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Doctor of Philosophy

Effectiveness and Safety of Anticoagulation in Nonvalvular Atrial Fibrillation Patients with a Non-sex-related CHA_2DS_2-VA Score of 0 or 1

The Graduate School of the University of Ulsan

Department of Medicine

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Supervisor: Gi-Byoung Nam

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ABSTRACT

BACKGROUND: There are limited real-world data on the effectiveness and safety of anticoagulation in nonvalvular atrial fibrillation (NVAF) patients with a non-sex-related CHA_2DS_2-VA score of 0 or 1. We aimed to compare the effectiveness and safety outcomes of anticoagulant treatment and no treatment in this population.

METHODS: Using datasets form the Asan BiomedicaL research Environment database (between 1998 and 2017), this study comprised 5,567 NVAF patients with a non-sex-related CHA_2DS_2-VA score of 0 and 5,039 with a score of 1. Study patients were divided into treatment or control groups according to prescription of warfarin or non-vitamin K oral anticoagulants. Primary outcomes included stroke or systemic embolism and major bleeding.

RESULTS: During the median follow-up of 17.3 months, anticoagulant treatment was associated with a similar risk of stroke or systemic embolism in comparison with control (hazard ratio [HR], 1.11; 95% confidence intervals [CI], 0.56–2.17) in patients with a score of 0, and with a non-significantly lower risk (HR, 0.58; 95% CI, 0.31–1.09) in those with a score of 1. Regarding safety outcomes, anticoagulant treatment had a non-significantly higher risk of major bleeding in comparison with control (HR, 1.43; 95% CI, 0.61–3.34) in patients with a score of 0, but the risk was similar (HR, 0.95; 95% CI, 0.50–1.90) in those with a score of 1. Among patients aged 65–74 years, anticoagulant treatment was associated with a significantly lower risk of stroke or systemic embolism in comparison with control (HR, 0.42; 95% CI, 0.18–0.98, *P* value = 0.046).

CONCLUSION: In an NVAF patients with a non-sex-related CHA_2DS_2-VA score of 0 or 1, anticoagulant treatment was associated with a non-significantly lower risk of stroke or systemic embolism in comparison with control, with no effect on major bleeding. Among patients with a non-sex-related CHA_2DS_2-VA score of 1, anticoagulant treatment was associated with a significant reduction of the incidence of stroke and systemic embolism versus control in patients aged 65–74 years.

Key words: anticoagulants, atrial fibrillation, bleeding, stroke, systemic embolism

CONTENTS

LISTS OF TABLES

LIST OF FIGURES

INTRODUCTION

Nonvalvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia and is associated with a fivefold increased risk of stroke.[1] Stroke prevention is the cornerstone of NVAF management. Currently, the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, sex category [female gender]) is used to calculate a simple risk stratification scheme for predicting individual's risk of stroke.[2] American and European guidelines agree that patients with a non-sex-related CHA_2DS_2-VA score of ≥2 should be anticoagulated and that those with a non-sex-related CHA_2DS_2-VA score of 0 can omit anticoagulant therapy.[3, 4] There is controversy about anticoagulant treatment in patients with a non-sex-related CHA_2DS_2-VA score of 1.

According to American and European studies, female sex, if it is the only risk factor, does not confer a CHA_2DS_2-VASc score of 1, but adds to the score only when other risk factor is present.[3, 4] Korean studies have reported that female sex is not a risk factor for stroke.[5, 6] Other Asian studies suggested that lowering the current age threshold (≥65 years) in the CHA_2DS_2-VASc score to ≥50 or ≥55 years might be appropriate in Asian NVAF patients.[7-9] So, Asian NVAF patients with a non-sex-related CHA_2DS_2-VA score of 0 may need anticoagulation for stroke prevention. Therefore, we aimed to evaluate the effectiveness and safety of anticoagulation in Korean NVAF patients with a non-sex-related CHA_2DS_2-VASc score of 0 or 1.

METHODS

Study Patients

The study cohort comprised patients diagnosed with NVAF between January 1, 1998 and December 31, 2017 in the Asan Medical Center, Seoul, Korea (Figure 1). Exclusion criteria were as follows: (1) a non-sex-related CHA_2DS_2-VA score ≥2; (2) valvular AF; (3) use of anticoagulants for <14 days; (4) use of ≥2 anticoagulants; (5) <18 years old; (6) prior pulmonary thromboembolism, deep vein thrombosis, or prior joint replacement surgery, which could be a potential alternative indication for oral anticoagulant treatment; (7) patients undergoing renal replacement therapy; and (8) less than 60 days of follow-up.

Study patients were divided into treatment and control groups according to prescription of warfarin or non-vitamin K oral anticoagulants (NOACs). Treatment group was defined as follows: (1) AF diagnosis before anticoagulant prescription; (2) use of an anticoagulant within 2 months from the date of the first AF diagnosis; and (3) at least 14 days of anticoagulant use after the date of the first AF diagnosis. Control group was defined as patients who did not receive anticoagulation prescription within 2 months from the index date. In this study, patients were censored at the discontinuation of the index treatment.

This study used records from the Asan BiomedicaL research Environment (ABLE) system, which included demographic characteristics, chemical laboratory, imaging study, and the diagnosis, treatment, procedure, and prescription records of all medical services. All diagnosis data were based on the *International Classification of Disease, Tenth Revision* (ICD-10). Details of all variables and ICD-10 codes are listed in Supplementary Table 1. This study was approved by the institutional review board of the Asan Medical Center, which waived the need for informed consent from patients based on the retrospective nature of the study.

Study Outcomes

The primary effectiveness outcome was the incidence of new-onset ischemic stroke or systemic embolism during follow-up. Ischemic stroke was diagnosed when ICD-10 code of ischemic stroke in hospitalization and concomitant imaging study (computed tomography or magnetic resonance imaging) were simultaneously present.[10] Systemic embolism was defined as a sudden loss of perfusion in a limb or organ, assessed using vascular imaging, ankle-brachial index, procedural findings, and laboratory findings along with clinical presentation.[11] Systemic embolism was diagnosed when it was principal diagnosis requiring hospitalization. The primary safety outcome was major bleeding, which was defined as (1) fatal bleeding, (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of <9 g/dL and requiring the transfusion of ≥ 1 units of whole blood or red cells.[12]

Statistical Analysis

The baseline characteristics and clinical outcomes of the treatment and control groups were evaluated. Categorical variables are shown as frequencies with percentage and continuous variables as mean ± standard deviation. Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's *t*-test.

Incidence rates per 100 person-years were calculated for all outcomes. The cohort entry date was a date after 2 months from the date of the first AF diagnosis. The censoring date was the earliest of the following: date of death, date of a study outcome, date of index drug initiation or cessation, date of a non-sex-related CHA_2DS_2-VA score change, or end date of the study period (December 31, 2017). Cumulative events of study outcomes were assessed using Kaplan–Meier estimates and compared with the log-rank test. Cox proportional hazards model was used to compare event rates between treatment and control groups. To minimize the effects of selection bias and potential confounding factors, a propensity score weighting method was applied. We fitted a weighted Cox proportional hazards model using the inverse probability of treatment weighting. The following variables associated with study outcomes or clinical relevance were included and were measured at baseline evaluation: age, sex, body mass index, serum creatinine level, congestive heart failure, diabetes mellitus, hypertension, vascular disease, liver cirrhosis, malignancy, antiplatelet treatment, anti-arrhythmic drug treatment, β-blocker treatment, calcium channel blocker treatment, and digoxin treatment. A propensity score was then calculated from the logistic equation for each patient. Model discrimination was assessed with c-statistics (0.75; 95% confidence interval [CI], 0.71–0.78), and model calibration was assessed with Hosmer–Lemeshow test ($P = 0.800$). After the study population had been weighted using the inverse probability of treatment weighting method, standardized differences in the included variables among the population were < 0.100.

All statistical analyses were performed using the software R version 3.3.1 (R Institute for Statistical Computing, Vienna, Austria). All p values were 2-sided, and p values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

We included 5,567 patients with a non-sex-related CHA_2DS_2-VA score of 0 and 5,039 with a score of 1. The baseline patient characteristics according to the score are summarized in Table 1. Of the patients with the score of 0, Anticoagulation treatment was prescribed to 2,016 (36.2%) patients with a non-sex-related CHA_2DS_2-VA score of 0 and 2,132 (42.3%) patients with a score of 1. Patients without anticoagulation had more comorbidities (liver cirrhosis and malignancy) regardless of the score. Among patients without anticoagulation, 46.5% of those with a non-sex-related CHA_2DS_2-VASc score of 0 and 53.8% of those with a score of 1 received antiplatelet treatment. The most common non-sex-related CHA_2DS_2-VA risk factor was age 65–74 years (42.8%), followed by hypertension (33.2%), congestive heart failure (14.1%), diabetes mellitus (9.3%), and vascular disease (0.5%).

Study Outcomes

The median follow-up period was 17.3 months (interquartile range, 6.9–44.3 months). The number of events or incidence rates per 100 person-years related to the primary and secondary outcomes in the entire cohort are summarized in Table 2. In patients with a non-sex-related CHA_2DS_2-VA score of 0, incidence rates of stroke or systemic embolism were 0.36 in control and 0.52 in treatment groups, and incidence rates of major bleeding were 0.19 in control and 0.4 in treatment groups. The incidence rates of stroke or systemic embolism were 0.73 in control and 0.56 in treatment, and incidences of major bleeding were 0.59 in control and 0.79 in treatment in patients with a score of 1. The adjusted hazard ratios (HR) for the effectiveness and safety outcomes between anticoagulant treatment versus control from the propensity score weighting method are shown in Table 3. In total patients with a non-sex-related CHA_2DS_2-VA score of 0 or 1, anticoagulant treatment tended to be lower risk of stroke of systemic embolism without increasing major bleeding significantly. In patients with a non-sex-related CHA_2DS_2-VA score of 0, anticoagulant treatment was associated with a similar risk of stroke or systemic embolism in comparison with control (hazard ratio [HR], 1.11; 95% confidence intervals [CI], 0.56–2.17), but anticoagulant treatment had a non-significantly higher risk of major bleeding in comparison with control (HR, 1.43; 95% CI, 0.61–3.34). In patients with a score of 1, anticoagulant treatment tended to be lower risk of stroke or systemic embolism (HR, 0.58; 95% CI, 0.31–1.09) compared to control without impacting major bleeding (HR,

0.95; 95% CI, 0.50–1.90). Figure 2 shows the weighted freedom from stroke or systemic embolism across anticoagulant treatment groups according to the non-sex-related CHA_2DS_2-VASc score.

Subgroup Analyses

Table 4 shows adjusted HR for the effective outcome of anticoagulant treatment in comparison to control in subgroups. In a subgroup analysis of patients aged 65–74 years, anticoagulant treatment significantly decreased the risk of stroke or systemic embolism in comparison with the control (HR, 0.42; 95% CI, 0.18–0.98, $P = 0.046$). Among patients aged 55–64 years, anticoagulant treatment non-significantly decreased the risk of stroke or systemic embolism in comparison with the control.

DISCUSSION

The following are the major findings of the present study: (1) anticoagulant treatment was not associated with a lower risk of stroke or systemic embolism in comparison with to control in patients with a non-sex-related CHA_2DS_2-VA score of 0; (2) in patients with a non-sex-related CHA_2DS_2-VA score of 1, anticoagulant treatment non-significantly decreased the risk of stroke or systemic embolism without affecting major bleeding; (3) among the stroke risk factors, anticoagulant treatment was significantly associated with a 58% reduced hazard of stroke or systemic embolism only in patients aged 65–74 years.

The CHA_2DS_2-VASc score is widely used in different populations and is recommended by most guidelines for stroke risk evaluation in NVAF.[3, 4, 13] The performance of this score was validated in identification of truly low-risk NVAF patients (a non-sex-related CHA_2DS_2-VA score of 0) for stroke in various studies that reported the incidence rates (per 100 person-years) of 0.26–1.15.[2, 5, 6, 14-17] For obtaining net clinical benefit, the annual risk of stroke threshold for initiating oral anticoagulant treatment has been reported as 1.7% for a vitamin K antagonist and 0.9% for the NOACs.[18] Therefore, anticoagulant treatment is not recommended in patients with very low stroke risk (a non-sex-related CHA_2DS_2-VA score of 0) by current guidelines.[3, 4, 13]

However, recent studies have reported that the age threshold of an increased risk of stroke may

be different in Asian populations.[7-9, 19] An observational study from Hong Kong reported that age ≥50 years was associated with a substantial stroke risk, with an annual stroke risk of 5.87% in patients aged 50–65 years.[7] This result was confirmed in a large nationwide cohort from Taiwan: using a cutoff of 50 years, patients could be further stratified into 2 subgroups with different stroke risks (≥50 years of age: 1.78%/year; <50 years of age: 0.53%/year).[8] This observation was consistent for males (1.95%/year vs. 0.46%/year, respectively) and females (1.58%/year vs. 0.64%/year, respectively).[8] In a Korean nationwide cohort, patients aged 55 to 59 years with no risk factors had a risk of stroke (1.94%/year; adjusted HR, 0.95; 95% CI, 0.90–1.00) similar to that of patient with 1 risk factor (2.06%/year), suggesting that lowering the current age threshold (≥65 years) in the CHA_2DS_2-VASc score to ≥55 years might be appropriate among Asian patients with NVAF.[9]

Thus, we hypothesized that anticoagulant treatment might be beneficial for preventing stroke in some Asian patients with a non-sex-related CHA_2DS_2-VA score of 0. However, in this cohort, the incidence rate of stroke or systemic embolism was very low (0.36%/year in control vs. 0.52%/year in treatment), and anticoagulant treatment did not reduce the risk of stroke or systemic embolism in comparison with control in patients with a non-sex-related CHA_2DS_2-VA score of 0. Our result is consistent with that for a Danish cohort, which also showed a neutral or negative association of treatment (aspirin or warfarin) on stroke, bleeding, or death in patients with no risk factors (i.e., a non-sex-related CHA_2DS_2-VA score of 0).[20] However, anticoagulant treatment tended to be associated with a lower risk of stroke or systemic embolism in comparison with control in patients aged 55–64 years in this study. A recent study of Taiwanese nationwide cohort has suggested that NOACs should be considered for patients aged ≥60 years who have no other risk factors included in the CHA_2DS_2-VA score, considering that the threshold for the use of NOACs was set at a stroke risk of 0.9%/year.[21] Therefore, future randomized trials of anticoagulants, especially NOACs, versus control in Asian NVAF patients aged 55–64 years are needed.

There has been uncertainty about whether anticoagulation is warranted in males and females who have NVAF with a CHA_2DS_2-VASc score of 1 or 2, respectively.[3, 4] Female sex does not appear to increase stroke risk in the absence of other stroke risk factors.[22, 23] Moreover, females had a significantly lower risk of stroke than males in Korean nationwide cohorts.[5, 6] Thus, we

conducted this study only for patients with a non-sex-related CHA_2DS_2-VA score of 1. Reported incidence rates of stroke or systemic embolism are generally low and vary considerably in patients with a non-sex-related CHA_2DS_2-VA score of 1 due to differences in outcomes, populations, and anticoagulation status.[17, 20, 24-26] Moreover, the benefit of anticoagulant treatment for these patients was not consistent in different studies.[20, 25, 27] A study of a Danish cohort reported a trend for a reduction in stroke incidence by warfarin at 1 year (HR, 0.76) and neutral effect in the entire follow-up period (mean follow-up period of 5.91 ± 4.45 years) (HR, 0.94), but a significant reduction in death (HR, 0.42 and 0.86, respectively).[20] Another European study found that warfarin treatment was associated with a small positive net clinical benefit (measured as ischemic stroke reduction balanced against increased intracranial hemorrhage) in comparison with no anticoagulation or antiplatelet therapy in patients with a non-sex-related CHA_2DS_2-VA score of 1.[27] However, a recent study found a significant positive net clinical benefit of warfarin in patients with the CHA_2DS_2-VASc score ≥2 in males and ≥3 in females, but the net clinical benefit of warfarin was positive but not-significant in patients whose score was 1.[25] In the present study, anticoagulant treatment tended to reduce the incidence of stroke or systemic embolism in comparison with control embolism in patients with a non-sex-related CHA_2DS_2-VA score of 1. In subgroup analysis, anticoagulant treatment was associated with a non-significantly lower risk of stroke or systemic embolism in patients with one risk factor of hypertension, diabetes mellitus, or congestive heart failure, but was associated with a significantly lower risk in those aged 65–74 years. These results might be explained if each risk factor in the CHA_2DS_2-VASc score do not carry an equal risk, and the age of 65–74 years is associated with the highest stroke rate.[6, 9, 26] Recently, a Western study reported that standard-dose rivaroxaban (20 mg once daily) was associated with a significant reduction in stroke or systemic embolism compared to warfarin, with no significant difference in overall major bleeding in NVAF patients with a non-sex-related CHA_2DS_2-VA score of 1.[28] Therefore, similar studies with NOACs compared to control are warranted in such Asian patients.

Limitations

This study has several limitations. First, our results rely on the completeness and accuracy of

data from an electronic database. There is a possibility of coding errors, missing data, and the lack of clinically relevant data because of unmeasured variables. Second, this was a retrospective review of a single-center registry, which carries the possibility of selection bias. Although analyses were performed using robust propensity score methods, the results may have been influenced by unknown confounding variables. Third, we identified primary events only recorded in our hospital. So, if patients visited to other hospital when they had a primary events, we could not identify the primary outcomes. Actually, the incidence rates of primary outcomes in this study were relatively low compared to those of previous reported studies. It might be caused by missing data of out-of-hospital events. Fourth, the proportion of warfarin prescription is about 80% in patients with anticoagulant treatment. However, the therapeutic range of the overall warfarin group could not be assessed, and, therefore, we cannot exclude that inappropriate dosing schedules for long periods could have resulted in inadequate clinical benefit and impacted the safety profile. Fifth, as the study period was over 10 years, indication for anticoagulation or antiplatelet changed over time. In addition, the government insurance began to fully reimburse all types of NOACs for NVAF patients with high thromboembolic risk (CHA_2DS_2-VASc score $\geq$2 points) in July 2015. In this study, females with a non-sex-related CHA_2DS_2-VA score of 1 received reimbursement of NOACs prescription from July 2015, but the others did not. Therefore, it is difficult to evaluate standard anticoagulation strategy in this low-thromboembolic-risk patients. Finally, we could not evaluate the specific reasons for anticoagulant prescription; for instance, the type of atrial fibrillation (paroxysmal, persistent, or permanent), preference of patients or attending physicians, or receiving rhythm control with cardioversion or radiofrequency catheter ablation. Despite these limitations, our results are meaningful and show the effect of anticoagulant treatment on the effectiveness and safety in patients with a non-sex-related CHA_2DS_2-VA score of 0 or 1.

CONCLUSIONS

Patients with a non-sex-related CHA_2DS_2-VA score of 0 who received anticoagulant treatment had similar risk of stroke or systemic embolism and a non-significantly higher risk of major bleeding in comparison with those with no treatment. In patients with a non-sex-related CHA_2DS_2-VA score of 1, anticoagulant treatment was associated with a non-significantly

lower risk of stroke or systemic embolism compared to control, whereas the risk of major bleeding was not affected; the risk of stroke or systemic embolism was significantly reduced by anticoagulant treatment in patients aged 65–74 years. Our findings suggest that anticoagulant treatment may be helpful to reduce the risk of stroke or systemic embolism in patients aged 65–74 years who have a non-sex-related CHA_2DS_2-VA score of 1.

Table 1. Baseline characteristics of patients by the non-sex-related CHA_2DS_2-VA score

Variable	Score = 0			Score = 1		
	Control (N = 3,551)	Treatment (N = 2,016)	*P* value	Control (N = 2,907)	Treatment (N = 2,132)	*P* value
Age (years)	50.9 ± 10.2	51.3 ± 9.1	0.098	62.0 ± 8.7	59.9 ± 9.6	<0.001
Sex (male)	2,517 (70.9)	1,436 (71.2)	0.807	2,041 (70.2)	1,439 (67.5)	0.042
Follow-up (days)	689 (255, 1,688)	340 (151, 1,092)	<0.001	609 (231, 1,451)	439 (189, 1,101)	<0.001
Weight (kg)	67.3 ± 11.6	68.4 ± 12.2	<0.001	65.8 ± 12.0	67.4 ± 12.4	<0.001
Height (cm)	166.8 ± 8.5	167.0 ± 8.9	0.428	164.5 ± 8.7	164.8 ± 9.0	0.359
BMI (kg/m^2)	24.1 ± 3.2	24.5 ± 3.1	<0.001	24.3 ± 3.4	24.8 ± 3.4	<0.001
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	<0.001	0.9 ± 0.4	0.9 ± 0.2	0.057
CHF	0 (0.0)	0 (0.0)		233 (8.0)	479 (22.5)	<0.001
DM	0 (0.0)	0 (0.0)		276 (9.5)	195 (9.1)	0.711
Hypertension	0 (0.0)	0 (0.0)		956 (32.9)	719 (33.7)	0.553
Vascular disease	0 (0.0)	0 (0.0)		12 (0.4)	13 (0.6)	0.435
Liver cirrhosis	103 (2.9)	24 (1.2)	<0.001	167 (5.7)	38 (1.8)	<0.001
Malignancy	528 (14.9)	86 (4.3)	<0.001	810 (27.9)	166 (7.8)	<0.001
Anticoagulant	0 (0.0)	2,016 (100)	<0.001	0 (0.0)	2,132 (100)	<0.001
Warfarin	0 (0.0)	1,637 (81.2)	<0.001	0 (0.0)	1,728 (81.1)	<0.001
NOACs	0 (0.0)	431 (21.4)	<0.001	0 (0.0)	467 (21.9)	<0.001
Apixaban	0 (0.0)	95 (4.7)	<0.001	0 (0.0)	125 (5.9)	<0.001
Dabigatran	0 (0.0)	184 (9.1)	<0.001	0 (0.0)	134 (6.3)	<0.001
Edoxaban	0 (0.0)	32 (1.6)	<0.001	0 (0.0)	48 (2.3)	<0.001
Rivaroxaban	0 (0.0)	134 (6.6)	<0.001	0 (0.0)	167 (7.8)	<0.001
Antiplatelet	1,652 (46.5)	451 (22.4)	<0.001	1,565 (53.8)	593 (27.8)	<0.001
Aspirin	1,594 (44.9)	441 (21.9)	<0.001	1,502 (51.7)	574 (26.9)	<0.001
Clopidogrel	218 (6.1)	96 (4.8)	0.037	318 (10.9)	168 (7.9)	<0.001
Ticagrelor	2 (0.1)	1 (0.0)	1.000	4 (0.1)	1 (0.0)	0.577
Beta blocker	1,225 (34.5)	913 (45.3)	<0.001	1,269 (43.7)	1,181 (55.4)	<0.001
CCB	962 (27.1)	623 (30.9)	0.003	827 (28.4)	674 (31.6)	0.017
Digoxin	430 (12.1)	598 (29.7)	<0.001	624 (21.5)	737 (34.6)	<0.001
AAD	1,274 (35.9)	998 (49.5)	<0.001	710 (24.4)	900 (42.2)	<0.001

Data are reported as mean ± standard deviation, median (inter-quartile range), or number (%). AAD, anti-arrhythmic drug; BMI, body mass index; CCB, calcium channel blocker; CHF, congestive heart failure; DM, diabetes mellitus; NOACs, non-vitamin K antagonists.

Table 2. Incidence rate of study outcomes according to anticoagulation treatment

	Score = 0				Score = 1			
	Control (N = 3,551)		Treatment (N = 2,016)		Control (N = 2,907)		Treatment (N = 2,132)	
Outcome	Events	IR*	Events	IR	Events	IR	Events	IR
Stroke or SE	41	0.36	26	0.52	58	0.73	27	0.56
Major bleeding	22	0.19	21	0.42	47	0.59	38	0.79
ICH	0		1		1		1	
Transfusion	22		19		41		33	
Critical organ bleeding	0		1		5		4	

*IR, incidence rate per 100 person-years; ICH, intra-cranial hemorrhage; SE, systemic embolism.

Table 3. Hazard ratios of anticoagulant treatment for study outcomes in comparison with control estimated by Cox regression analysis with inverse probability of treatment weighting

Outcome	Non-sex-related CHA_2DS_2-VA score					
	Score = 0 or 1		Score = 0		Score = 1	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Stroke or SE	0.75 (0.47-1.19)	0.232	1.11 (0.56-2.17)	0.761	0.58 (0.31-1.09)	0.091
Major bleeding	1.14 (0.68-1.92)	0.605	1.43 (0.61-3.34)	0.399	0.95 (0.50-1.90)	0.963

SE, systemic embolism.

Table 4. Hazard ratios of anticoagulant treatment for effectiveness outcomes in comparison with control in patient subgroups estimated by Cox regression analysis with inverse probability of treatment weighting

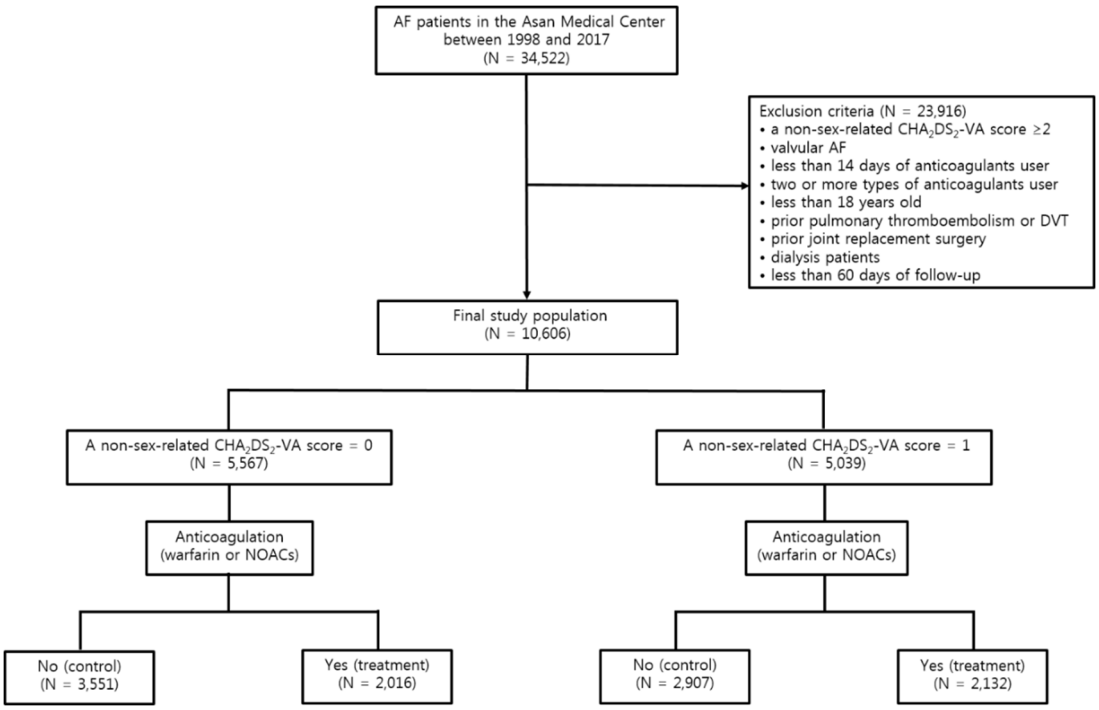
	Hazard Ratio (95% CI)	*P* value
Non-sex-related CHA_2DS_2-VA score = 0		
Age (years)		
<55	1.65 (0.66–4.11)	0.277
55–59	0.72 (0.17–2.99)	0.653
60–64	0.70 (0.16–3.01)	0.636
Non-sex-related CHA_2DS_2-VA score = 1		
Age (years) ≥65, <75	0.42 (0.18–0.98)	0.046
DM	0.97 (0.27–3.46)	0.968
Hypertension	0.58 (0.21–1.59)	0.297
CHF	0.55 (0.17–1.75)	0.316

CHF, congestive heart failure; DM, diabetes mellitus.

Supplementary Table 1. Definition of comorbidities and clinical outcomes

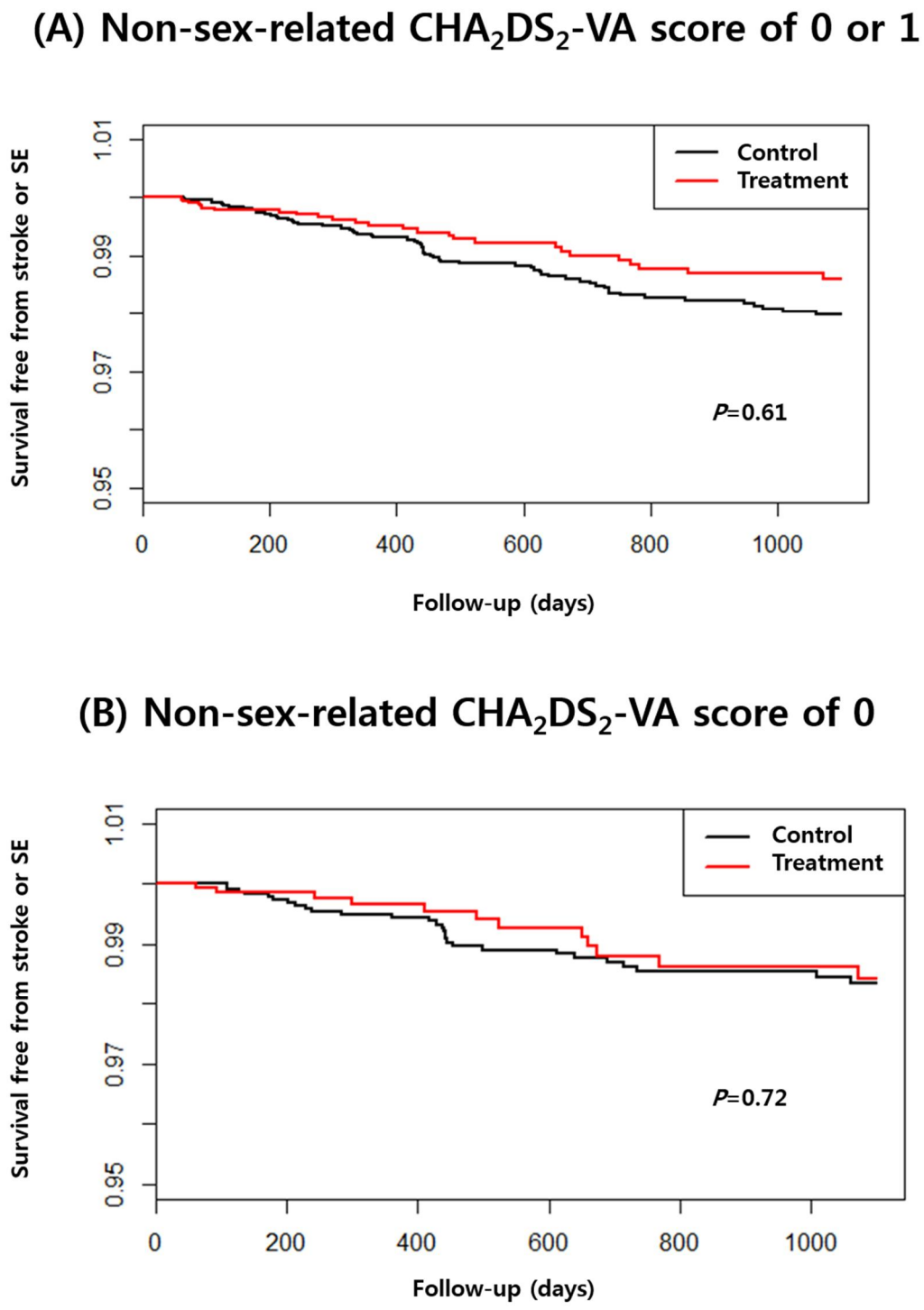
Disease	ICD-10 Codes	Additional definition
Atrial fibrillation	I48	
Mitral stenosis	I05.0 I05.2	Or claim code for open commissurotomy or percutaneous valvuloplasty
Mechanical valve	Z95.2-Z95.4	Or claim code for surgical valve replacement
Received joint replacement	Z96.6 Z96.7 Z97.1	Claim code for surgical joint replacement
End-stage renal disease	N18, Y84.1, Z49, Z 99.2	Claim code for hemodialysis or peritoneal dialysis
Deep vein thrombosis	I80.2	
Pulmonary embolism	I26	
Congestive heart failure	I11.0, I13.0, I13.2, I42, I50	
Hypertension	I10-I13, I15	
Diabetes	E10-E14	
Myocardial infarction	I21-I23	
Aortic plaque	I70.0	
Peripheral artery disease	I70.1-I70.9	
Ischemic stroke	I63, I64	With hospitalization and brain imaging (CT or MRI)
Systemic embolism	I74	
Transient ischemic attack	G45	
Intracranial hemorrhage	I60-I62	With hospitalization and brain imaging (CT or MRI)
Abnormal kidney function	I12, I13, N00-05, N07, N11, N14, N17-19, Q61	
Abnormal liver function	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	
Alcoholism	E24.4, F10, K70, T51, X45, X65, Y15, Y90, Y91, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, O35.4, Z71.4, Z72.1	
Gastrointestinal bleeding	I85.0, K22.1, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.8, K55.2, K57.0, K57.1, K57.2, K57.3, K57.4, K57.5, K57.8, K57.9, K62.5, K66.1 K92.0, K92.1, K92.2	
Extracranial or unclassified major bleeding	D62, H05.2, H35.6, H43.1, J94.2, M25.0, R04	Or intracranial hemorrhage or gastrointestinal bleeding
Cardiovascular death	I00.X–I99.X or R96, R98, R99	

Figure 1. Flowchart of the study patients

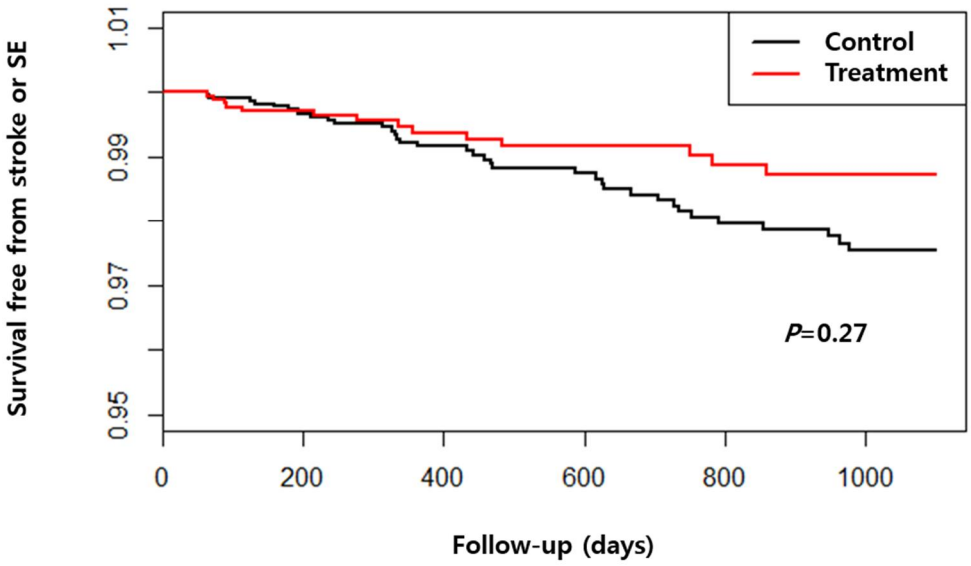


AF, atrial fibrillation; NOACs, non-vitamin K antagonists; DVT, deep vein thrombosis.

Figure 2. Kaplan–Meier curves for freedom from stroke or systemic embolism according to anticoagulant treatment



(C) Non-sex-related CHA_2DS_2-VA score of 1



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국문요약

배경: 비판막성 심방세동 환자에서 뇌졸중 예측 점수인 CHA_2DS_2-VASc score 에서 성별 인자를 제외한 CHA_2DS_2-VA score 0 점 혹은 1 점인 환자들에게서 항응고 치료의 효과와 안전성에 대한 임상 연구들이 부족한 실정으로 이런 환자들에게서 항응고 치료의 효과와 안전성을 조사해볼 필요가 있다.

방법: 서울아산병원 전자의무기록 시스템을 이용하여 1998 년부터 2017 년까지 자료를 분석하여 총 5,567 명의 CHA_2DS_2-VA score 0 점인 비판막성 심방세동 환자와 총 5,039 명의 CHA_2DS_2-VA score 1 점인 환자들을 추출하였다. 환자들은 와파린이나 새로운 항응고제 처방을 받은 치료군과 처방을 받지 않은 비치료군으로 나누었으며 두 군간의 뇌졸중, 전신 색전증, 주요 출혈의 발생 정도를 비교하였다.

결과: 17.3 개월의 중간 추적 관찰 기간 동안 뇌졸중 혹은 전신 색전증의 위험을 보자면 CHA_2DS_2-VA score 0 점 환자군에서는 항응고제 치료군과 비치료군은 큰 차이가 없었으며 (위험비, 1.11; 95% 신뢰구간, 0.56–2.17), 1 점인 환자군에서는 치료군이 비치료군에 비해 위험율이 낮은 경향을 보였으나 통계적으로 의미는 없었다 (위험비, 0.58; 95% 신뢰구간, 0.31–1.09). 안전성 면에서는 항응고 치료가 CHA_2DS_2-VA score 0 점 환자군에서는 비치료군에 비해 주요 출혈은 증가하는 경향을 보였으나 통계학적 의미는 없었으며 (위험비, 1.43; 95% 신뢰구간, 0.61–3.34), CHA_2DS_2-VA score 1 점 환자군에서는 두 군간의 발생율은 비슷하였다 (위험비, 0.95; 95% 신뢰구간, 0.50–1.90). CHA_2DS_2-VA score 1 점 환자군 중 연령 점수 (65–74 세)를 가지는 군에서는 항응고 치료군이 비치료군에 비해 뇌졸중 혹은 전신 색전증의 발생율을 의미 있게 낮추었다 (위험비, 0.42; 95% 신뢰구간, 0.18–0.98, *P* value = 0.046).

결론: 성별 인자를 제외한 CHA_2DS_2-VA score 0 혹은 1 점인 비판막성 심방세동 환자들에서는 항응고 치료가 비치료군에 비해 주요 출혈의 증가 없이 뇌졸중 혹은 전신 색전증을 낮추는 경향을 보여 주었다. CHA_2DS_2-VA score 1 점 환자 중 연령 점수 (65–74 세)를 가지는 군에서는 항응고 치료가 뇌졸중 혹은 전신 색전증의 발생을 의미 있게 낮추었다.

중심단어: 항응고제, 심방 세동, 출혈, 뇌졸중, 전신 색전증