Korean Circ J. 2022 Aug;52(8):593-603
https://doi.org/10.4070/kcj.2021.0399
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

Check for updates

# Association of Gender With Clinical Outcomes in a Contemporary Cohort of Patients With Atrial Fibrillation Receiving Oral Anticoagulants

**Minjeong Kim, MD[1], Jun Kim, MD[2], Jin-Bae Kim, MD[3], Junbeom Park, MD[4], Jin-Kyu Park, MD[5], Ki-Woon Kang, MD[6], Jaemin Shim, MD[7], Eue-Keun Choi, MD[8], Young Soo Lee, MD[9], Hyung Wook Park, MD[10], and Boyoung Joung, MD, PhD[11]**

[1]Division of Cardiology, Department of Internal Medicine, Myongji Hospital, Goyang, Korea
[2]Heart Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, Seoul, Korea
[4]Department of Cardiology, School of Medicine, Ewha Womans University, Seoul, Korea
[5]Department of Cardiology, Hanyang University Seoul Hospital, Seoul, Korea
[6]Division of Cardiology, Eulji University Hospital, Daejeon, Korea
[7]Division of Cardiology, Department of Internal Medicine, Korea University Medical Center, Seoul, Korea
[8]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[9]Division of Cardiology, Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu, Korea
[10]Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University School of Medicine, Gwangju, Korea
[11]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea

OPEN ACCESS

**Received:** Dec 8, 2021
**Revised:** Mar 25, 2022
**Accepted:** Mar 30, 2022
**Published online:** Apr 26, 2022

**Correspondence to**
**Boyoung Joung, MD, PhD**
Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: cby6908@yuhs.ac



**ORCID iDs**
Minjeong Kim
https://orcid.org/0000-0002-4937-2126
Jun Kim
https://orcid.org/0000-0002-3573-638X
Jin-Bae Kim
https://orcid.org/0000-0002-0293-0901
Junbeom Park
https://orcid.org/0000-0003-2192-9401
Jin-Kyu Park
https://orcid.org/0000-0001-7931-777X
Ki-Woon Kang
https://orcid.org/0000-0002-1361-0022
Jaemin Shim
https://orcid.org/0000-0001-8251-1522
Eue-Keun Choi
https://orcid.org/0000-0002-0411-6372

## AUTHOR'S SUMMARY

We evaluated the relationship between biological sex and adverse clinical events in a contemporary atrial fibrillation (AF) cohort, mainly those taking direct oral anticoagulants, among patients with more-than-intermediate risk of stroke. Sex-based differences are noted in the outcomes of patients with AF who used anticoagulants, primarily vitamin K antagonist. The stroke or systemic embolism risk and major bleeding risk did not differ between the sexes, although women had a lower risk of all-cause mortality in contemporary anticoagulation for AF. Female may not be a risk factor for adverse clinical events associated with anticoagulation for AF.

## ABSTRACT

**Background and Objectives:** In patients with atrial fibrillation (AF), females taking vitamin K antagonist are at higher risk of stroke or systemic embolism (SSE), bleeding and all-cause death than males. This study investigated the relationship between sex and adverse clinical events in a contemporary AF patient cohort taking anticoagulation.
**Methods:** This prospective multicenter AF registry study comprised 6,067 patients with AF (mean age, 70±9 years; men, 59%) with intermediate to high risk of stroke ($CHA_2DS_2$-VAscore

Young Soo Lee
https://orcid.org/0000-0002-8229-8300
Hyung Wook Park
https://orcid.org/0000-0002-9630-0467
Boyoung Joung
https://orcid.org/0000-0001-9036-7225

**Trial Registration**
ClinicalTrials.gov Identifier: NCT02786095

**Funding**
This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC19C0130).

**Conflict of Interest**
The authors have no financial conflicts of interest.

**Data Sharing Statement**
The data generated in this study is available from the corresponding author upon reasonable request.

**Author Contributions**
Conceptualization: Joung B, Kim J, Kim JB, Park J, Park JK, Kang KW, Shim J, Choi EK, Lee YS, Park HW; Data curation: Joung B, Kim J, Kim JB, Park J, Park JK, Kang KW, Shim J, Choi EK, Lee YS, Park HW; Formal analysis: Joung B, Kim M, Kim J, Kim JB, Park J, Park JK, Kang KW, Shim J, Choi EK, Lee YS, Park HW; Funding acquisition: Joung B; Investigation: Joung B, Kim M; Methodology: Joung B, Kim M; Project administration: Joung B, Kim M; Resources: Joung B; Supervision: Joung B, Kim J, Kim JB, Park J, Park JK, Kang KW, Shim J, Choi EK, Lee YS, Park HW; Validation: Joung B, Kim J, Kim JB, Park J, Park JK, Kang KW, Shim J, Choi EK, Lee YS, Park HW; Visualization: Joung B; Writing - original draft: Kim M; Writing - review & editing: Joung B, Kim M.

≥1) and receiving oral anticoagulation therapy. Adverse clinical outcomes, including SSE, bleeding, death were evaluated in patients stratified by sex and anticoagulation patterns. **Results:** Women were older and used more direct oral anticoagulants (85% vs. 78%, p<0.001) than men. During a median (25th and 75th percentiles) follow-up of 30 (24, 38) months, the incidence rate and risk of SSE (0.7 in women vs. 0.7 in men per 100 person-years) and major bleeding (0.1 in women vs. 0.1 in men per 100 person-years) were not different between the sexes. However, women had a lower all-cause death rate (0.4 in women vs. 0.6 in men per 100 person-years, hazard ratio: 0.48, 95% confidence interval: 0.25–0.91, p=0.025) than men. **Conclusions:** In contemporary anticoagulation for AF, SSE and major bleeding risks did not differ between sexes. However, women showed a lower risk of all-cause death rate than men, indicating that the use of oral anticoagulants for treating AF in females does not appear to be a risk factor for adverse clinical events.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT02786095

**Keywords:** Atrial fibrillation; Female; Anticoagulants

## INTRODUCTION

Atrial fibrillation (AF) is one of the most notable and common cardiac arrhythmias[1-3] associated with a higher incidence of stroke.[3][4] AF shows biological sex-based differences in pathophysiology, epidemiology, presentation, and prognosis.[5] For several decades, Vitamin K antagonist (VKA) has been the preferred oral anticoagulants (OACs) for patients with AF, reducing all-cause death (26%) and stroke (64%) risks. Overall, women have an elevated risk of stroke, mortality, and cardiac events than men.[6][7] Several studies have reported that females taking VKA are still at higher risk of stroke or systemic embolism (SSE).[8][9] One of the possible reasons was that there was a significant biological sex-based difference in the proportion of patients with AF who use anticoagulants. Lower anticoagulation rate of women might be due to a higher concern of increased bleeding risk in women, especially in old age.[7]

In multiple major randomized controlled trials, direct oral anticoagulants (DOACs) are safer than VKA, with a low incidence of intracranial hemorrhage.[10][11] Moreover, DOACs have several additional advantages over VKA; these include lower frequency of monitoring the routine coagulation status and fewer drug-drug interactions.[12] Current guidelines propose that it is preferable to use DOACs in patients with non-valvular atrial fibrillation (NVAF) at risk of stroke or systemic thromboembolism.[3][13][14] In contemporary AF cohorts, the use of DOACs is more prevalent than that of VKA.

Patients who have a low risk of stroke are not recommended OACs, whereas patients with a higher stroke risk benefit from antithrombotic therapy.[3][13] There is a lack of large contemporary cohort-based data comparing anticoagulant usage patterns and outcomes between both sexes. This study evaluated the relationship between biological sex and adverse clinical events in a contemporary AF patient cohort, those mainly taking DOACs, with intermediate to high risk of stroke ($CHA_2DS_2$-VASc score ≥1 for men and ≥2 for women).

kcj
Korean Circulation Journal

# METHODS

## Ethical statement

Patients provided informed consent before participation, and the study received approval from the ethics committee of each center. This research was registered on ClinicalTrials.gov (NCT02786095) and approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0105).

A previous report has described the research design of the comparison study of drugs for symptom control and complication prevention of atrial fibrillation (CODE-AF).[15] The CODE-AF registry is a prospective, multi-center study of patients with AF over 18 years old, conducted at 18 tertiary centers across the Korea.[15] Eligible patients were recruited from June 2016 to May 2019.

The primary goal of the CODE-AF registry was to evaluate the outcomes of medical therapy for AF, including anticoagulation and rate or rhythm control.[15] The secondary aim was to understand the epidemiology and diagnostic flow of AF as well as clinical management.[15] The Korea Heart Rhythm Society organized this CODE-AF registry.[15] To minimize inconsistencies or errors, we obtained data from a commonly used electronic database.[15]

From June 2016 to May 2021, 12,232 patients with NVAF aged >18 years were enrolled in the registry. The patients were excluded with more than a moderate grade of mitral stenosis and those with a history of valve surgery because VKA is required in such patients. Furthermore, patients with a history of cancer, pulmonary embolism, or deep vein thrombosis were excluded. Patients with missing data on usage of VKA or DOAC (n=47) and those who transitioned from VKA to DOAC or vice versa (n=203) were excluded from the 12,232 enrolled patients. Patients with missing follow-up data were also excluded (n=1,523). After exclusion, 9,476 patients were included. Stroke risk was assessed and the patients were grouped according to the $CHA_2DS_2$-VA score (sex-independent thromboembolism risk). Each component of the $CHA_2DS_2$-VA score was defined as C = congestive heart failure (1 point); H: hypertension (1 point); A: age ≥75 years (2 points); D: diabetes mellitus (1 point); S: stroke or TIA (2 points); V: vascular disease (1 point); and A: age 65–74 years (1 point). The patients with more than an intermediate risk of stroke ($CHA_2DS_2$-VA score ≥1) with taking anticoagulation therapy (n=6,067, mean age 70±9 years, men 59%) were finally analyzed. The patients were stratified based on their biological sex. The data on adverse clinical events, such as SSE, major or minor bleeding, and all-cause death in these patients were obtained. Every 6 months, all patients were scheduled for outpatient clinic interviews or telephone consultations.

The primary endpoint of this study was SSE occurrence during the period of follow-up. The safety endpoint was the incidence of major bleeding. The other clinical endpoints comprised all-cause death and minor bleeding during the period of follow-up. Stroke was defined as a neurological deficit due to a cerebrovascular cause, persisting for over 24 hours, confirmed the diagnosis of ischemic stroke due to thrombosis or embolism with computed tomography or magnetic resonance imaging.[16] Systemic embolism (SE) was defined as a acute loss of perfusion of a vessel supplying an extremity or end-organ. It was diagnosed using various imaging modalities, including computed tomography or ultrasonography.[16]

All normally distributed continuous variables were expressed in mean ± standard deviation and compared using Student's t-test. For variables with a skewed distribution, medians with


https://doi.org/10.4070/kcj.2021.0399

interquartile ranges and the Mann–Whitney *U*-test was used. Categorical variables were expressed in numbers (percentages) and compared using the $\chi^2$ test and Fisher's exact test. We conducted a multivariable cox regression analysis of the outcome of interest to identify factors associated with sex-based differences. Clinical variables were selected based on previous studies and experiences.[10] The results are expressed in hazard ratio (HR) and 95% confidence intervals (CI). All p values were two-sided, and values below 0.05 were considered statistically significant. We performed all statistical analyses using SPSS software (v.25.0; IBM Corp., Armonk, NY, USA).

## RESULTS

### Sex differences in intermediate to high risk of stroke

**Table 1** describes the patients' baseline characteristics. Compared to men, women were older (71.9±8.5 vs. 68.3±9.7 years, p<0.001). The $CHA_2DS_2$-VA score did not differ between women and men. Men had a higher incidence of diabetes, myocardial infarction, and peripheral arterial occlusive disease than women. In women, interventions for control of cardiac rhythms, such as catheter ablation (9.7% vs. 14.5%, p<0.001) and cardioversion (10.7% vs. 17.5%, p<0.001) were less frequently performed than in men. Analysis of antiarrhythmic drugs revealed that amiodarone (8.6% vs. 13.9%, p<0.001) was used significantly in a lower proportion of women than in men.

**Table 2** describes the usage pattern of OACs. VKA was prescribed to a higher proportion of men than to women (22.4% vs. 14.8%, p<0.001). However, DOACs were more frequently prescribed to women than to men (85.2% vs. 77.6%, p<0.001). In the individual analysis of DOACs, apixaban and edoxaban were prescribed to a higher proportion of women. Dual antithrombotic agents (DAT; OAC + P2Y12 inhibitor or aspirin) was less frequently prescribed to women (6.7% vs. 9.6%, p<0.001); however, the prescription frequency of triple antithrombotic agents (TAT; OAC+ P2Y12 inhibitor + aspirin) did not differ between men and women.

During a median ($25^{th}$, $75^{th}$ percentiles) follow-up of 30 months (24, 38), women and men experienced 41 and 61 SSE events, respectively, with annualized rates of 0.7 and 0.7 per 100 person-years (**Table 3**). Women and men experienced 7 and 14 major bleeding events, respectively, with annualized rates of 0.1 and 0.2 per 100 person-years (p=0.60). The cumulative incidence rates of SSE (p=0.89, **Figure 1A**) and major bleeding (p=0.46, **Figure 1B**) did not differ between the sexes. The adjusted risks of SSE or major bleeding were the same for both sexes (**Table 3**).

Among individual outcomes, women exhibited a significantly lower incidence rate and risk of all-cause death than men (0.37 vs. 0.58 per 100 person-years, adjusted HR, 0.48; 95% CI, 0.25–0.91; p=0.025) when adjusting for confounding clinical variables. However, cardiovascular death rates did not differ between women and men (**Table 3**). The cumulative incidence of all-cause death was also lower in women than in men significantly (p=0.03, **Figure 1C**). The occurrences and risks of stroke, SE, and minor bleeding did not differ across sexes (**Table 3**).

When analyzed the differences in the occurrence of clinical events between men and women by dividing into DOAC group and the VKA group, women showed lower risk of all-cause death than men (0.29 vs. 0.47 per 100 person years, adjusted HR, 0.43; 95% CI, 0.20–0.94;


https://doi.org/10.4070/kcj.2021.0399

**Table 1.** Baseline characteristics of patients according to sex in intermediate-to-high-risk group of stroke

| Variables | Male (n=3,567) | Female (n=2,500) | p value |
|---|---|---|---|
| Age in years | 68.3±9.7 | 71.9±8.5 | <0.001 |
| Body mass index (kg/m$^2$) | 25.4 (22.8–26.7) | 22.3 (22.3–26.9) | 0.241 |
| Systolic BP (mmHg) | 122.5±15.8 | 123.7±23.2 | 0.009 |
| Diastolic BP (mmHg) | 75.1±12.4 | 73.4±21.1 | 0.001 |
| Heart rate (/min) | 76 (65–87) | 75 (64–85) | 0.075 |
| Type of AF | | | |
| Paroxysmal AF | 2,090 (58.6) | 1,581 (63.0) | <0.001 |
| Persistent AF | 1,317 (36.9) | 814 (32.6) | <0.001 |
| Permanent AF | 145 (4.1) | 97 (3.9) | 0.632 |
| $CHA_2DS_2$-VA score | 3 (2–4) | 3 (2–4) | 0.092 |
| Congestive heart failure | 464 (13.0) | 299 (39.2) | 0.226 |
| Hypertension | 2,717 (76.2) | 1,893 (75.7) | 0.686 |
| Diabetes | 1,201 (33.7) | 703 (28.1) | <0.001 |
| Dyslipidemia | 1,260 (35.3) | 983 (39.3) | 0.002 |
| Chronic kidney disease | 356 (10.0) | 247 (9.9) | 0.898 |
| End-stage renal disease | 38 (1.1) | 27 (1.1) | 0.956 |
| History of catheter ablation | 516 (14.5) | 242 (9.7) | <0.001 |
| History of cardioversion | 623 (17.5) | 267 (10.7) | <0.001 |
| Implantable cardiac device | 216 (6.1) | 240 (9.6) | <0.001 |
| History of stroke/TIA | 728 (20.4) | 458 (18.3) | 0.043 |
| History of myocardial infarction | 132 (3.7) | 2,448 (2.1) | <0.001 |
| History of bleeding | 271 (7.6) | 204 (8.2) | 0.422 |
| Peripheral arterial occlusive disease | 240 (6.7) | 111 (4.4) | <0.001 |
| LAVI (mL/m$^2$) | 47.7 (32.9–56.4) | 53.8 (35.3–63.9) | <0.001 |
| LV ejection fraction | 62.0 (56.0–67.0) | 64.0 (58.0–69.0) | <0.001 |
| E/E' | 11.4 (8.1–13.0) | 13.9 (10.0–13.0) | <0.001 |
| Antiarrhythmic drug | | | |
| Codarone | 520 (14.6) | 222 (8.9) | <0.001 |
| Dronedarone | 101 (2.8) | 89 (3.6) | 0.109 |
| Sotalon | 37 (1.0) | 13 (0.5) | 0.028 |
| Propafenone | 471 (13.2) | 324 (13.0) | 0.781 |
| Flecainide | 704 (19.7) | 471 (18.8) | 0.384 |
| Pilsicainide | 57 (1.6) | 43 (1.7) | 0.713 |
| Rate control/HF medication | | | |
| ARB/ACEi | 1,634 (45.8) | 1,144 (45.8) | 0.970 |
| Beta-blocker | 1,896 (53.2) | 1,305 (52.2) | 0.464 |
| Calcium channel blocker | 1,060 (29.7) | 731 (29.2) | 0.689 |
| Digitalis | 250 (7.0) | 243 (9.7) | <0.001 |
| Diuretics | 288 (8.1) | 249 (10.0) | 0.011 |
| Statin | 1,347 (37.8) | 1,009 (40.4) | 0.041 |

Values are presented as mean ± standard deviation for normally distributed variables, median (IQR) for non-normally distributed variables, or number (%).
ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BP = bood pressure; HF = heart failure; LAVI = left atrial volume index; LV = left ventricle; TIA = transient ischemic attack.

p=0.045) in DOAC group (**Supplementary Table 1**). However, in the VKA group, there was no significant difference between men and women in any clinical events including all-cause of death (**Supplementary Table 2**).

In a subgroup analysis after adjusting the confounding clinical factors for SSE occurrence, patients with a history of previous heart failure exhibited significantly higher HR among women (HR, 4.91; CI, 1.80–13.4; p for interaction: <0.001). In other subgroups, including the type of anticoagulant used, there were not any significant sex-based differences in SSE occurrence (**Figure 2**).


https://doi.org/10.4070/kcj.2021.0399

kcj
Korean Circulation Journal

**Table 2.** Comparison of anticoagulation status between men and women in the intermediate-to-high-risk group of stroke

| Anticoagulants | Male (n=3,567) | Female (n=2,500) | p value |
|---|---|---|---|
| Warfarin | 798 (22.4) | 369 (14.8) | <0.001 |
| DOAC | 2,769 (77.6) | 2,131 (85.2) | <0.001 |
| Dabigatran | 720 (20.2) | 415 (16.6) | 0.003 |
| Rivaroxaban | 637 (17.9) | 477 (19.1) | 0.138 |
| Apixaban | 960 (26.9) | 816 (32.6) | <0.001 |
| Edoxaban | 452 (12.7) | 423 (16.9) | <0.001 |
| DAT | 341 (9.6) | 167 (6.7) | <0.001 |
| OAC + Aspirin | 199 (5.6) | 104 (4.2) | 0.015 |
| OAC + $P_2Y_{12}$ inhibitor | 142 (4.0) | 63 (2.5) | <0.001 |
| TAT | 52 (1.5) | 38 (1.5) | 0.880 |

Values are presented as number (%).
DAT = Dual antithrombotic agents; DOAC = direct oral anticoagulants; OAC = oral anticoagulants; TAT = triple antithrombotic agents.

**Table 3.** Incidence rates and adjusted hazard ratios of all-cause death and other clinical events according to sex in the intermediate-to-high-risk group of stroke

| Outcomes | Male (n=3,567) | | Female (n=2,500) | | Adjusted HR* (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Events, No. | Incidence rate, No. per 100 person-year | Events, No. | Incidence rate, No. per 100 person-year | | |
| Primary endpoint | | | | | | |
| Stroke or SE | 61 | 0.74 | 41 | 0.70 | 0.92 (0.56–1.50) | 0.726 |
| Safety endpoint | | | | | | |
| Major bleeding | 14 | 0.16 | 7 | 0.12 | 0.76 (0.26–2.16) | 0.600 |
| Other clinical endpoints | | | | | | |
| All-cause death | 48 | 0.58 | 22 | 0.37 | 0.48 (0.25–0.91) | 0.025 |
| Cardiogenic death | 10 | 0.09 | 9 | 0.12 | 1.04 (0.30–3.63) | 0.946 |
| Stroke | 49 | 0.59 | 37 | 0.63 | 0.90 (0.54–1.51) | 0.900 |
| SE | 7 | 0.08 | 4 | 0.07 | 1.05 (0.18–6.12) | 0.956 |
| Minor bleeding | 5 | 0.06 | 8 | 0.13 | 1.19 (0.34–4.15) | 0.789 |

AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; HF = heart failure; HR = hazard ratio; LAVI = left atrial volume index; PAOD = peripheral artery occlusive disease; SE = systemic embolism.
*Adjusted for age, blood pressure, type of AF, diabetes, dyslipidemia, prior myocardial infarction, PAOD, prior implantable cardiac device, history of catheter ablation, history of cardioversion, statin use, HF medications, antiarrythmic drugs, LAVI, EF, and E/e'.

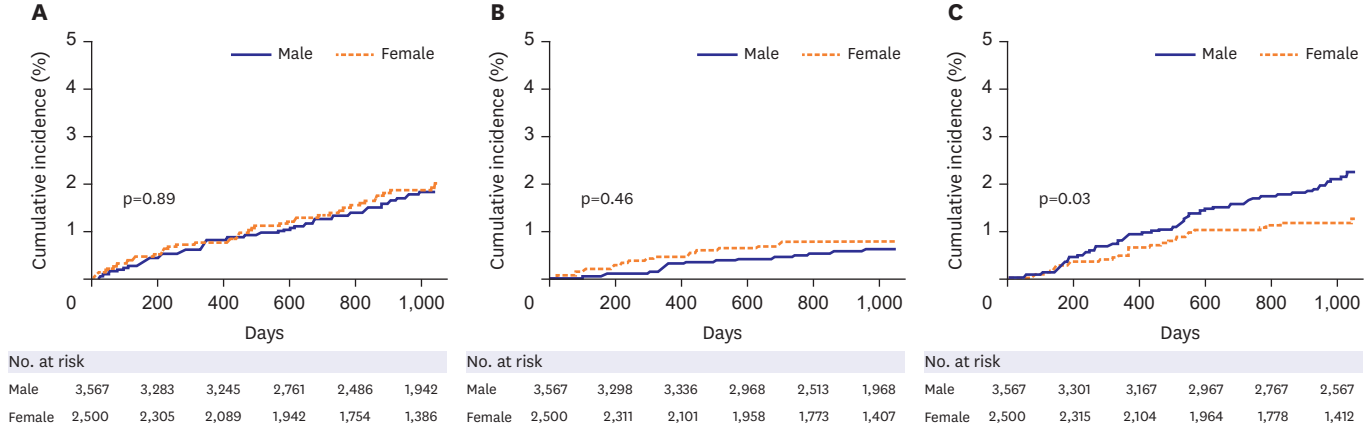


**Figure 1.** Cumulative incidence of stroke or systemic embolism (A), major bleeding (B), and all-cause death (C).

## Sex differences in all patients

**Supplementary Tables 3** and **4** provide the baseline characteristics and anticoagulation status of patients in the all patients in CODE-AF registry. Similar to those in the intermediate to high-risk group, the proportion of men who used VKA was higher than that of women (15.0%


https://doi.org/10.4070/kcj.2021.0399

| Variables | Men | Women | HR (95% CI) | p for interaction |
|---|---|---|---|---|
| Age | | | | |
| ≤ 75 | 2,924/4,002 (73.1) | 1,723/2,706 (63.7) | 0.94 (0.65–1.36) | 0.94 |
| > 75 | 1,078/4,002 (26.9) | 983/2,706 (36.3) | 0.94 (0.59–1.50) | |
| HTN | | | | |
| No | 942/4,002 (23.5) | 657/2,706 (24.3) | 0.59 (0.35–1.11) | 0.09 |
| Yes | 3,060/4,002 (76.5) | 2,049/2,706 (75.7) | 1.14 (0.82–1.58) | |
| Dyslipidemia | | | | |
| No | 2,594/4,002 (64.8) | 1,637/2,706 (60.5) | 0.88 (0.60–1.28) | 0.36 |
| Yes | 1,408/4,002 (35.2) | 1,069/2,706 (39.5) | 1.15 (0.73–1.82) | |
| History of stroke/TIA | | | | |
| No | 3,192/4,002 (79.8) | 2,208/2,706 (81.6) | 1.00 (0.72–1.40) | 0.84 |
| Yes | 810/4,002 (20.2) | 498/2,706 (18.4) | 0.97 (0.55–1.72) | |
| Congestive heart failure | | | | |
| No | 3,492/4,002 (87.3) | 2,379/2,706 (87.9) | 0.81 (0.59–1.11) | <0.001 |
| Yes | 510/4,002 (12.7) | 327/2,706 (12.1) | 4.91 (1.80–13.4) | |
| History of MI | | | | |
| No | 3,859/4,002 (96.4) | 2,651/2,706 (98.0) | 0.99 (0.73–1.33) | 0.28 |
| Yes | 143/4,002 (3.6) | 55/2,706 (2.0) | 1.45 (0.53–3.91) | |
| History of bleeding | | | | |
| No | 3,921/4,002 (98.0) | 2,652/2,706 (98.0) | 1.00 (0.74–1.35) | 0.67 |
| Yes | 81/4,002 (2.0) | 54/2,706 (2.0) | 0.84 (0.33–2.17) | |
| Antiplatelet | | | | |
| No | 3,525/4,002 (88.1) | 2,474/2,706 (91.4) | 1.03 (0.76–1.39) | 0.35 |
| Yes | 477/4,002 (11.9) | 232/2,706 (8.6) | 0.64 (0.23–1.76) | |
| CHADS2-Vasc score | | | | |
| <3 | 1,911/4,002 (47.8) | 499/2,706 (18.4) | 0.67 (0.31–1.42) | 0.73 |
| ≥3 | 1,658/4,002 (41.4) | 1,421/2,706 (52.5) | 0.88 (0.63–1.23) | |
| Anticoagulation | | | | |
| VKA | 859/4,002 (21.5) | 395/2,706 (14.6) | 1.37 (0.85–2.19) | 0.32 |
| DOAC | 3,143/4,002 (78.5) | 2,311/2,706 (85.4) | 0.91 (0.63–1.31) | |


**Figure 2.** Forest plot representation of clinical factors including anticoagulation associated with the primary endpoint (stroke or systemic embolism).
CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; HTN = hypertension; MI = myocardial infarction; TIA = transient ischemic attack; VKA = vitamin K antagonist.

vs. 12.1%, p<0.001), while the proportion of women who used DOACs was higher than that of men (64.3% vs. 48.8%) in the all patients in CODE-AF registry. Women used all DOACs more frequently than men, except dabigatran. In the analysis of DAT and TAT, the use of DAT was lower in women compared to men (5.0% vs. 5.8%, p<0.001) and TAT did not differ between sexes.

In the all risk of stroke groups, the adjusted risk of SSE was not different between women and men (1.3 vs. 0.7 per 100 person-years, adjusted HR, 0.70; 95% CI, 0.44–1.10; p=0.123). However, the adjusted risk of all-cause death in women was lower than in men (0.4 vs. 0.4 per 100 person-years, adjusted HR, 0.53; 95% CI, 0.30–0.96; p=0.034). Other individual outcomes such as cardiovascular death, stroke, SE or bleeding did not show any difference (**Supplementary Table 5**).


https://doi.org/10.4070/kcj.2021.0399

kcj
Korean Circulation Journal

## DISCUSSION

The main findings in our multicenter-prospective study are as follows; 1) In the contemporary AF cohort with anticoagulation therapy using DOACs (81%) and VKA (19%), women with intermediate to high risk of stroke were older, but there was no difference of stroke risk based on CHADS2-VA score between the sexes. 2) SSE, as a primary endpoint and major bleeding, as a safety endpoint did not differ between the sexes. 3) Women had a lower adjusted all-cause mortality rate than men but there was no difference in cardiovascular death rate.

Among the possible sex-based differences in the contemporary use of mainly DOACs, and relatively small number of VKA with concomitant antiplatelet therapy in AF, the biggest concern is whether women still have more increased risk of mortality and cardiovascular events than men.[6] Women with AF treated with VKA had a higher risk of SSE than men.[8][9] It was probably due to women's tendency to spend less time in the therapeutic range of VKA.[17][18] Moreover, AF is diagnosed and treated at a relatively old age in women,[19] and multi-morbidity was prevalent in old age patients despite of anticoagulation therapy.[20] However, with more DOAC treatment, SSE rates were known to be comparable between women and men. Furthermore, women exhibited a significantly lower major bleeding risk with the preferred use of DOACs over VKA than with the use of VKA only.[10][11][21] Previous studies on biological sex-based differences in adverse clinical outcomes related to AF revealed minor heterogeneity. Although several studies have compared the effect of VKA and DOACs, nothing is known regarding the effect of sex on clinical outcomes, such as current anticoagulation patterns in a contemporary AF patient cohort using DOACs. It might be meaningful that our study shows that women no longer have a higher stroke risk compared to men in contemporary cohort mainly using DOACs.

DOACs are safer than VKA showing decreased risk of intracranial hemorrhage.[10][11] The proportion of patients who use VKA has steadily decreased with the introduction of DOACs.[22] At the end of 2018, there was a trend of increase in the usage of DOACs, with more than 60% of all patients on anticoagulants using DOACs.[23] In a recent study based on the data from the CODE-AF registry 2018, among patients with an intermediate to high risk of stroke, women were taking anticoagulants at higher rates compared with men, and the use of DOACs was more prevalent in women.[19] This is consistent with the findings of this study. According to our study, when divided into DOAC treatment group and VKA treatment group, it was found that the primary endpoint was not different between sexes in both of the DOAC and VKA groups. Women's all cause of death risk was significantly lower than men's in DOAC group but not in VKA group. Therefore, it was thought that the decrease in the adverse clinical outcomes among women receiving anticoagulation therapy in AF might be related to the favorable outcome of contemporary treatment mainly using DOACs.

It is relatively common to treat patients with AF with DAT or TAT. Following the recent guidelines, patients with AF who underwent percutaneous coronary intervention were recommended TAT in the short-term, DAT for one year, and then single OAC after percutaneous coronary intervention.[3][24] Previous studies revealed that patients with DAT or TAT in AF experienced high major bleeding than those with warfarin single therapy.[25][26] Our study showed men had a higher usage of DAT in patients with intermediate to high risk of stroke. However, men did not show a higher bleeding risk than women.


https://doi.org/10.4070/kcj.2021.0399

There are limitations to this study. This is a transverse observational study. Medication use, including anticoagulants, was mostly studied using prescription data completed within the first few months after enrollment; thus, long-term medication compliance is a concern. Moreover, Korean patients were only included in this study, and the results cannot be generalized to other populations. This study is inevitable of referral bias because all patients were recruited from the tertiary centers alone, and patient data before referral was unknown. Finally, the incidence rate of clinical outcomes of this study was much lower than in previous studies.[27] There are several possible reasons; First, our study included only patients with intermediate to high risk of stroke who received anticoagulation therapy so that stroke events or stroke-related mortality could be quite lower compared to other studies including both non-anticoagulated and anticoagulated patients. Second, there was a trend that clinical adverse outcomes of AF decreased continuously,[1] and our study may also reflect this trend like other latest studies of AF. As shown in recent AF cohort, it seems that risk of stroke is low for the high usage of OACs therapy. The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) showed low SSE rate (1.2%) with high frequency of OACs therapy (60.8%).[28] GLORIA-AF trial showed considerably low from 0.60 to 0.82 with high usage of OACs (79.7%).[29] Finally, treatment with DOACs was typically known to reduce the bleeding risk. Our study included a contemporary AF cohort that used a higher proportion of DOACs (79% in men, 85% in women), which may reflect well the advantage of DOACs.

Conclusively, in a contemporary AF cohort using DOACs in 81% of patients who were at intermediate to high risk of stroke, women were older and showed a higher risk of stroke compared to men. However, the incidence and risk of SSE did not differ between the sexes. Additionally, women exhibited a lower incidence and risk of all-cause mortality than men, significantly. Considering that women use DOACs more than men, the use of DOACs for managing AF does not appear to be a risk factor for adverse clinical events in females.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Incidence rates and adjusted hazard ratios of all-cause death and other clinical events according to sex in the intermediate-to-high-risk group of stroke with DOAC treatments

Click here to view

### Supplementary Table 2

Incidence rates and adjusted hazard ratios of all-cause death and other clinical events according to sex in the intermediate-to-high-risk group of stroke with vitamin K antagonist treatment

Click here to view

### Supplementary Table 3

Baseline characteristics of the subjects according to gender in all risk groups of stroke

Click here to view


https://doi.org/10.4070/kcj.2021.0399

### Supplementary Table 4

Comparison of anticoagulation status between males and females in all risk groups of stroke

Click here to view

### Supplementary Table 5

Incidence rates and adjusted HR of all cause death and other clinical events according to gender in females in all risk groups of stroke

Click here to view

## REFERENCES

1. Kim D, Yang PS, Jang E, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J* 2018;202:20-6.
PUBMED | CROSSREF
2. Kim D, Yang PS, Jang E, et al. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. *Heart* 2018;104:2010-7.
PUBMED | CROSSREF
3. Joung B, Lee JM, Lee KH, et al. 2018 Korean guideline of atrial fibrillation management. *Korean Circ J* 2018;48:1033-80.
PUBMED | CROSSREF
4. Yoon M, Yang PS, Jang E, et al. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a nationwide cohort study. *Thromb Haemost* 2018;118:1296-304.
PUBMED | CROSSREF
5. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;13:321-32.
PUBMED | CROSSREF
6. Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;532:h7013.
PUBMED | CROSSREF
7. Yong CM, Tremmel JA, Lansberg MG, Fan J, Askari M, Turakhia MP. Sex differences in oral anticoagulation and outcomes of stroke and intracranial bleeding in newly diagnosed atrial fibrillation. *J Am Heart Assoc* 2020;9:e015689.
PUBMED | CROSSREF
8. Poli D, Antonucci E, Testa S, Ageno W, Palareti G; FCSA (Italian Federation of Anticoagulation Clinics). Gender differences of bleeding and stroke risk in very old atrial fibrillation patients on VKA treatment: results of the EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics). *Thromb Res* 2013;131:12-6.
PUBMED | CROSSREF
9. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol* 2014;113:485-90.
PUBMED | CROSSREF
10. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62.
PUBMED | CROSSREF
11. Haas S, Camm AJ, Bassand JP, et al.; GARFIELD-AF Investigators. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Am Heart J* 2019;213:35-46.
PUBMED | CROSSREF
12. Lee SR, Lee YS, Park JS, et al. Label adherence for non-vitamin K antagonist oral anticoagulants in a prospective cohort of Asian patients with atrial fibrillation. *Yonsei Med J* 2019;60:277-84.
PUBMED | CROSSREF

13. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962.
PUBMED | CROSSREF

14. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* 2018;20:1231-42.
PUBMED | CROSSREF

15. Kim H, Kim TH, Cha MJ, et al. A prospective survey of atrial fibrillation management for real-world guideline adherence: COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) Registry. *Korean Circ J* 2017;47:877-87.
PUBMED | CROSSREF

16. Takabayashi K, Hamatani Y, Yamashita Y, et al. Incidence of stroke or systemic embolism in paroxysmal versus sustained atrial fibrillation: the Fushimi atrial fibrillation registry. *Stroke* 2015;46:3354-61.
PUBMED | CROSSREF

17. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol* 2012;110:1799-802.
PUBMED | CROSSREF

18. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J* 2015;170:141-8, 148.e1.
PUBMED | CROSSREF

19. Lee JM, Kim TH, Cha MJ, et al. Gender-related differences in management of nonvalvular atrial fibrillation in an Asian population. *Korean Circ J* 2018;48:519-28.
PUBMED | CROSSREF

20. Dalgaard F, Xu H, Matsouaka RA, et al. Management of atrial fibrillation in older patients by morbidity burden: insights from get with the guidelines-atrial fibrillation. *J Am Heart Assoc* 2020;9:e017024.
PUBMED | CROSSREF

21. Law SW, Lau WC, Wong IC, et al. Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;72:271-82.
PUBMED | CROSSREF

22. Yu HT, Yang PS, Hwang J, et al. Social inequalities of oral anticoagulation after the introduction of non-vitamin K antagonists in patients with atrial fibrillation. *Korean Circ J* 2020;50:267-77.
PUBMED | CROSSREF

23. Afzal S, Zaidi ST, Merchant HA, Babar ZU, Hasan SS. Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. *J Thromb Thrombolysis* 2021;52:646-53.
PUBMED | CROSSREF

24. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498.
PUBMED | CROSSREF

25. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation* 2019;139:775-86.
PUBMED | CROSSREF

26. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;170:1433-41.
PUBMED | CROSSREF

27. Wilkinson C, Wu J, Searle SD, et al. Clinical outcomes in patients with atrial fibrillation and frailty: insights from the ENGAGE AF-TIMI 48 trial. *BMC Med* 2020;18:401.
PUBMED | CROSSREF

28. Dalgaard F, Pieper K, Verheugt F, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. *BMJ Open* 2019;9:e033283.
PUBMED | CROSSREF

29. Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF registry phase 2. *J Am Coll Cardiol* 2017;69:777-85.
PUBMED | CROSSREF