Temporal trends in ischemic stroke and female sex as a risk modifier in atrial fibrillation: insights from non-anticoagulated Asian patients in a nationwide cohort study

Dong-Seon Kang,[a,g] Pil-Sung Yang,[b,g] Jinseob Kim,[c] Daehoon Kim,[a] Eunsun Jang,[a] Hee Tae Yu,[a] Tae-Hoon Kim,[a] Jung Hoon Sung,[b] Hui-Nam Pak,[a] Gregory Y. H. Lip,[a,d,e,f,h] and Boyoung Joung[a,h,*]

[a]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[b]Division of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea
[c]Zarathu Co., Ltd, Seoul, Republic of Korea
[d]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[e]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[f]Medical University of Bialystok, Bialystok, Poland

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Summary

Background Previous studies from Western populations have reported changing temporal trends in ischemic stroke (IS) incidence in females with atrial fibrillation (AF) when compared with males. Nationwide data on such temporal trends in AF-related IS incidence by sex are limited in Asian populations.

Methods This population-based retrospective cohort study included patients with incident AF diagnosed between 2005 and 2016 from the Korean National Health Insurance Service. Patients with valvular heart disease, prior IS, or anticoagulant use were excluded. Incidence rates (IRs) per 100 person-years and hazard ratios (HRs) for IS were calculated by Fine and Gray competing risk regression.

Findings After exclusions, 290,081 females (mean age: 64.4 years, SD 16.3) and 338,100 males (mean age: 60.1 years, SD 14.9) were included. The mean follow-up duration was 5.7 (SD 4.1) years. At baseline, the CHA_2DS_2-VA scores were higher in females than in males (2.0 vs. 1.6, $P < 0.0001$). IRs for IS declined over time in both sexes (*P for trend* < 0.0001). The IS incidence in females compared to males was significantly higher in 2005–2006 (1.55 vs. 1.40; HR_{unadj}: 1.12, 95% confidence interval: 1.06–1.19); however, it was no longer significant in 2015–2016 (1.20 vs. 1.17; HR_{unadj}: 1.03, 95% confidence interval: 0.99–1.08). The reduction in relative risk primarily originated from the subgroup with CHA_2DS_2-VA scores 0–1. Females with CHA_2DS_2-VA scores ≥3 consistently showed higher IRs for IS compared to males regardless of adjustment.

Interpretation Sex differences in IS incidence decreased over calendar-year intervals, mainly in low-risk patients with AF. The persistently high IS incidence in high-risk females with AF suggests that sex still remains an important risk modifier.

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Keywords: Atrial fibrillation; Ischemic stroke; Temporal trend; Females

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder in adults, accounting for approximately 20% of ischemic stroke (IS) cases and complications such as heart failure and dementia.[1–3] The IS risk is not homogeneous and depends on the presence or absence of risk factors and comorbidities. Early oral anticoagulant (OAC) trials and observational studies in AF demonstrated that females had a higher IS risk than males.[4] Consequently, female sex was incorporated into

*Corresponding author. 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea.
E-mail address: cby6908@yuhs.ac (B. Joung).
[g]These two authors contributed equally to this work.
[h]Co-senior author.

Research in context

Evidence before this study

Using PubMed and Google Scholar, we searched for English-language studies investigating temporal trends in the incidence of ischemic stroke (IS) among patients with atrial fibrillation (AF) up to July 2024. Two prior studies conducted in Finland and Denmark were identified, reporting that over time, the risk of IS in women was no longer significantly higher than that in men. However, major AF-related studies have indicated that Asians possess distinct thromboembolic and bleeding profiles compared to Western populations and are underrepresented in major cardiovascular studies, limiting the generalizability of these findings. These results underscore the need for accurate data specific to Asian populations and for validating the applicability of the non-sex CHA_2DS_2-VASc score (i.e., CHA_2DS_2-VA).

Added value of this study

This population-based cohort study compared the temporal trends in IS incidence and male-to-female hazard ratios among patients with newly diagnosed AF from 2005 to 2016. The study accounted for the competing risk of all-cause mortality and excluded patients with prior oral anticoagulant (OAC) use to eliminate its effects. Additionally, follow-up was censored if OAC was prescribed during the follow-up period. The results demonstrated a gradual decline in IS incidence over time for both sexes, with the previously higher IS risk in women becoming statistically nonsignificant. However, among high predicted IS risk populations or those in the bottom income decile, who may have limited access to healthcare service, women continued to show higher estimated IS risks compared to men.

Implications of all the available evidence

To the best of our knowledge, this study represents the largest nationwide cohort study in Asia to investigate sex differences in the risk of IS among patients with newly diagnosed AF not receiving OAC therapy. In contrast to previous studies, our findings suggest that sex remains a significant risk-modifier. This underscores the need for prior validation based on country-specific data and diverse healthcare settings (e.g., differences between Asia and Europe) before uncritically adopting existing guidelines to replace the CHA_2DS_2-VASc score with the CHA_2DS_2-VA score.

stroke risk stratification using the CHA_2DS_2-VASc score and included in AF management guidelines globally.[5,6]

Subsequent studies have suggested that female sex is a risk modifier rather than a risk factor per se,[7] and can be influenced by non-sex-specific IS risk factors and that disparities in cardiovascular care may partly explain the observed differences.[8] Recent studies from Finland and Denmark have also shown a general decline in AF-related IS incidence and no significant sex difference in IS rates, eventually suggesting that the CHA_2DS_2-VASc could be replaced by the non-sex CHA_2DS_2-VASc score (ie. CHA_2DS_2-VA).[9–11] However, substantial regional and national variations in thrombotic and bleeding profiles and healthcare access highlight the importance of validating AF-related outcomes, using country-specific data.[12,13] Indeed, the primary treatment approach for AF, including OAC use, depends on estimated risks without OAC therapy.

In this study, we used claims-based data to examine sex-specific OAC prescription patterns and temporal trends in the associations between female sex and IS risk in OAC-censored patients with incident AF from 2005 to 2016.

Methods

This retrospective cohort study utilized data from the National Health Insurance Service (NHIS) database in South Korea. The NHIS database encompasses 97.1% of the Korean population covered under the NHIS, as well as information on medical aid beneficiaries, providing a representative dataset of the entire population. It includes sociodemographic data, inpatient and outpatient visits, prescriptions, and mortality information.[14] All data were accessed via the NHIS data-sharing service website (http://nhiss.nhis.or.kr) and were provided to certified researchers in approved research settings after review by the research support review committee and payment of a processing fee. Personal identifiers were anonymized following strict confidentiality guidelines, eliminating the need for informed consent.

Cohort design and study population

Patients aged 18 years or older who were newly diagnosed with AF between 1st January 2005 and 31st December 2016 were identified. AF was defined using the International Classification of Diseases, 10th Revision (ICD-10) code I48, as validated in prior studies utilizing the same database.[14] To exclude prior AF diagnoses, a minimum 3-year look-back period was applied, leveraging diagnostic records available from January 1, 2002. Based on ICD-10 codes, claims for heart valve surgery, and imaging studies, patients with valvular heart disease and a history of IS were excluded (Supplemental Table S1). Subsequently, the proportion of OAC prescriptions across calendar-year intervals was calculated. For the main analysis, patients with a history of venous thromboembolism or those already taking OACs were excluded to avoid the influence of OAC use during follow-up (Supplemental Figure S1).

Outcomes and covariates

The primary outcome, IS, was defined as the first occurrence of ICD-10 codes I63 or I64, confirmed in conjunction with relevant imaging studies, including brain CT or MRI (Supplemental Table S1).[14] Follow-up ended at the time of OAC prescription being initiated,[15] IS, emigration, death, or the database follow-up end date (December 31, 2016), whichever occurred first. Comorbidities were identified using inpatient and outpatient diagnostic and prescription claims data collected during the look-back period starting January 1, 2002. Details are provided in Supplemental Table S1. No missing values remained for comorbidities.

Statistical analyses

Descriptive statistics characterized the baseline characteristics. Differences between females and males in baseline characteristics were assessed using standardized mean differences (SMD), with values exceeding 0.1 considered significant.[16] Considering the relatively long follow-up period, Lexis-type data were constructed based on the follow-up period, 2-year calendar-year intervals, and age. The incidence rates and hazard ratios (HRs) for IS were calculated for the entire follow-up period as well as for each calendar-year interval.[10] IS incidence rates by sex were determined by dividing the number of clinical events by 100 person-years at risk during follow-up. Time-trend dependencies were tested using Cox regression models. Male-to-female HRs and 95% confidence intervals (CIs) were calculated using Fine and Gray competing risk regression models, considering all-cause mortality as a competing event. Adjusted analyses included the following variables: calendar-year interval, age, hypertension, diabetes mellitus, dyslipidemia, heart failure, myocardial infarction, peripheral arterial disease, history of bleeding, chronic kidney disease, liver disease, cancer, hospital level (primary, secondary, tertiary, and others), and income level. The proportional hazards assumption was verified using Schoenfeld residuals, and no violations were detected.[17] Interaction terms between calendar-year intervals and sex were included in the regression model to assess linear temporal trends of unadjusted and adjusted HRs, and the linear trends were presented as *P for trend*.

As sensitivity analyses, follow-up was first performed regardless of OAC use during the observation period, ending at the first occurrence of IS, emigration, death, or the database follow-up end date. Second, an analysis did not consider all-cause mortality as a competing risk factor. Third, to account for the dynamic changes in CHA_2DS_2-VA scores over time, follow-up ended at the time of OAC prescription being initiated, new diagnosis of heart failure, hypertension, diabetes mellitus, IS, or peripheral arterial disease (i.e., non-age components of the CHA_2DS_2-VA score), emigration, death, or December 31, 2016, whichever occurred first. Two subgroup analyses were performed. First, analyses stratified CHA_2DS_2-VA scores at cohort entry into three risk categories: low risk (0 or 1), intermediate risk (2), and high risk ($\geq$3). Second, patients were categorized into the medical aid group (the bottom decile of income) and the NHIS group (income above the bottom decile) based on their income level.

A two-sided $P < 0.05$ was considered statistically significant. Subgroup analyses were interpreted with caution due to the potential for type I errors from multiple comparisons. All statistical analyses were performed using R version 4.2.1 (The R Foundation, www.R-project.org).

Ethics approval

The Institutional Review Board of Yonsei University Health System (4-2016-0179) approved the study. The requirement for informed consent was waived due to data anonymization. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, as revised in 2013.

Role of the funding source

This research was supported by a grant from the Patient-Centered Clinical Research Coordinating Center funded by the Ministry of Health & Welfare, Republic of Korea (RS-2024-00397290). The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Supplemental Figure S2 illustrates the proportion of OAC prescriptions across calendar-year intervals. This proportion increased over time for both females and males, with 51,896 (21.5%) of females and 73,803 (25.6%) of males using OACs in 2015–2016. Following exclusions, the study comprised 290,081 females and 338,100 males, with a mean follow-up duration of 5.7 (SD 4.1) years. Females diagnosed with incident AF were 4.3 years older than males (mean age: 64.4 [SD 16.3] vs. 60.1 [SD 14.9] years, SMD: 0.27) and had a higher proportion of medical aid recipients (63,967 [22.0%] vs. 55,961 [16.6%], SMD: 0.14) (Table 1). Females had a higher predicted IS risk (mean CHA_2DS_2-VA score: 2.0 vs. 1.6, SMD: 0.29), largely due to a higher prevalence of hypertension (193,628 [66.7%] vs. 204,661 [60.5%], SMD: 0.13) and heart failure (75,620 [26.1%] vs. 59,798 [17.7%], SMD: 0.20).

Supplemental Table S2 presents the baseline characteristics across calendar-year intervals. Over the follow-up period, the mean age at AF diagnosis increased for both sexes, whereas the mean CHA_2DS_2-VA score showed a declining trend. The prevalence of dyslipidemia, prior bleeding, chronic kidney disease, liver disease, and cancer—conditions not included in the CHA_2DS_2-VA score—progressively increased.

	Females (N = 290,081)	Males (N = 338,100)	SMD
Age at baseline, years	64.4 (16.3)	60.1 (14.9)	0.27
Income level[a]			0.14
Medical aid	63,967 (22.0)	55,961 (16.6)	
NHIS	226,114 (78.0)	282,139 (83.4)	
CHA_2DS_2-VA score[b]	2.0 (1.6)	1.6 (1.4)	0.29
CHA_2DS_2-VASc score	3.0 (1.6)	1.6 (1.4)	0.95
Medical history			
Hypertension	193,628 (66.7)	204,661 (60.5)	0.13
Diabetes mellitus	52,883 (18.2)	65,503 (19.4)	0.03
Dyslipidemia	147,040 (50.7)	161,288 (47.7)	0.06
Heart failure	75,620 (26.1)	59,798 (17.7)	0.20
Myocardial infarction	17,370 (6.0)	23,795 (7.0)	0.04
Peripheral artery disease	21,495 (7.4)	23,188 (6.9)	0.02
Prior bleeding	55,978 (19.3)	76,704 (22.7)	0.08
Chronic kidney disease	12,134 (4.2)	15,749 (4.7)	0.02
Liver disease	84,562 (29.2)	132,246 (39.1)	0.21
Cancer	49,637 (17.1)	76,951 (22.8)	0.14

NHIS, National Health Insurance Service; SMD, standardized mean difference. [a]Medical aid refers to the bottom income decile, while NHIS represents the remaining income groups. [b]CHA_2DS_2-VA score = heart failure, 1 point; hypertension, 1 point; age ≥75 years, 2 points; diabetes mellitus, 1 point; history of stroke or transient ischemic attack, 2 points; vascular disease, 1 point; age 65–74 years, 1 point.

Table 1: **Baseline characteristics of the cohort.**

Differences and temporal trends in IS risk between females and males

Over the follow-up period, 70,949 females and 83,130 males were censored due to death. A total of 20,197 IS events were identified in females and 20,214 in males, with females showing a significantly higher crude incidence rate (1.37 [95% CI: 1.36–1.39] vs. 1.30 [95% CI: 1.28–1.31], $P < 0.0001$) (Supplemental Table S3). In unadjusted analyses, females exhibited a higher IS risk compared with males (HR_{unadj}: 1.07 [95% CI: 1.05–1.09], $P < 0.0001$); however, this difference was no longer significant after adjusting for potential confounders (HR_{adj}: 1.00 [95% CI: 0.98–1.03], $P = 0.86$).

Fig. 1A shows that IS incidence rates declined over time in both sexes (*P for trend* < 0.0001), with a more pronounced reduction observed in females. In 2005–2006, the incidence rate in females was higher than that in males (1.55 [95% CI: 1.50–1.61] vs. 1.40 [95% CI: 1.35–1.45], $P = 0.01$), but by 2015–2016, the 95% CI for the incidence rates overlapped, and the difference was no longer significant (1.20 [95% CI: 1.17–1.23] vs. 1.17 [95% CI: 1.14–1.20], $P = 0.30$). This trend was consistent with HR_{unadj} across calendar-year intervals, with a significant difference in 2005–2006 (HR_{unadj}: 1.12 [95% CI: 1.06–1.19], $P < 0.0001$) but not in 2015–2016 (HR_{unadj}: 1.03 [95% CI: 0.99–1.08], $P = 0.16$; *P for trend* = 0.01) (Fig. 1B, Supplemental Table S4). In adjusted analyses, no significant association was found between female sex and IS risk across the calendar-year intervals (*P for trend* = 0.10) (Fig. 1C).

Results consistent with the main findings were observed in the analyses allowing for OAC prescription during follow-up (Supplemental Table S5, Supplemental Figure S3), without accounting for the competing risk of all-cause mortality (Supplemental Table S6, Supplemental Figure S4), and censored follow-up at the time of CHA_2DS_2-VA score changes due to non-age components (Supplemental Table S7, Supplemental Figure S5).

Female vs. male differences in risks for IS in relation to stroke risk strata and income level

In the low-risk (CHA_2DS_2-VA score ≤1) group, females had a significantly lower IS risk regardless of adjustment (HR_{unadj}: 0.67 [95% CI: 0.64–0.69], $P < 0.0001$; HR_{adj}: 0.69 [95% CI: 0.66–0.72], $P < 0.0001$), with this difference becoming more prominent in more recent calendar-year intervals (*P for trend* = 0.01 in HR_{unadj}; *P for trend* = 0.01 in HR_{adj}) (Fig. 2A, Table 2). In the intermediate-risk (CHA_2DS_2-VA score = 2) group, IS risk was similar between sexes in unadjusted analyses (HR_{unadj}: 0.98 [95% CI: 0.95–1.02], $P = 0.38$) but lower in females in adjusted analyses (HR_{adj}: 0.90 [95% CI: 0.86–0.95], $P < 0.0001$) (Fig. 2B).

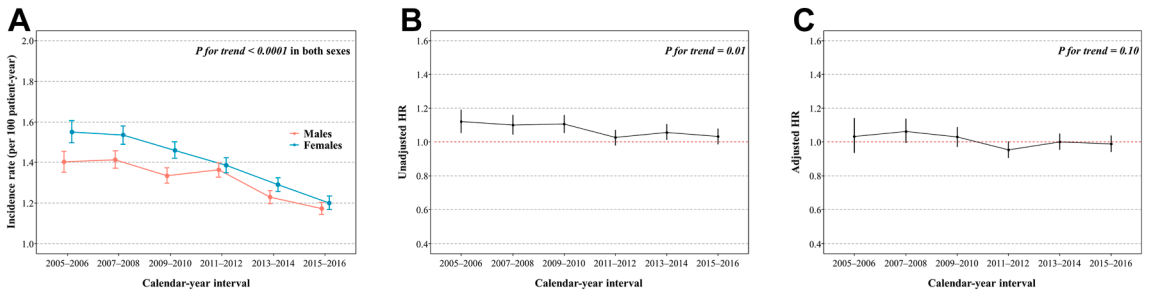

Fig. 1: Crude incidence rates and hazard ratios for ischemic stroke by the calendar-year intervals in females and males. Crude incidence rates (A), unadjusted (B), and adjusted (C) hazard ratios for each calendar-year interval are presented. Hazard ratios for females are shown in panels (B) and (C), with males regarded as the reference group. The error bars indicate the 95% confidence intervals. HR, hazard ratio.

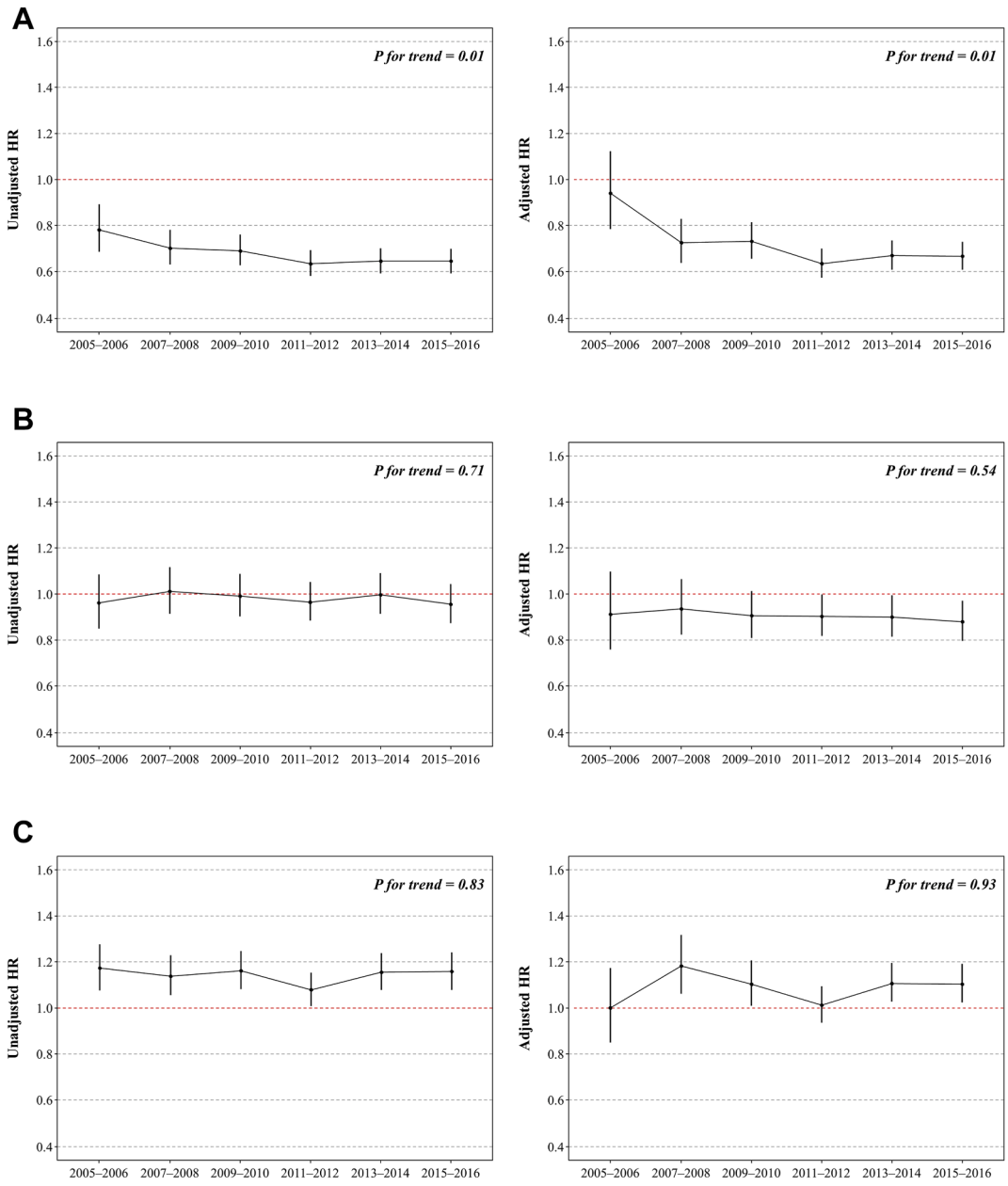

Fig. 2: Hazard ratios for ischemic stroke by the calendar-year intervals according to predicted ischemic stroke risk. Analyses stratified predicted ischemic stroke risk at cohort entry into three categories: low risk (CHA_2DS_2-VA score 0 or 1; A), intermediate risk (CHA_2DS_2-VA score 2; B), and high risk (CHA_2DS_2-VA score ≥3; C). Hazard ratios for females are shown in the panels, with males regarded as the reference group. The error bars indicate the 95% confidence intervals. HR, hazard ratio.

In the high-risk (CHA_2DS_2-VA score ≥3) group, females had a higher IS risk regardless of adjustment (HR_{unadj}: 1.14 [95% CI: 1.11–1.18], $P < 0.0001$; HR_{adj}: 1.09 [95% CI: 1.05–1.13], $P < 0.0001$), and this trend persisted across all calendar-year intervals (*P for trend* = 0.83 in HR_{unadj}; *P for trend* = 0.93 in HR_{adj}) (Fig. 2C).

In the adjusted analyses, females in the medical aid group were associated with a higher IS risk compared to males (HR_{adj}: 1.13 [95% CI: 1.07–1.19], $P < 0.0001$), whereas in the NHIS group, females tended to have a lower IS risk (HR_{adj}: 0.96 [95% CI: 0.93–0.98], $P = 0.01$) (Fig. 3, Table 2).

The higher IS risk observed in females with CHA_2DS_2-VA scores ≥3 and in the medical aid group was consistently observed across all previously described sensitivity analyses (Supplemental Table S8).

	Incidence rate	Unadjusted HR	Adjusted HR
Predicted IS risk			
Low risk			
Males	0.78 (0.76–0.79)	(Reference)	(Reference)
Females	0.51 (0.50–0.52)	0.67 (0.64–0.69)	0.69 (0.66–0.72)
Intermediate risk			
Males	1.78 (1.74–1.82)	(Reference)	(Reference)
Females	1.71 (1.67–1.75)	0.98 (0.95–1.02)	0.90 (0.86–0.95)
High risk			
Males	2.48 (2.44–2.53)	(Reference)	(Reference)
Females	2.78 (2.74–2.83)	1.14 (1.11–1.18)	1.09 (1.05–1.13)
Income level			
Medical aid			
Males	1.40 (1.36–1.44)	(Reference)	(Reference)
Females	1.62 (1.59–1.66)	1.16 (1.11–1.21)	1.13 (1.07–1.19)
NHIS			
Males	1.28 (1.26–1.29)	(Reference)	(Reference)
Females	1.30 (1.28–1.32)	1.03 (1.01–1.05)	0.96 (0.93–0.98)

Patients were classified into three risk categories based on their CHA_2DS_2-VA score at cohort entry: low-risk (0 or 1), intermediate-risk (2), and high-risk ($\geq$3). The crude incidence rate is expressed per 100 person-years. HR, hazard ratio; IS, ischemic stroke; NHIS, National Health Insurance Service.

Table 2: **Overall incidence of ischemic stroke in females and males over the follow-up period in subgroups.**

Discussion

The principal findings of the study, which investigated temporal trends and sex difference in IS risk among OAC-naïve patients with incident AF in Asia, are as follows. First, the incidence of IS continuously declined over the follow-up period for both sexes. Second, the excess IS risk observed in females compared with males also decreased over time, and by 2015–2016, the association between female sex and higher IS risk was no longer statistically significant. Third, this declining trend was primarily seen in low-risk (CHA_2DS_2-VA score $\leq$1), whereas in high-risk (CHA_2DS_2-VA score $\geq$3) or medical aid patients (ie. low income or socioeconomic group), females remained at a higher IS risk compared with males (Graphical Abstract).

AF is associated with adverse clinical outcomes, including IS, systemic thromboembolism, and mortality.[18] In particular, various risk stratification systems based on biological and clinical markers have been developed to predict and prevent IS. Female sex has been evaluated as a component of the CHA_2DS_2-VASc score for several years, as data from multinational cohort studies conducted 10–20 years ago indicated that females had a higher incidence of IS compared with

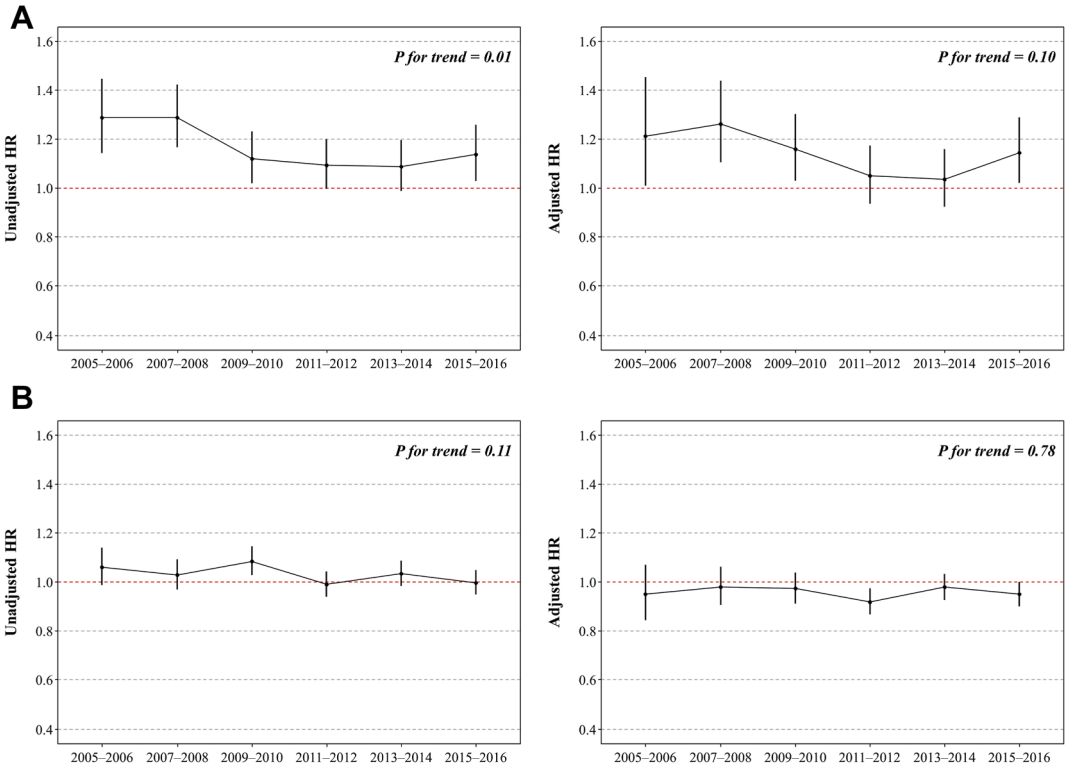

Fig. 3: Hazard ratios for ischemic stroke by the calendar-year intervals according to income level. Analyses stratified income level at cohort entry into two categories: medical aid (A), and NHIS (B). The unadjusted and adjusted hazard ratios for each calendar-year interval are presented. Hazard ratios for females are shown in the panels, with males regarded as the reference group. The error bars indicate the 95% confidence intervals. HR, hazard ratio; NHIS, National Health Insurance Service.

males.[19] This sex difference was particularly prominent in individuals aged ≥75 years, independent of OAC use.[19] However, most AF cohorts established in the 2000s relied on limited hospital-level clinical data, making them vulnerable to selection and information biases, such as the inclusion of predominantly older patients or those diagnosed with AF during hospitalization. This also hindered the adequate adjustment for various confounders.[19,20]

Furthermore, the CHA_2DS_2-VASc score was designed with a simplified structure to facilitate its application,[21] which inherently limits its ability to account for newly diagnosed risk factors, changes in the severity of preexisting risk factors, unmeasured lifestyle factors (e.g., smoking, alcohol, physical inactivity, obesity, and poor-quality diet), and changes in pharmacological therapy during the follow-up period. Consequently, the accuracy of its risk stratification remains modest, with a C-indexes ranging from 0.60 to 0.65.[18,22]

For example, contemporary management of AF extends beyond anticoagulation for IS prevention to include patient-centered decisions on rate or rhythm control, proactive lifestyle modifications, and comorbidity management. This holistic integrated care is encapsulated in the Atrial fibrillation Better Care (ABC) pathway, and adherence to the ABC pathway has been associated with reduced adverse clinical outcomes, including IS, bleeding, and mortality.[23] In other words, it is necessary to investigate how various confounders represented by the ABC pathway—and their temporal trends—may influence the established role of "female sex" as a risk factor for IS.

In contrast to prior studies, the present study was conducted in an East Asian population and included the entire national population regardless of hospital level, thereby minimizing the potential for selection bias. Moreover, the use of a large cohort comprising over one million individuals enabled rigorous adjustment for various confounders, and the extended follow-up period of over 10 years allowed for the assessment of temporal trends. These strengths provide a more robust basis for evaluating the association between sex and the IS risk.[24]

Recent nationwide cohort studies have highlighted evolving trends in IS risk between the sexes. In a Finnish study, the IS risk in females was significantly higher than that in males in 2007, but over the following decade, overall IS risk decreased, and the sex difference was no longer statistically significant.[10] Similarly, in a Danish study of OAC-naive incident AF patients, the sex difference in IS risk diminished in more recent years whereby the female relative risk of 1.16 (95% CI: 1.04–1.29) observed during 1997–2000 was no longer evident in 2017–2020.[9]

In previous individual-level ecological studies comparing healthy East Asians and Caucasians without comorbidities or medication history, we reported that East Asians had a higher incidence of both IS and intracranial hemorrhage, but a lower incidence of major bleeding excluding intracranial hemorrhage compared to Caucasians.[12,13] These differences may be partially explained by varying genetic predispositions, differences in body mass index and the prevalence of underweight status, salt sensitivity, and other lifestyle factors. Based on these findings, we concluded that region-specific approaches are necessary to prevent both IS and hemorrhagic complications. Despite the regional and national differences in thrombotic and bleeding profiles among patients with AF, the results of the present Korean nationwide cohort study suggests that the awareness (and management) of globally shared factors may have contributed to the improved relative IS risks in females.[12,13] As demonstrated in this study, the gradual decrease in CHA_2DS_2-VA scores despite an increase in the mean age at AF diagnosis suggests, as hypothesized by previous studies, that improvements and standardization in AF screening and risk factor management have been achieved.[8–10] This might be interpreted as a reduction in differences in cardiovascular care provision between the sexes. Indeed, a recent Canadian cohort study, in which females continued to exhibit a higher IS risk than males owing to poorer access to cardiovascular care, supports this hypothesis.[8]

Some important considerations are needed regarding the exclusion of female sex as a component of the CHA_2DS_2-VASc score. According to the findings of the present study, a reduction in IS risk among females was primarily observed in the low-risk groups, whereas high-risk females, who may perhaps have lower healthcare accessibility and suboptimal risk factor management, remained at a higher IS risk. This aligns with previous studies reporting higher IS risk in females with non-sex-specific risk factors, supporting the notion that female sex still acts as a risk modifier.[25] The CHA_2DS_2-VA score, while providing some simplicity for determining anticoagulation indications, does not exhibit statistically significant differences in overall discriminatory performance compared to the CHA_2DS_2-VASc score.[11] However, it may lead to confusion in clinical practice, particularly by fostering the misconception that females do not generally have a higher IS risk than males. This misunderstanding could deprive females of appropriate evidence-based management.[26]

Considering that females tend to experience more severe outcomes following IS in cases where OACs are not prescribed, therefore, the universal application of the CHA_2DS_2-VA score does not align with the latest trends emphasizing a holistic integrated approach rather than simple risk stratification in decision-making for OAC use, and may hinder positive advancements in IS prevention therapy.[27] In the study by Pilcher et al., for example, female sex was an independent negative

predictor of OAC prescribing.[26] In other words, the inclusion of female sex into the CHA_2DS_2-VASc score raised awareness of sex differences in AF-related IS and improved treatment accessibility for females, ultimately contributing to the decline in male-female differences in IS rates.[4,10] Therefore, there is a concern that removal of the Sc criterion may reverse this decline over the next years.

Recent 2024 European guidelines have adopted the sexless CHA_2DS_2-VA score (albeit with Level of Evidence: C) to assist the decisions on anticoagulation therapy "*in the absence of other locally validated alternatives*", as 'inclusion of gender complicates clinical practice both for healthcare professionals and patients' and 'omits individuals who identify as non-binary, transgender, or are undergoing sex hormone therapy.[28] However, this is in contrast to the present study, in which sex difference in OAC use persists, and the proportion of OAC prescription was below 30%. Taken together, adopting the sexless CHA_2DS_2-VA score requires prior validation based on country-specific data and different healthcare settings (e.g., in Asia, compared to Europe) rather than the uncritically following the existing guidelines based on Level of Evidence C (i.e., Consensus opinion) and limited data.[29] As demonstrated in previous studies from Finland and Denmark, the use of the CHA_2DS_2-VA score may be more efficient in settings where no significant sex differences are observed across all subgroups.[9,10] However, in cases such as the present study, where female sex continues to act as a risk modifier depending on the risk strata, maintaining use of the CHA_2DS_2-VASc score would be a more reasonable approach to align with an integrated, patient-centered approach.

This study has limitations. First, as a retrospective cohort study based on claims data, challenges such as the potential for information bias are inherent. For instance, if certain comorbidities are not included due to operational definitions, the possibility of misclassification of CHA_2DS_2-VA scores cannot be entirely excluded. Additionally, specific clinical information, such as lifestyle factors, AF type and sinus rhythm status on electrocardiography, echocardiographic parameters, and stroke subtypes observed on brain MRI, were not available, leaving room for residual confounding from unmeasured factors. The remaining sex differences in stroke risk also warrant further focused research on sex-specific risk factors, including menopause and estrogen use. Second, excluding patients who received OAC therapy from the analysis may raise concerns about informative censoring, because patients with a higher IS risk are more likely to initiate treatment. Furthermore, the inability to determine the exact reasons why patients with a CHA_2DS_2-VA score $\geq$1 did not receive OAC therapy introduces the potential for selection bias. This limits the generalizability of the findings to patients with AF undergoing IS prevention therapy, however, in clinical practice, the CHA_2DS_2-VASc score is used to determine whether to initiate anticoagulation in patients newly diagnosed with AF who are not yet on OAC therapy. Accordingly, we designed the study to minimize the influence of OAC exposure by excluding patients who were receiving OAC at baseline and censoring follow-up at the time of OAC initiation during follow-up. Hence, we are taking the appropriate methodological approach, as shown by Nielsen PB et al.[15] Third, the number of events of interest in the subgroup analyses was limited, potentially reducing the precision of the risk estimates, but these subgroup analyses should be regarded as exploratory and hypothesis generating. Fourth, as this study did not include data beyond 2016, further research is warranted to evaluate the impact of recent advances in AF management—such as improvements in catheter ablation—on the IS incidence. Fifth, there are limitations in generalizing the findings of this study to populations or geographic regions not included in the analysis.

Sex differences in IS incidence decreased over calendar-year intervals, mainly in low-risk patients with AF. The persistently high IS incidence in high-risk females with AF suggests that sex remains an important risk modifier, when considering stroke risk stratification.

Contributors

Dong-Seon Kang and Pil-Sung Yang contributed equally to this work. Boyoung Joung and Gregory Y.H. Lip are contributed to the conception and design of the work and critical revision of the manuscript. Dong-Seon Kang contributed to the conception and design of the work, analysis and interpretation of data, and drafting of the manuscript. Jinseob Kim contributed to the analysis and interpretation of data. Daehoon Kim, Pil-Sung Yang, and Eunsun Jang contributed to data extraction and analysis. Dong-Seon Kang, Pil-Sung Yang, and Eunsun Jang had directly accessed and verified the underlying data. Hee Tae Yu, Tae-Hoon Kim, Jung-Hoon Sung, and Hui-Nam Pak contributed to the conception and design of the work and revision of the manuscript. All authors approved the final version to be published. Also, they are responsible for ensuring that questions relating to accuracy or integrity of all parts of the work are properly investigated and resolved.

Data sharing statement

All data were accessed via the NHIS data-sharing service website (http://nhiss.nhis.or.kr) and were provided to certified researchers in approved research settings after review by the research support review committee and payment of a processing fee. Data supporting this study cannot be therefore shared by the authors, but are available from NHIS website with access subject to approval.

Declaration of interests

Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. No fees have been received directly or personally. Gregory Lip has been a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement No 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101619.

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