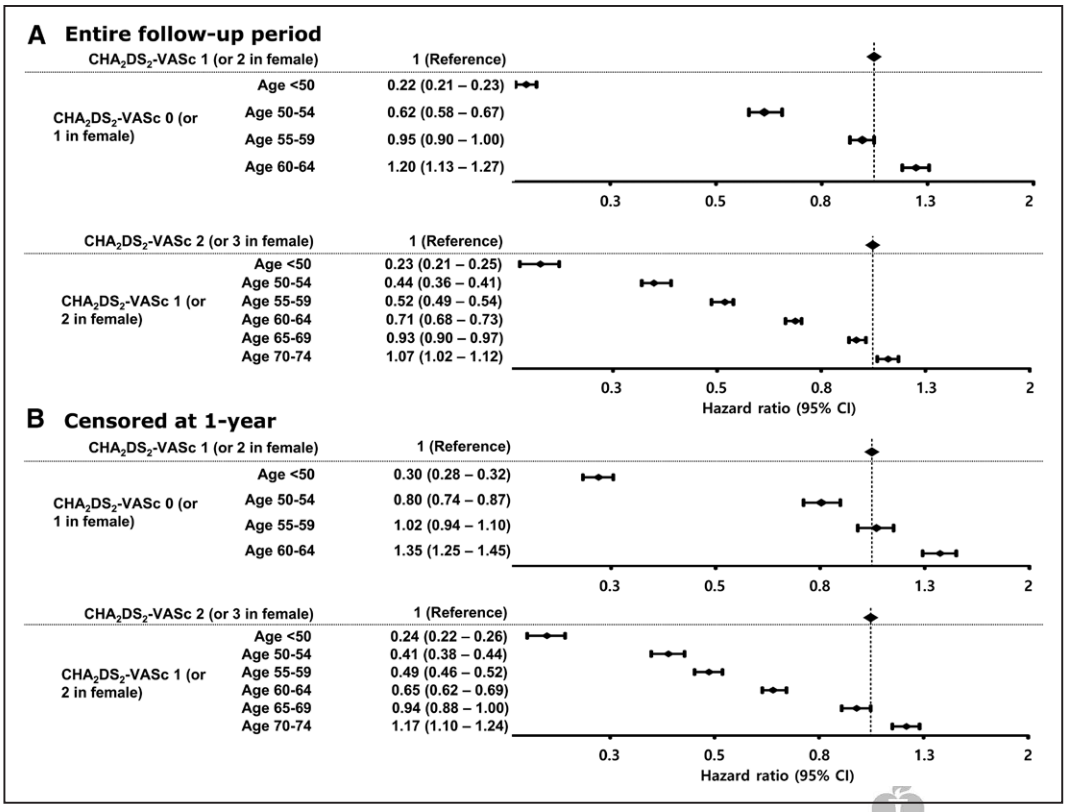

Figure 3. Adjusted hazard ratios for risk of ischemic stroke during the entire follow-up period (**A**) and 1-year ischemic stroke (**B**) in patients with no nongender-related risk factors and those with 1 nongender-related risk score in comparison to patients with higher (+1) risk score, stratified by age. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years, female; and CI, confidence interval.

to 65 years may be appropriate, given the risk of stroke in patients aged 65 to 69 years was comparable to that seen in patients with 2 NGR risk factors.

Resetting the upper age threshold for 2 points (from age ≥75 to ≥65 years), as well as the lower age threshold for 1 point (from age 65–74 to 55–64 years), would have significant clinical implications as current treatment recommendations are not identical for patients with single risk factors. For example, the 2014 American College of Cardiology/American Heart Association guideline[7] states that "no antithrombotic therapy, aspirin, or an OAC" may be considered for AF patients with a CHA_2DS_2-VASc score of 1 (class IIb recommendation), whereas the European guidelines[6] recommend that OAC may be considered even with 1 NGR stroke risk factor. The clinical implications of our work are even more evident especially in the Korean population, given that NOACs are reimbursed by NHIS for patients with CHA_2DS_2-VASc score≥2, but not for those with CHA_2DS_2-VASc score 1. Our consistency with data from Chinese cohorts[16,17,20–23] would also have implications for treatment guidelines in the Asian region.

Strength and Limitations

To our knowledge, this is the first comprehensive investigation to compare the risk of ischemic stroke between the age risk criterion and other risk factors in the Korean population and presents the largest Asian population data set in the literature to investigate the association between age and ischemic stroke in OAC-naive AF patients. Our study suggests that stroke risk schemes for Asian patients with AF could potentially be improved by resetting the age risk criterion.

Nonetheless, the present study has several limitations. Although administrative databases are increasingly used for clinical research, such studies are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that we already validated in previous studies that used a Korean NHIS sample cohort.[2,3,27–29] Inaccurate reporting of comorbidities, particularly from primary care, can lead to misclassification of AF patients with risk factors into the category of lone AF. However, the NHIS system in Korea does not reimburse the medications for specific disease if the reporting is incomplete; therefore, the possibility of misclassification seems to be low. We were unable to define the type (paroxysmal versus persistent) of AF. Despite these limitations, this study included the evaluation of longitudinal data from the entire Korean adult population. Therefore, our findings reflect the ischemic stroke risk of real-world AF regarding the effect of age and appropriate age threshold for the prediction of ischemic stroke in OAC-naive AF on a nationwide scale.

Conclusions

Older age is the most important predictor of ischemic stroke in AF, particularly for patients with low to intermediate risk of stroke. These nationwide data suggest that lowering the current age threshold (age, ≥65 years) in the CHA_2DS_2-VASc score to age ≥55 years might be appropriate among Asian

patients with AF. Further randomized trials of oral anticoagulation versus placebo in Asians with lone AF aged 55 to 64 years are warranted.

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Disclosures

Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and he also acts as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No fees are directly received personally. The other authors report no conflicts.

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Age Threshold for Ischemic Stroke Risk in Atrial Fibrillation: Cohort Data Covering the Entire Korean Population

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

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Supplemental Material

Supplementary Table I. 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*	ICD10: I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis*	ICD10: I70.0, I70.1, I70.2, I70.8, I70.9
ESRD	Defined from national registry for severe illness.	Patients with ESRD undergoing chronic dialysis or received a kidney transplant.
CKD	Defined from eGFR (if laboratory value was not available, diagnosis code was used)	eGFR <45 mL/min per 1.73 m^2 (ICD10: N18, N19)
Dyslipidemia	Defined from diagnosis*	E78

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database. CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, MI = myocardial infarction, TIA = transient ischemic attack.

Supplementary Table II. The estimated HAS-BLED score and crude incidence rates of major bleeding (100 person-years) according to the baseline patients' risk number and age strata.

Patients group	Mean HAS-BLED score	HAS-BLED score ≥3	Major bleeding rate per 100 person-years (95% CI)
No risk factors	0.44 ± 0.63	0.5% (509/108,553)	1.12 [1.09 to 1.14]
Age <50	0.39 ± 0.59	0.3% (203/66,935)	0.84 [0.81 to 0.87]
Age 50-54	0.50 ± 0.66	0.7% (104/15,592)	1.47 [1.38 to 1.57]
Age 55-59	0.52 ± 0.67	0.7% (94/13,750)	1.75 [1.64 to 1.86]
Age 60-64	0.52 ± 0.68	0.9% (108/12,276)	2.19 [2.06 to 2.33]
1 NGR risk factor	1.81 ± 0.85	19.9% (23,980/120,224)	1.65 [1.61 to 1.68]
2 NGR risk factors	2.67 ± 0.98	57.1% (112,939/197,873)	2.70 [2.66 to 2.74]

Values are expressed in % (n) or mean±SD. CI = confidence interval, NGR = non-gender related, The HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio (INR), Elderly (age >65), Drugs/Alcohol.

Abnormal renal/liver function was defined from ICD-10 diagnosis code (chronic kidney and/or liver disease). Labile INR/alcohol history were not included in these analyses.

The patient's index date for these analyses was the AF diagnosis date. The patients were censored at the date when the major bleeding occurred, at the date of their death, at the date of OAC initiation during follow-up period, or at end of follow-up.

Supplementary Figure I. Adjusted Hazard ratios for the risk of ischemic stroke during follow-up period before patients developing new NGR risk factors. Patients with no non-gender related risk factors and those with 1 non-gender related risk score in comparison to patients with higher (+1) risk score, stratified by age.