Sex difference in effectiveness of early rhythm- over rate-control in patients with atrial fibrillation

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ABSTRACT

Sex difference in effectiveness of early rhythm- over rate-control in patients with atrial fibrillation

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Background: This study aimed to investigate the associations between sex and the relative effect of rhythm control over rate control in patients with atrial fibrillation. Methods: We used the National Health Insurance Service database to select patients treated for atrial fibrillation within one year after diagnosis. The primary composite outcome comprised cardiovascular death, ischemic stroke, heart failure hospitalization, or acute myocardial infarction. Results: During the mean follow-up (4.9 ± 3.2 years), the benefit of rhythm control over rate control on the primary composite outcome became statistically insignificant after 3 months from atrial fibrillation diagnosis in women while remained steadily until 12 months in men. The risk of primary composite outcome for rhythm control was lower than that for rate control in both sexes if it was initi-ated within 6 months (men: hazard ratio 0.86, 95% confidence interval 0.79–0.94; women: hazard ratio 0.85, 95% confidence interval 0.78–0.93; P for interaction = 0.84). However, there was significant interaction between sex and the relative effect of rhythm control if it was initiated after 6 months (men: hazard ratio 0.72, 95% confidence interval 0.52–0.99; women: hazard ratio 1.32, 95% confidence interval 0.92–1.88; P for interaction = 0.018). Conclusion: Rhythm control resulted in lower risk of primary composite outcome than rate control in both sexes; however, the treatment initiation at an earlier stage might be considered in women.

Key words : atrial fibrillation; early rhythm control; cardiovascular outcome

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I. Introduction

Atrial fibrillation (AF) is associated with increased risks of stroke, congestive heart failure (HF), and mortality.[1] Rhythm control and rate control are representative treatment strategies for atrial fibrillation and previous randomized trials have attempted to demonstrate differences in long-term outcomes between the two strategies. The landmark Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial reported no significant differences between these two strategies with respect to mortality and stroke incidence.[2-4] Similarly, a meta-analysis of randomized clinical trials com-paring rate and rhythm control showed no significant differences in the risk of all-cause death.[5] In contrast, recent studies have demonstrated that early rhythm control (defined as rhythm control initiated ≤12 months from AF diagnosis) compared to rate control in patients with AF is associated with a lower risk of the first primary outcome, comprising stroke, HF hospitalization, acute coronary syndrome, and cardiovascular death.[6-8]

Many studies highlighten sex differences in the epidemiology, pathophysiology, and prognosis of AF.[1] In this regard, several studies have demonstrated that despite the tendency of women to be more symptomatic compared to men, they are less likely to undergo rhythm control.[9-12] In women with AF, the use of antiarrhythmic drugs (AADs) were associated with higher rate of life-threatening adverse events.[13] Moreover, female sex was associated with higher AF recurrence rates after radiofrequency ablation compared to male sex, which

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may influence the effectiveness of AF treatment.[14] However, the effect of sex differences on outcomes of rhythm and rate control has not been well elucidated yet. Similarly, it is not clear whether the effect of timing of treatment initiation (duration from AF diagnosis to the first initiation of rhythm or rate control) on outcomes is affected by sex differences. Therefore, this study was designed to analyze the effect of sex on the compara-tive effectiveness of early rhythm control over rate control and clarify whether sex makes a difference in the timing of treatment initiation to improve cardiovascular outcomes.

II. Materials and methods

1. Study design and population

This retrospective cohort study was based on the National Health Claims Database established by the National Health Insurance Service (NHIS) of Korea, which incorporates the data of 558,147 participants recruited from a total of 5.5 million individuals aged ≥60 years included in the database.

Table 1 presents the details of this study design. Adults (age ≥18 years) who were treated for AF within one year after AF diagnosis between January 1, 2005 and December 31, 2015, were screened.

Table 1. Summary of strategies for emulating target trial

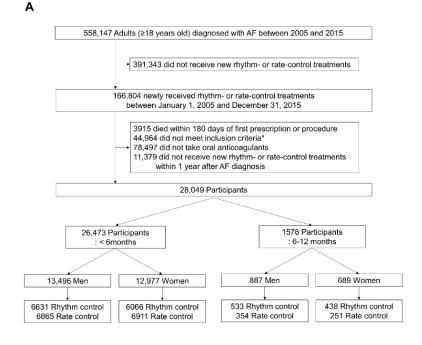| Components	Target trial (EAST-AFNET4)	This study
Inclusion period	28 July 2011 – 30 December 2016	1 January 2005 – 31 December 2015
Eligibility criteria	1) Adults (≥18 years of age) who were older than 75 years of age, had had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, and left ventricular hypertrophy 2) Early AF (diagnosed ≤12 months before enrolment)	1) Selected adults (≥18 years of age) that received a rhythm-control or rate-control treatments within 12 months after AF diagnosis 2) Participants have no prior history of prescriptions and no records of ablation in the database who were older than 75 years of age, had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, myocardial infarction, and chronic kidney disease 3) Undergoing oral anticoagulation (>90 days of supply within 180 days after their first recorded prescription of rhythm- or rate-control medications or ablation procedure)

Exposed group	Rhythm control: AADs, AF ablation, cardioversion of persistent AF, to be initiated early after randomization	Rhythm control: a prescription of more than a 90-day supply of any rhythm–control drugs in the 180-day period since the first prescription or the performance of an ablation procedure for AF.
Unexposed group	Usual care: initially treated with rate-control therapy without rhythm-control therapy	Rate control: a prescription of more than a 90-day supply of any rate-control drugs in the 180-day period since the first prescription and with no prescription of rhythm-control drug and no ablation within this period. Patients prescribed rhythm-control drugs for more than 90 days or who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified as intention–to–treat with rhythm control.
Primary outcome	1) A composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome 2) The number of nights spent in the hospital per year.	A composite of death from cardiovascular causes, ischemic stroke, hospitalization for heart failure, or acute myocardial infarction
Secondary outcome	Each component of the primary outcome, rhythm, left ventricular function, quality of life, AF-related symptom	Each component of the primary outcome
Safety outcome	A composite of death from any cause, stroke, or pre-specified serious adverse events of special interest capturing complications of rhythm-control therapy	A composite of death from any cause, intracranial or gastrointestinal bleeding requiring hospitalization, or pre–specified serious adverse events of special interest capturing complications of rhythm-control therapy
Follow-up	From randomization until the end of the trial, death, or withdrawal from the trial.	From 180 days after their first recorded prescription or procedure to avoid immortal time bias until the end of follow-up of the database (31 December 2016) or death.

AAD, antiarrhythmic drug; AF, atrial fibrillation.

Inclusion criteria were as follows: individuals aged ≥ 75 years; individuals with a previous transient ischemic attack or stroke; and those who at least met two of the following criteria: age ≥ 65 years, women, hypertension, diabetes mellitus, HF, previous myocardial infarction (MI), or chronic kidney disease.[6,8] Accordingly, patients were excluded from the study if within a six-month period from the initiation of AF treatment, did not receive adequate oral anticoagulants (for at least three months) or died. (Figure 1A).

A

558,147 Adults (≥18 years old) diagnosed with AF between 2005 and 2015

→ 391,343 did not receive new rhythm- or rate-control treatments

166,804 newly received rhythm- or rate-control treatments
between January 1, 2005 and December 31, 2015

→ 3915 died within 180 days of first prescription or procedure
44,964 did not meet inclusion criteria*
78,497 did not take oral anticoagulants
11,379 did not receive new rhythm- or rate-control treatments
within 1 year after AF diagnosis

28,049 Participants

26,473 Participants
: < 6months

1576 Participants
: 6-12 months

13,496 Men

12,977 Women

887 Men

689 Women

6631 Rhythm control
6865 Rate control

6066 Rhythm control
6911 Rate control

533 Rhythm control
354 Rate control

438 Rhythm control
251 Rate control

B

Initial Choice of Rhythm Control

Men N=7164: RF ablation 1.7%, Amiodarone 44.6%, Dronedarone 1.2%, Flecainide 23.4%, Pilsicainide 2.9%, Propafenone 24.0%, Sotalol 2.2%; → 7.4% At the end of follow-up

Women N=6504: RF ablation 1.4%, Amiodarone 44.1%, Dronedarone 1.2%, Flecainide 21.5%, Pilsicainide 3.1%, Propafenone 27.0%, Sotalol 1.7%; → 4.5% At the end of follow-up

Legend: RF ablation, Pilsicainide, Amiodarone, Propafenone, Dronedarone, Sotalol, Flecainide
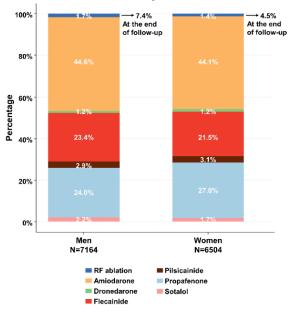
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Figure 1. Flow chart. Selection of study participants (A) and initial rhythm control strategies ac-cording to sex and the timing of treatment initiation (B). *Age ≥ 75 years, previous transient ischemic attack or stroke, or two of the following criteria: age ≥ 65 years, women, hypertension, diabetes mellitus, heart failure, previous myocardial infarction, or chronic kidney disease. AF, atrial fibrillation.

The Tenth Revision of International Classification of Disease (ICD-10) code I48 was used to define AF. The positive predictive value for AF diagnosis was 94.1% in the NHS database.[15] We adopted a new-user and intention-to-treat design to compare outcomes of rhythm- or rate control. Patients who have never been prescribed the drugs of interest or undergone radiofrequency ablation for AF were regarded as new users. Intention-to-treat with rhythm control was defined as performance of radiofrequency ablation or over three-months' administration of any AADs within the six-month period since the first prescription. Intention to treat with rate control was defined as a prescription any rate control drugs for at least three months within a six-month period since the first prescription, without prescription of AADs and radiofrequency ablation. Accordingly, patients who had received both rhythm- and rate control simultaneously were regarded as the rhythm control group. Claim codes for antiarrhythmic- and rate control drugs, and radiofrequency ablation are demonstrated in Table 2. To assess the effect of the timing of treatment initiation, patients were divided into two groups as following: AF treatment initiation <6 months group and ≥6 months group after AF diagnosis.

Table 2. Definitions and ICD–10 codes used for defining comorbidities, rate- and rhythm-control methods for atrial fibrillation

Comorbidities	Definitions	ICD-10 codes or conditions
Atrial fibrillation	Defined from diagnosis[a]	I48
Heart failure	Defined from diagnosis[a]	ICD-10: I11.0, I50, I97.1
Previous hospitalization for heart failure	Defined from principal or first secondary admission diagnoses of heart failure	ICD-10: I11.0, I50, I97.1
Hypertension	Defined from diagnosis[a] plus treatment	I10, I11, I12, I13, I15 Treatment: all kinds of blood pressure lowering medications (>1 month).
Diabetes mellitus	Defined from diagnosis[a] plus treatment	E10, E11, E12, E13, E14 Treatment: all kinds of oral antidiabetics and insulin
Dyslipidemia	Defined from diagnosis[a]	E78
Ischemic stroke	Defined from diagnosis[a]	ICD-10: I63, I64
Transient ischemic attack	Defined from diagnosis[a]	ICD-10: G45
Hemorrhagic stroke	Defined from diagnosis[a]	ICD-10: I60, I61, I62
Myocardial infarction	Defined from diagnosis[a]	ICD-10: I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis[a]	I70, I71
Valvular heart disease	Defined from diagnosis[a] mitral stenosis or claims for heart valve surgery	ICD-10: I05.0, I05.2, I34.2, Z95.2–4 Claim for valve replacement or valvuloplasty: O1781, O1782, O1783, O1791, O1792, O1793, O1797, O1794, O1795, O1796, O1798
Chronic kidney disease	Defined from eGFR (if laboratory value was not available, diagnosis code was used)	eGFR <60 mL/min per 1.73 m^2 N18, N19

Rate- and rhythm control for atrial fibrillation (available in South Korea)	Definitions	ICD-10 codes or conditions
Rate control		
Beta-blocker	atenolol, bisoprolol, carvedilol, metoprol, nebivolol, propranolol, labetalol	
Calcium channel blocker	diltiazem, verapamil	
Cardiac glycosides	digoxin	
Rhythm control		
Class Ic	flecainide, pilsicainide, propafenone	
Class III	amiodarone, dronedarone, sotalol	
Catheter ablation for AF	Defined from admission diagnosis of AF plus claims for ablation procedures	ICD-10: I48 Claim codes: M6542 (Conventional Radiofrequency Ablation of Atrial fibrillation) or M6547 (Radiofrequency Ablation of Atrial fibrillation Through Intracardiac Electrophysiologic 3-Dimensional Mapping)
Cardioversion	Defined from diagnosis of AF plus claims for cardioversion	ICD-10: I48 Claim codes:M5880

[a]To ensure accuracy, diagnosis was established based on one inpatient or two outpatient records of ICD-10 codes in the database.

AF, atrial fibrillation; ICD, International Classification of Diseases-10th revision; eGFR, estimated glomerular filtration rate

2. Outcome and follow-up

The primary composite outcome constituted of is chemic stroke, HF hospitalization, acute MI, and cardiovascular death. We also examined the risks of each component of the primary composite outcome. The definition of the outcomes is detailed in Table 3.

Table 3. Definitions and ICD-10 codes used for defining study outcomes

Outcomes	Definitions	Codes or conditions	PPV
Primary composite outcome			
Cardiovascular death[a]			
Ischemic stroke	Defined from admission diagnosis with concomitant imaging studies of the brain or related death	ICD-10: I63, I64	90.6%[b] (2347/2591)
Hospitalization for heart failure	Defined from principal or first secondary admission diagnoses of heart failure	ICD-10: I11.0, I50, I97.1	82.1%[b] (110/134)
Acute myocardial infarction	Defined from admission diagnosis of acute myocardial infarction concurrently with coronary angiography or related death	ICD-10: I21, I22	86.5%[c] (4054/4688)
Safety outcomes			
All–cause death[d]			
Intracranial bleeding	Defined from admission diagnosis with concomitant imaging studies of the brain or related death	ICD-10: I60–I62	87.5%[b] (286/327)
Gastrointestinal bleeding	Defined from admission diagnosis or related death	ICD-10: K25–28 (subcodes 0–2 and 4–6 only), K62.5, K92.0, K92.1, K92.2, I85.0, I98.3	92.0%[e] (184/200)
Serious adverse events related to rhythm control			
Cardiac tamponade	Defined from claims for pericardiocentesis	Claim codes:C8060, C8061	–
Syncope	Defined from either one diagnosis during hospitalization or more than twice at outpatient clinics	ICD-10: R55.x	–
Sick sinus syndrome	Defined from either one diagnosis during hospitalization or more than twice at outpatient clinics	ICD-10: I495.	91.1%[b] (307/337)
Atrioventricular block	Defined from either one diagnosis during hospitalization or more than twice at outpatient clinics	ICD-10: I44.1, I44.2, I44.3, I45.3, I45.8, I45.9	95.7%[b] (264/276)
Pacemaker implantation	Defined from claims for pacemaker implantation	Claim codes: O2003, O2004, O0203, O0204, O0205, O0206, O0207	-
Sudden cardiac arrest	Defined from admission diagnosis or related death[f]	ICD-10: I46, I49.0	80.2%[g] (586/731)

PPV was represented as % (number of true positive cases / number of examined cases).
[a]Defined as a death mainly due to ischemic stroke, heart failure, or acute myocardial infarction, similar to our previous studies (Kim, D. et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population–based cohort. Eur Heart

J. 2019;40(28):2313–2323.; Yang, PS. et al. Changes in Cardiovascular Risk Factors and Cardiovascular Events in the Elderly Population. J Am Heart Assoc. 2021;10(11):e019482.). [b]Authors conducted a validation study using hospital administrative data from two tertiary hospitals. [c]Validated in a study by Lee, HY. et al. (Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. Sci Rep 2017;7(1):12716). [d]Information on death (date and causes) was confirmed from the National Population Registry of the Korea National Statistical Office, which conducts central registration of death based on death certificates. It is a national agency covering the entire Korean population. [e]Validated in a study by Park, J. et al. (Validation of diagnostic codes of major clinical outcomes in a National Health Insurance database. Int J Arrhythm 2019;20:5). [f]To avoid erroneous inclusion of the patients with non–cardiac arrest, we excluded the patient with sudden arrest diagnosis accompanied by respiratory arrest (R09.0, R09.2), gastrointestinal bleeding (I85.0, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K92.0–K92.2), brain hemorrhage (I60.x–I62.x, S06.4–S06.6), septic shock (A41.9, R57.2), pregnancy and delivery (O00–O99), diabetic ketoacidosis (E14.1), anaphylaxis (T78.2), and accidents including suicide (T71, T75.1, T36–T65, V80–V89, W76.x, X60–X84). [g]Validated in a study by Kim, IJ. et al. (Relationship Between Anemia and the Risk of Sudden Cardiac Arrest – A Nationwide Cohort Study in South Korea. Circ J 2018;82(12):2962–9)

The composite safety outcome consisted of all-cause death, intracranial or gastrointestinal bleeding that required hospital admission, or prespecified serious adverse events related to rhythm control. Accordingly, cardiac tamponade, syncope, sick sinus syndrome, atrioventricular block, pacemaker implantation, and sudden cardiac arrest were defined as prespecified serious adverse events related to rhythm control. The study outcomes were followed up from 180 days after the first recorded prescription or procedure until December 31, 2016, or death. Details of the variables are also presented in Table 2.

3. Statistical analysis

Descriptive data were reported as means (standard deviations) for continuous variables and numbers (percentages) for categorical variables. After dividing into two groups according to treatment initiation, overlap weighting based on a propensity score (ps) was used to assess the differences in baseline characteristics between the rhythm- and rate control groups among men and women, respectively. The propensity score, which indicates the probability of being assigned to a rhythm control group, was calculated by lo-gistic regression analysis based on socio-demographic factors, AF duration, year in which treatment was initiated, level of care at which the AF treatment was provided, clinical risk scores, medical history, and concurrent medication use (variables in Table 4). Continuous variables were modelled as cubic spline functions. Figure 2 depicted the distribution of propensity scores before and after overlap weighting, respectively.
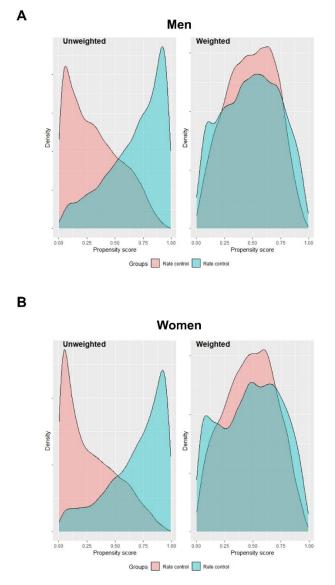
Figure 2. Distributions of the propensity scores in men (A) and women (B) before and after overlap weighting.

The overlap weight was calculated as '1-ps' in rhythm control groups and as 'ps' in rate control groups.[16] A standardized mean difference < 0.1 was considered to indicate acceptable differences in all baseline variables between the two groups. Competing risk regression by the Fine and Gray method was used to consider all-cause death as a competing event when estimating the risks of clinical outcomes.[17] Cofactors with a standardized mean difference of 0.1 or more after weighting were included as covariates in the competing risk regression analysis. Schoenfeld residuals were used to evaluate the proportional hazards assumption and violation of the assumption was not found. To explore the treatment timing-dependent effect of rhythm control on the out-comes, Cox proportional hazards models were fit to the entire weighted study population using an interac-tion term for the treatment timing after AF diagnosis (modelled as a natural spline) and treatment (rhythm- or rate control). Standard errors were estimated using 1,000 bootstrap replicates. Statistical analyses were performed by SAS, version 9.3 (SAS Institute, Cary, NC, USA) and R version 4.1.0 (The R Foundation, www.R-project.org (accessed on 1 September 2021)).

4. Sensitivity analyses

First, one-to-one ps matching (without replacement with a caliper of 0.01) was used instead of overlap weighting. Second, we performed an analysis after including patients treated with AADs as the initial choice of rhythm control. Third, we performed falsification analysis to measure systematic bias in this study by employing 24 prespecified falsification endpoints, with true hazard ratios of 1.

III. RESULTS

1. Baseline characteristics

Among 28,049 patients who underwent AF treatment within 1 year from AF diagnosis, 14,383 (51.3%) were men. Compared to men, women were older (68.5±11.4 vs. 66.0±11.2 years, $p < 0.001$) and had a higher CHA2DS2-VASc score (4.3±1.7 vs. 3.4±1.4, $p < 0.001$) (Table 4).

Table 4. Baseline characteristics of men and women treated with rhythm– or rate control before overlap weighting

Treatment initiation*	Men <1 year since AF diagnosis Overall	Women <1 year since AF diagnosis Overall	P–value	Men <6 months Rhythm control	Men <6 months Rate control	Men 6–12 months Rhythm control	Men 6–12 months Rate control	Women <6 months Rhythm control	Women <6 months Rate control	Women 6–12 months Rhythm control	Women 6–12 months Rate control
	N = 14383	N = 13666		N = 6631	N = 6865	N = 533	N = 354	N = 6066	N = 6911	N = 438	N = 251
Sociodemographic											
Age, years	66.0 (11.2)	68.5 (11.4)	<0.001	65.1 (11.1)	67.0 (11.2)	64.5 (10.5)	67.6 (11.4)	67.6 (11.0)	69.4 (11.6)	66.3 (10.9)	68.9 (11.9)
<65 years	5432 (37.8)	4167 (30.5)	<0.001	2768 (41.7)	2325 (33.9)	228 (42.8)	111 (31.4)	2024 (33.4)	1912 (27.7)	153 (34.9)	78 (31.1)
65–74 year	5532 (38.5)	5064 (37.1)	0.016	2490 (37.6)	2677 (39.0)	223 (41.8)	142 (40.1)	2329 (38.4)	2457 (35.6)	191 (43.6)	87 (34.7)
≥75 years	3419 (23.8)	4435 (32.5)	<0.001	1373 (20.7)	1863 (27.1)	82 (15.4)	101 (28.5)	1713 (28.2)	2542 (36.8)	94 (21.5)	86 (34.3)
AF duration, months	1.1 (2.3)	0.9 (2.2)	<0.001	0.9 (1.4)	0.3 (0.9)	8.8 (1.7)	8.8 (1.8)	0.7 (1.3)	0.3 (0.9)	8.8 (1.8)	8.8 (1.8)
Enroll year											
2005–2007	3082 (21.4)	3377 (24.7)	<0.001	1066 (16.1)	1830 (26.7)	95 (17.8)	91 (25.7)	1030 (17.0)	2168 (31.4)	98 (22.4)	81 (32.3)
2008–2010	2814 (19.6)	2648 (19.4)	0.702	1150 (17.3)	1480 (21.6)	104 (19.5)	80 (22.6)	1090 (18.0)	1425 (20.6)	74 (16.9)	59 (23.5)
2011–2013	4163 (28.9)	3790 (27.7)	0.025	2035 (30.7)	1858 (27.1)	166 (31.1)	104 (29.4)	1879 (31.0)	1712 (24.8)	145 (33.1)	54 (21.5)
2014–2015	4324 (30.1)	3851 (28.2)	0.001	2380 (35.9)	1697 (24.7)	168 (31.5)	79 (22.3)	2067 (34.1)	1606 (23.2)	121 (27.6)	57 (22.7)
High tertile of income	6252 (43.5)	5412 (39.6)	<0.001	5513 (83.1)	5098 (74.3)	458 (85.9)	270 (76.3)	5159 (85.0)	5293 (76.6)	379 (86.5)	202 (80.5)
Living in metropolitan areas	6600 (45.9)	6101 (44.6)	0.038	3260 (49.2)	2938 (42.8)	264 (49.5)	138 (39.0)	2936 (48.4)	2858 (41.4)	204 (46.6)	103 (41.0)
Level of care initiating treatment											
Tertiary	7590 (52.8)	6849 (50.1)	<0.001	4148 (62.6)	2926 (42.6)	354 (66.4)	162 (45.8)	3647 (60.1)	2806 (40.6)	281 (64.2)	115 (45.8)
Secondary	6089 (42.3)	5961 (43.6)	0.031	2276 (34.3)	3494 (50.9)	159 (29.8)	160 (45.2)	2244 (37.0)	3463 (50.1)	144 (32.9)	110 (43.8)
Primary	704 (4.9)	856 (6.3)	<0.001	207 (3.1)	445 (6.5)	20 (3.8)	32 (9.0)	175 (2.9)	642 (9.3)	13 (3.0)	26 (10.4)
Risk scores											
CHA2DS2-VASc score	3.4 (1.4)	4.3 (1.7)	<0.001	3.4 (1.4)	3.3 (1.3)	3.6 (1.5)	3.8 (1.4)	4.4 (1.8)	4.2 (1.6)	4.7 (1.7)	4.7 (1.7)
HAS-BLED score†	2.4 (1.1)	2.3 (1.1)	<0.001	2.5 (1.1)	2.3 (1.0)	2.7 (1.1)	2.7 (1.1)	2.4 (1.1)	2.1 (1.1)	2.6 (1.1)	2.6 (1.1)
Charlson comorbidity index	3.5 (2.8)	3.3 (2.8)	<0.001	4.0 (2.8)	2.9 (2.6)	4.7 (2.8)	4.4 (2.9)	4.0 (2.8)	2.6 (2.5)	4.5 (2.7)	4.3 (2.9)
Hospital Frailty Risk score	3.5 (4.8)	3.8 (5.3)	<0.001	3.4 (4.6)	3.5 (4.8)	3.7 (5.1)	5.5 (6.7)	4.0 (5.4)	3.4 (5.1)	4.5 (5.5)	5.7 (7.6)
Medical history											
Heart failure	7013 (48.8)	7258 (53.1)	<0.001	3083 (46.5)	3482 (50.7)	290 (54.4)	158 (44.6)	3049 (50.3)	3820 (55.3)	262 (59.8)	127 (50.6)
Heart failure hospitalization	1974 (13.7)	2186 (16.0)	<0.001	778 (11.7)	1100 (16.0)	65 (12.2)	31 (8.8)	852 (14.0)	1223 (17.7)	80 (18.3)	31 (12.4)
Hypertension	10748 (74.7)	10037 (73.4)	0.015	5574 (84.1)	4403 (64.1)	484 (90.8)	287 (81.1)	5107 (84.2)	4317 (62.5)	404 (92.2)	209 (83.3)
Diabetes	4324 (30.1)	3130 (22.9)	<0.001	2214 (33.4)	1840 (26.8)	181 (34.0)	89 (25.1)	1618 (26.7)	1343 (19.4)	111 (25.3)	58 (23.1)
Dyslipidemia	10376 (72.1)	9626 (70.4)	0.002	5340 (80.5)	4312 (62.8)	460 (86.3)	264 (74.6)	4875 (80.4)	4184 (60.5)	379 (86.5)	188 (74.9)
Ischemic stroke	5104 (35.5)	3822 (28.0)	<0.001	2156 (32.5)	2568 (37.4)	183 (34.3)	197 (55.6)	1652 (27.2)	1906 (27.6)	148 (33.8)	116 (46.2)
Transient ischemic attack	1307 (9.1)	1070 (7.8)	<0.001	699 (10.5)	508 (7.4)	70 (13.1)	30 (8.5)	587 (9.7)	396 (5.7)	58 (13.2)	29 (11.6)
Hemorrhagic stroke	301 (2.1)	256 (1.9)	0.203	146 (2.2)	127 (1.8)	15 (2.8)	13 (3.7)	120 (2.0)	120 (1.7)	6 (1.4)	10 (4.0)
Myocardial infarction	1454 (10.1)	1003 (7.3)	<0.001	757 (11.4)	603 (8.8)	64 (12.0)	30 (8.5)	520 (8.6)	413 (6.0)	54 (12.3)	16 (6.4)
Peripheral arterial disease	1641 (11.4)	1442 (10.6)	0.023	937 (14.1)	567 (8.3)	82 (15.4)	55 (15.5)	838 (13.8)	514 (7.4)	68 (15.5)	22 (8.8)

Valvular heart disease	1388 (9.7)	2843 (20.8)	<0.001	673 (10.1)	625 (9.1)	49 (9.2)	41 (11.6)	1082 (17.8)	1612 (23.3)	78 (17.8)	71 (28.3)
Chronic kidney disease	802 (5.6)	525 (3.8)	<0.001	448 (6.8)	286 (4.2)	46 (8.6)	22 (6.2)	320 (5.3)	169 (2.4)	24 (5.5)	12 (4.8)
Hyperthyroidism	1205 (8.4)	1796 (13.1)	<0.001	684 (10.3)	423 (6.2)	76 (14.3)	22 (6.2)	959 (15.8)	722 (10.4)	86 (19.6)	29 (11.6)
Hypothyroidism	1005 (7.0)	1801 (13.2)	<0.001	553 (8.3)	368 (5.4)	66 (12.4)	18 (5.1)	1034 (17.0)	653 (9.4)	90 (20.5)	24 (9.6)
Malignancy	3032 (21.1)	2051 (15.0)	<0.001	1496 (22.6)	1297 (18.9)	142 (26.6)	97 (27.4)	1072 (17.7)	858 (12.4)	78 (17.8)	43 (17.1)
Hypertrophic cardiomyopathy	260 (1.8)	256 (1.9)	0.716	146 (2.2)	95 (1.4)	14 (2.6)	5 (1.4)	160 (2.6)	76 (1.1)	19 (4.3)	1 (0.4)
Sleep apnea	86 (0.6)	17 (0.1)	<0.001	58 (0.9)	24 (0.3)	3 (0.6)	1 (0.3)	10 (0.2)	7 (0.1)	438 (100.0)	251 (100.0)
Concurrent medication‡											
Oral anticoagulant	14383 (100.0)	13666 (100.0)	-	6631 (100.0)	6865 (100.0)	533 (100.0)	354 (100.0)	6066 (100.0)	6911 (100.0)	438 (100.0)	251 (100.0)
Warfarin	12778 (88.8)	12163 (89.0)	0.682	5724 (86.3)	6265 (91.3)	467 (87.6)	322 (91.0)	5175 (85.3)	6365 (92.1)	391 (89.3)	232 (92.4)
Direct oral anticoagulant	1734 (12.1)	1586 (11.6)	0.251	977 (14.7)	651 (9.5)	72 (13.5)	34 (9.6)	935 (15.4)	581 (8.4)	49 (11.2)	21 (8.4)
Beta–blocker	8271 (57.5)	7320 (53.6)	<0.001	3093 (46.6)	4695 (68.4)	237 (44.5)	246 (69.5)	2674 (44.1)	4278 (61.9)	206 (47.0)	162 (64.5)
Non–dihydropyridine CCB	2149 (14.9)	2079 (15.2)	0.536	944 (14.2)	1065 (15.5)	88 (16.5)	52 (14.7)	779 (12.8)	1206 (17.5)	62 (14.2)	32 (12.7)
Digoxin	3659 (25.4)	4342 (31.8)	<0.001	631 (9.5)	2863 (41.7)	59 (11.1)	106 (29.9)	667 (11.0)	3536 (51.2)	53 (12.1)	86 (34.3)
Aspirin	3482 (24.2)	2701 (19.8)	<0.001	1627 (24.5)	1640 (23.9)	127 (23.8)	88 (24.9)	1245 (20.5)	1316 (19.0)	96 (21.9)	44 (17.5)
P2Y12 inhibitor	1372 (9.5)	827 (6.1)	<0.001	672 (10.1)	616 (9.0)	46 (8.6)	38 (10.7)	389 (6.4)	395 (5.7)	30 (6.8)	13 (5.2)
Statin	5524 (38.4)	5002 (36.6)	0.002	2667 (40.2)	2511 (36.6)	211 (39.6)	135 (38.1)	2418 (39.9)	2293 (33.2)	200 (45.7)	91 (36.3)
Dihydropyridine CCB	2459 (17.1)	2147 (15.7)	0.002	1389 (20.9)	879 (12.8)	128 (24.0)	63 (17.8)	1251 (20.6)	781 (11.3)	73 (16.7)	42 (16.7)
ACEi/ARB	8352 (58.1)	7514 (55.0)	<0.001	3746 (56.5)	4102 (59.8)	307 (57.6)	197 (55.6)	3317 (54.7)	3826 (55.4)	244 (55.7)	127 (50.6)
Loop/thiazide diuretics	6646 (46.2)	8029 (58.8)	<0.001	2596 (39.1)	3678 (53.6)	209 (39.2)	163 (46.0)	3039 (50.1)	4605 (66.6)	237 (54.1)	148 (59.0)
K+ sparing diuretics	2844 (19.8)	3399 (24.9)	<0.001	1001 (15.1)	1726 (25.1)	67 (12.6)	50 (14.1)	1128 (18.6)	2121 (30.7)	100 (22.8)	50 (19.9)

Data are presented as means (standard deviations) or n (%). *Duration from AF diagnosis to the first initiation of rhythm- or rate control. †Modified HAS-BLED=hypertension, 1 point; age > 65 years, 1 point; previous stroke, 1 point; history of bleeding or predisposition, 1 point; liable in-ternational normalized ratio, not assessed; alcohol or drug abuse, 1 point; and drug predisposing to bleeding, 1 point. ‡Defined as a prescription supply of over three months within the six months after the first prescription for antiarrhythmic or rate control drugs or the performance of a radiofrequency ablation for AF. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fi-brillation; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Further, the time period between the treatment initiation and AF diagnosis was shorter for women (0.9 ± 2.2 vs. 1.1 ± 2.3 months, $p < 0.001$), and they were less treated with rhythm control (47.6% vs. 49.8%, $p < 0.001$).

Among the initial rhythm control strategies, amiodarone accounted for the largest portion (2874 [44.1%] of 6504 women and 3193 [44.6%] of 7164 men), followed by propafenone and flecainide (Figure 1B). Radiofrequency ablation was performed in 88 (1.4%) of women and 120 (1.7%) of men at the time of enrollment and was eventually performed in 294 (4.5%) of women and 530 (7.4%) of men until the end of follow-up, respectively.

Baseline characteristics of men and women treated with rhythm- or rate control before and after overlap weighting are presented in Table 4 and Table 5. Compared to rate-control patients, rhythm-control patients were younger and tended to have a higher prevalence of comorbidities for both men and women. After weighting, all baseline characteristics were well-balanced between rhythm- and rate control group in both sexes.

Table 5. Baseline characteristics of men and women treated with rhythm– or rate control after overlap weighting

Treatment initiation*	Men						Women					
	<6 months since AF diagnosis			6–12 months since AF diagnosis			<6 months since AF diagnosis			6–12 months since AF diagnosis		
	Rhythm control	Rate control	SMD	Rhythm control	Rate control	SMD	Rhythm control	Rate control	SMD	Rhythm control	Rate control	SMD
	N = 2123	N = 2123		N = 132	N = 132		N = 1912	N = 1912		N = 100	N = 100	
Sociodemographic												
Age, years	66.0 (11.1)	66.0 (11.5)	<0.001	66.0 (11.2)	66.0 (12.0)	<0.001	68.7 (11.1)	68.7 (11.8)	<0.001	67.5 (10.1)	67.5 (12.2)	<0.001
<65	823.3 (38.8)	802.2 (37.8)	0.02	49.2 (37.1)	46.6 (35.2)	0.04	569.3 (29.8)	569.5 (29.8)	<0.001	30.2 (30.3)	33.1 (33.2)	0.062
65–74	798.1 (37.6)	809.1 (38.1)	0.011	56.4 (42.6)	55.8 (42.1)	0.009	712.9 (37.3)	699.6 (36.6)	0.014	44.1 (44.2)	36.2 (36.3)	0.161
≥75	501.7 (23.6)	511.8 (24.1)	0.011	26.9 (20.3)	30.0 (22.7)	0.058	629.9 (32.9)	643.1 (33.6)	0.015	25.4 (25.5)	30.4 (30.5)	0.112
AF duration, months	0.6 (1.1)	0.6 (1.2)	<0.001	8.8 (1.8)	8.8 (1.8)	<0.001	0.5 (1.1)	0.5 (1.2)	<0.001	8.8 (1.7)	8.8 (1.8)	<0.001
Enroll year												
2005–2007	412.0 (19.4)	412.0 (19.4)	<0.001	28.5 (21.5)	28.5 (21.5)	<0.001	417.0 (21.8)	417.0 (21.8)	<0.001	25.8 (25.9)	25.8 (25.9)	<0.001
2008–2010	404.1 (19.0)	404.1 (19.0)	<0.001	29.2 (22.0)	29.2 (22.0)	<0.001	372.2 (19.5)	372.2 (19.5)	<0.001	21.5 (21.5)	21.5 (21.5)	<0.001
2011–2013	627.5 (29.6)	627.5 (29.6)	<0.001	39.3 (29.7)	39.3 (29.7)	<0.001	553.4 (28.9)	553.4 (28.9)	<0.001	27.4 (27.5)	27.4 (27.5)	<0.001
2014–2015	679.5 (32.0)	679.5 (32.0)	<0.001	35.5 (26.8)	35.5 (26.8)	<0.001	569.5 (29.8)	569.5 (29.8)	<0.001	25.0 (25.1)	25.0 (25.1)	<0.001
High tertile of income	915.0 (43.1)	915.0 (43.1)	<0.001	62.6 (47.2)	62.6 (47.2)	<0.001	785.1 (41.1)	785.1 (41.1)	<0.001	37.6 (37.7)	37.6 (37.7)	<0.001
Living in metropolitan areas	980.4 (46.2)	980.4 (46.2)	<0.001	61.6 (46.5)	61.6 (46.5)	<0.001	869.0 (45.4)	869.0 (45.4)	<0.001	46.1 (46.2)	46.1 (46.2)	<0.001
Level of care initiating treatment												
Tertiary	1102.7 (51.9)	1102.7 (51.9)	<0.001	74.8 (56.5)	74.8 (56.5)	<0.001	966.1 (50.5)	966.1 (50.5)	<0.001	55.2 (55.4)	55.2 (55.4)	<0.001
Secondary	924.0 (43.5)	924.0 (43.5)	<0.001	49.1 (37.1)	49.1 (37.1)	<0.001	856.4 (44.8)	856.4 (44.8)	<0.001	38.2 (38.3)	38.2 (38.3)	<0.001
Primary	96.4 (4.5)	96.4 (4.5)	<0.001	8.5 (6.4)	8.5 (6.4)	<0.001	89.6 (4.7)	89.6 (4.7)	<0.001	6.3 (6.4)	6.3 (6.4)	<0.001
Risk score												
CHA$_2$DS$_2$-VASc score	3.4 (1.4)	3.4 (1.4)	<0.001	3.7 (1.5)	3.7 (1.4)	<0.001	4.4 (1.8)	4.4 (1.7)	<0.001	4.7 (1.8)	4.7 (1.8)	<0.001
HAS-BLED score†	2.5 (1.1)	2.5 (1.1)	<0.001	2.7 (1.1)	2.7 (1.1)	<0.001	2.3 (1.2)	2.3 (1.1)	<0.001	2.6 (1.1)	2.6 (1.1)	<0.001
Charlson comorbidity index	3.6 (2.6)	3.6 (2.9)	<0.001	4.5 (2.8)	4.5 (2.9)	<0.001	3.5 (2.6)	3.5 (2.8)	<0.001	4.3 (2.5)	4.3 (3.0)	<0.001
Hospital Frailty Risk Score	3.6 (4.8)	3.6 (4.9)	<0.001	4.4 (5.9)	4.4 (5.8)	<0.001	4.0 (5.4)	4.0 (5.4)	<0.001	5.0 (6.1)	5.0 (6.3)	<0.001
Medical history												
Heart failure	1030.7 (48.5)	1030.7 (48.5)	<0.001	68.6 (51.8)	68.6 (51.8)	<0.001	1003.6 (52.5)	1003.6 (52.5)	<0.001	55.2 (55.4)	55.2 (55.4)	<0.001
Heart failure hospitalization	294.9 (13.9)	294.9 (13.9)	<0.001	16.0 (12.1)	16.0 (12.1)	<0.001	310.9 (16.3)	310.9 (16.3)	<0.001	14.0 (14.0)	14.0 (14.0)	<0.001
Hypertension	1653.9 (77.9)	1653.9 (77.9)	<0.001	116.2 (87.7)	116.2 (87.7)	<0.001	1475.9 (77.2)	1475.9 (77.2)	<0.001	88.1 (88.4)	88.1 (88.4)	<0.001
Diabetes	659.6 (31.1)	659.6 (31.1)	<0.001	40.5 (30.6)	40.5 (30.6)	<0.001	468.1 (24.5)	468.1 (24.5)	<0.001	22.3 (22.4)	22.3 (22.4)	<0.001
Dyslipidemia	1592.2 (75.0)	1592.2 (75.0)	<0.001	106.2 (80.2)	106.2 (80.2)	<0.001	1401.3 (73.3)	1401.3 (73.3)	<0.001	81.0 (81.2)	81.0 (81.2)	<0.001
Ischemic stroke	767.8 (36.2)	767.8 (36.2)	<0.001	56.7 (42.8)	56.7 (42.8)	<0.001	557.3 (29.1)	557.3 (29.1)	<0.001	39.6 (39.7)	39.6 (39.7)	<0.001
Transient ischemic attack	194.9 (9.2)	194.9 (9.2)	<0.001	14.7 (11.1)	14.7 (11.1)	<0.001	154.5 (8.1)	154.5 (8.1)	<0.001	11.1 (11.1)	11.1 (11.1)	<0.001
Hemorrhagic stroke	45.3 (2.1)	45.3 (2.1)	<0.001	3.7 (2.8)	3.7 (2.8)	<0.001	38.4 (2.0)	38.4 (2.0)	<0.001	2.0 (2.0)	2.0 (2.0)	<0.001
Myocardial infarction	221.9 (10.5)	221.9 (10.5)	<0.001	13.6 (10.3)	13.6 (10.3)	<0.001	137.5 (7.2)	137.5 (7.2)	<0.001	7.4 (7.5)	7.4 (7.5)	<0.001
Peripheral arterial disease	244.0 (11.5)	244.0 (11.5)	<0.001	22.6 (17.1)	22.6 (17.1)	<0.001	216.0 (11.3)	216.0 (11.3)	<0.001	12.0 (12.0)	12.0 (12.0)	<0.001
Valvular heart disease	207.6 (9.8)	207.6 (9.8)	<0.001	15.4 (11.6)	15.4 (11.6)	<0.001	373.1 (19.5)	373.1 (19.5)	<0.001	22.0 (22.1)	22.0 (22.1)	<0.001
Chronic kidney disease	123.2 (5.8)	123.2 (5.8)	<0.001	8.9 (6.7)	8.9 (6.7)	<0.001	73.7 (3.9)	73.7 (3.9)	<0.001	4.4 (4.4)	4.4 (4.4)	<0.001
Hyperthyroidism	172.7 (8.1)	172.7 (8.1)	<0.001	11.5 (8.7)	11.5 (8.7)	<0.001	247.4 (12.9)	247.4 (12.9)	<0.001	14.6 (14.6)	14.6 (14.6)	<0.001
Hypothyroidism	146.4 (6.9)	146.4 (6.9)	<0.001	9.6 (7.3)	9.6 (7.3)	<0.001	255.4 (13.4)	255.4 (13.4)	<0.001	13.1 (13.2)	13.1 (13.2)	<0.001

Malignancy	459.7 (21.7)	459.7 (21.7) <0.001	33.1 (25.0)	33.1 (25.0) <0.001	301.8 (15.8)	301.8 (15.8) <0.001	17.7 (17.8)	17.7 (17.8) <0.001
Hypertrophic cardiomyopathy	39.5 (1.9)	39.5 (1.9) <0.001	2.0 (1.5)	2.0 (1.5) <0.001	32.6 (1.7)	32.6 (1.7) <0.001	0.6 (0.6)	0.6 (0.6) <0.001
Sleep apnea	12.6 (0.6)	12.6 (0.6) <0.001	0.2 (0.2)	0.2 (0.2) <0.001	2.7 (0.1)	2.7 (0.1) <0.001	99.7 (100.0)	99.7 (100.0) <0.001
Concurrent medication‡								
Oral anticoagulant	2123.1 (100.0)	2123.1 (100.0) <0.001	132.4 (100.0)	132.4 (100.0) <0.001	1912.1 (100.0)	1912.1 (100.0) <0.001	99.7 (100.0)	99.7 (100.0) <0.001
Warfarin	1880.1 (88.6)	1880.1 (88.6) <0.001	117.4 (88.7)	117.4 (88.7) <0.001	1687.5 (88.3)	1687.5 (88.3) <0.001	90.1 (90.4)	90.1 (90.4) <0.001
Direct oral anticoagulant	267.0 (12.6)	267.0 (12.6) <0.001	15.9 (12.0)	15.9 (12.0) <0.001	236.1 (12.3)	236.1 (12.3) <0.001	10.1 (10.1)	10.1 (10.1) <0.001
Beta-blocker	1416.8 (66.7)	1416.8 (66.7) <0.001	82.0 (61.9)	82.0 (61.9) <0.001	1194.6 (62.5)	1194.6 (62.5) <0.001	63.5 (63.6)	63.5 (63.6) <0.001
Non–dihydropyridine CCB	370.2 (17.4)	370.2 (17.4) <0.001	25.7 (19.4)	25.7 (19.4) <0.001	338.3 (17.7)	338.3 (17.7) <0.001	16.7 (16.7)	16.7 (16.7) <0.001
Digoxin	445.0 (21.0)	445.0 (21.0) <0.001	31.5 (23.8)	31.5 (23.8) <0.001	480.3 (25.1)	480.3 (25.1) <0.001	23.0 (23.1)	23.0 (23.1) <0.001
Aspirin	535.3 (25.2)	535.3 (25.2) <0.001	33.2 (25.1)	33.2 (25.1) <0.001	390.9 (20.4)	390.9 (20.4) <0.001	19.6 (19.6)	19.6 (19.6) <0.001
P2Y$_{12}$ inhibitor	224.8 (10.6)	224.8 (10.6) <0.001	13.4 (10.1)	13.4 (10.1) <0.001	123.9 (6.5)	123.9 (6.5) <0.001	6.2 (6.2)	6.2 (6.2) <0.001
Statin	868.7 (40.9)	868.7 (40.9) <0.001	49.6 (37.4)	49.6 (37.4) <0.001	741.4 (38.8)	741.4 (38.8) <0.001	42.6 (42.7)	42.6 (42.7) <0.001
Dihydropyridine CCB	347.0 (16.3)	347.0 (16.3) <0.001	25.0 (18.8)	25.0 (18.8) <0.001	297.4 (15.6)	297.4 (15.6) <0.001	16.1 (16.1)	16.1 (16.1) <0.001
ACEI/ARB	1229.2 (57.9)	1229.2 (57.9) <0.001	75.3 (56.9)	75.3 (56.9) <0.001	1041.3 (54.5)	1041.3 (54.5) <0.001	52.3 (52.5)	52.3 (52.5) <0.001
Loop/thiazide diuretic	979.7 (46.1)	979.7 (46.1) <0.001	60.4 (45.6)	60.4 (45.6) <0.001	1096.7 (57.4)	1096.7 (57.4) <0.001	55.9 (56.1)	55.9 (56.1) <0.001
K+-sparing diuretic	419.4 (19.8)	419.4 (19.8) <0.001	19.8 (15.0)	19.8 (15.0) <0.001	447.4 (23.4)	447.4 (23.4) <0.001	20.7 (20.8)	20.7 (20.8) <0.001

Data are presented as means (standard deviations) or n (%). *Duration from AF diagnosis to the first initiation of rhythm- or rate control. †Modified HAS-BLED=hypertension, 1 point; age > 65 years, 1 point; previous stroke, 1 point; history of bleeding or predisposition, 1 point; liable international normalized ratio, not assessed; alcohol or drug abuse, 1 point; and drug predisposing to bleeding, 1 point. ‡Defined as a prescription supply of over three months within the six months after the first prescription for antiarrhythmic or rate control drugs or the performance of a radiofrequency ablation for AF. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; SMD, standard mean difference.

2. Sex difference of the primary composite outcome according to the timing of rhythm control

The mean follow-up times were 4.9 ± 3.2 years. Cox proportional hazard models with an interaction term showed that women had a linear relationship, wherein the relative effect of rhythm control over rate control on the primary composite outcome became attenuated as the timing of treatment initiation was delayed (Figure 3A, B). Rhythm control was associated with a significantly lower risk of the primary composite outcome compared to rate control if it was initiated within 3 months from AF diagnosis; however, the benefit became statistically insignificant after 3 months. On the other hand, in men, relative effect of rhythm control over rate control on the primary composite outcome was maintained until 12 months after AF diagnosis.
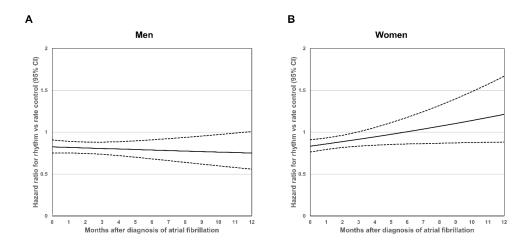

Figure 3. Relationship between treatment timing and primary composite outcome risk. Data shown are within 1 year after the first diagnosis of atrial fibrillation. (A) Men. (B) Women. Hazard ratio = 1 means an equal risk of outcomes in participants treated with rhythm- and rate-control. Dashed black lines show the 95% confidence interval.

In the group with AF treatment initiated within 6 months after the first diagnosis of AF, the risk of primary composite outcome for rhythm control tended to be lower than that of

rate control in both the sexes (men: HR = 0.86, 95% CI, 0.79–0.94, P = 0.001; women: HR = 0.85, 95% CI, 0.78–0.93, P < 0.001; P for interaction = 0.844) (Table 6). In the group with AF treatment initiated after 6 months, significant interaction was demonstrated between sex and the relative effect of rhythm control over rate control (men: HR = 0.72, 95% CI, 0.52–0.99, P = 0.045; women: HR = 1.32, 95% CI, 0.92–1.88, P = 0.134; P for interaction = 0.018).

Table 6. Relative effect of rhythm control over rate control on primary composite outcome after overlap weighting.

Primary Outcome	Composite	Number of Events	Person-Years	IR *	Number of Events	Person-Years	IR *	Absolute Rate Difference Per 100 Person-Years * (95% CI)	Hazard Ratio * (95% CI)	p-Value	p for Interaction
AF treatment (<6 months since AF diagnosis)											0.844
Men		Rhythm control (N = 2123)			Rate control (N = 2123)						
		461	7905	5.83	521	7586	6.87	−1.03 (−1.83 to −0.24)	0.86 (0.79–0.94)	0.001	
Women		Rhythm control (N = 1912)			Rate control (N = 1912)						
		516	7200	7.17	590	6956	8.48	−1.31 (−2.24 to −0.39)	0.85 (0.78–0.93)	<0.001	
AF treatment (6–12 months since AF diagnosis)											0.018
Men		Rhythm control (N = 132)			Rate control (N = 132)						
		30	527	5.80	40	471	8.55	−2.75 (−6.09 to 0.59)	0.72 (0.52–0.99)	0.043	
Women		Rhythm control (N = 100)			Rate control (N = 100)						
		33	392	8.40	26	404	6.46	1.94 (−1.85 to 5.73)	1.32 (0.92–1.88)	0.134	

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

The relative effects of rhythm control over rate control on the individual outcomes are presented in Table 7. Among the individual cardiovascular outcomes, there was a significant interaction between the relative effect of rhythm control over rate control on the prevention of ischemic stroke and sex.

Table 7. Relative effect of rhythm control over rate control on individual components of the primary composite outcome after overlap weighting.

	Men				Women			
	IR	IR	Hazard Ratio (95% CI)	p-Value	IR	IR	Hazard Ratio (95% CI)	p-Value	p for Interaction
AF treatment (<6 months since AF diagnosis)								
	Rhythm contr ol (N = 2123)	Rate control (N = 2123)			Rhythm control (N = 1912)	Rate control (N = 1912)		
Cardiovascular death	1.63	1.93	0.86 (0.73–1.00)	0.053	2.38	2.29	1.05 (0.91–1.21)	0.517	0.063
Ischemic stroke	2.51	2.94	0.87 (0.77–0.99)	0.035	2.65	3.69	0.72 (0.63–0.82)	<0.001	0.036
Hospitalization for HF	2.25	2.81	0.82 (0.71–0.94)	0.004	3.67	4.08	0.90 (0.81–1.01)	0.086	0.271
Acute myocardial infarction	0.30	0.44	0.70 (0.49–0.99)	0.049	0.20	0.29	0.70 (0.46–1.06)	0.091	0.989
AF treatment (6–12 months since AF diagnosis)								
	Rhythm contr ol (N = 132)	Rate control (N = 132)			Rhythm control (N = 100)	Rate control (N = 100)		
Cardiovascular death	1.67	2.60	0.68 (0.39–1.18)	0.171	1.81	2.03	0.91 (0.48–1.73)	0.772	0.512
Ischemic stroke	2.44	3.46	0.74 (0.47–1.18)	0.208	3.91	2.48	1.63 (0.97–2.73)	0.063	0.027
Hospitalization for HF	2.51	3.94	0.68 (0.43–1.10)	0.114	3.49	3.23	1.08 (0.64–1.81)	0.770	0.196
Acute myocardial infarction	0.22	0.45	0.54 (0.13–2.13)	0.376	0.54	0.70	0.79 (0.23–2.74)	0.716	0.677

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; IR, incidence rate.

The relative effects of rhythm control over rate control on safety outcomes are presented in Table 8. There was a trend of the composite safety outcome to-wards an increased risk in women and reduced risk in men, irrespective of timing of treatment initiation (<6 months: HR = 0.97 in men, HR = 1.10 in women, p for interaction = 0.040; ≥6 months: HR = 0.85 in men, HR = 1.27 in women, p for interaction = 0.093).

Table 8. Relative effect of rhythm over rate control on safety outcomes after overlap weighting.

	Men				Women				
	IR	IR	Hazard ratio (95% CI)	*P*-value	IR	IR	Hazard ratio (95% CI)	*P*-value	*P* for interaction
AF treatment (<6 months since the first diagnosis of AF)									
	Rhythm control (N=2123)	Rate control (N=2123)			Rhythm control (N=1912)	Rate control (N=1912)			
Composite safety outcome	7.97	8.20	0.97 (0.90–1.05)	0.471	8.36	7.62	1.10 (1.01–1.19)	0.027	0.040
All-cause death	4.60	5.27	0.87 (0.79-0.96)	0.005	4.38	4.56	0.96 (0.87–1.06)	0.443	0.175
Intracranial bleeding	0.59	0.78	0.78 (0.60-1.01)	0.057	0.74	0.75	0.99 (0.77–1.27)	0.954	0.185
Gastrointestinal bleeding	1.67	2.01	0.85 (0.72-0.99)	0.042	1.74	1.97	0.89 (0.76–1.05)	0.156	0.671
Serious adverse event related to rhythm control	2.91	2.15	1.37 (1.20–1.57)	<0.001	3.36	2.00	1.68 (1.46–1.94)	<0.001	0.041
Cardiac tamponade	0.09	0.06	1.68 (0.76–3.72)	0.199	0.07	0.03	2.64 (1.02–6.83)	0.046	0.511
Syncope	1.23	1.04	1.20 (0.98–1.47)	0.071	1.30	0.97	1.34 (1.09–1.65)	0.005	0.445
Sick sinus syndrome	0.67	0.15	4.44 (2.97–6.64)	<0.001	1.05	0.37	2.86 (2.12–3.86)	<0.001	0.083
Atrioventricular block	0.47	0.19	2.51 (1.70–3.72)	<0.001	0.43	0.24	1.83 (1.25–2.67)	0.002	0.252
Pacemaker implantation	0.39	0.11	3.75 (2.26–6.22)	<0.001	0.49	0.23	2.12 (1.44–3.11)	<0.001	0.078
Sudden cardiac arrest	0.50	0.63	0.81 (0.61–1.06)	0.126	0.56	0.43	1.29 (0.95–1.75)	0.099	0.024
AF treatment (6–12 months since the first diagnosis of AF)									
	Rhythm control (N=132)	Rate control (N=132)			Rhythm control (N=100)	Rate control (N=100)			
Composite safety outcome	7.82	9.26	0.85 (0.63–1.14)	0.279	7.67	6.04	1.27 (0.89–1.82)	0.196	0.093
All-cause death	4.50	6.66	0.67 (0.47–0.95)	0.025	2.82	3.43	0.82 (0.50–1.34)	0.427	0.525
Intracranial bleeding	0.81	0.90	0.96 (0.40–2.28)	0.925	1.13	0.81	1.41 (0.61–3.26)	0.424	0.541
Gastrointestinal bleeding	1.26	3.05	0.44 (0.24–0.78)	0.005	1.42	1.19	1.18 (0.56–2.47)	0.658	0.034

Serious adverse event related to rhythm control	3.60	2.51	1.55 (0.94–2.55)	0.087	2.70	1.80	1.52 (0.79–2.91)	0.211	0.959
Cardiac tamponade	0.06	0.12	0.50 (0.04–5.66)	0.572	0.05	0	-	-	-
Syncope	1.69	1.13	1.60 (0.77–3.33)	0.207	1.57	0.86	1.87 (0.76–4.63)	0.176	0.799
Sick sinus syndrome	0.40	0.21	2.05 (0.57–7.40)	0.274	1.23	0.54	2.35 (0.76–7.29)	0.139	0.888
Atrioventricular block	0.49	0.15	3.42 (0.70–16.78)	0.129	0.33	0.49	0.69 (0.13–3.57)	0.661	0.174
Pacemaker implantation	0.39	0.03	16.81 (1.95–144.90)	0.010	0.32	0.28	1.14 (0.25–5.23)	0.862	0.047
Sudden cardiac arrest	0.83	0.88	1.00 (0.42–2.41)	0.997	0.08	0.12	0.66 (0.10–4.27)	0.661	0.692

AF, atrial fibrillation; CI, confidence interval; IR, incidence rate.

3. Sensitivity analyses

Among the patients in whom AF treatment was initiated ≥6 months, significant interaction between sex and the relative effect of rhythm control over rate control on the primary composite outcome was consistently observed in one-to-one ps matching analysis (Table 9).

Table 9. The relative effect of rhythm control over rate control on primary composite outcome in men and women after 1:1 propensity score matching

Primary composite outcome	Number of events	Person-years	IR	Number of events	Person-years	IR	Absolute rate difference per 100 person-years (95% CI)	Hazard ratio (95% CI)	P-value	P for interaction
AF treatment (<6 months since the first diagnosis of AF)										0.935
Men	Rhythm control (N=3097)			Rate control (N=3097)						
	676	11558	5.85	752	11093	6.78	-0.93 (-1.59 to -0.27)	0.89 (0.80–0.98)	0.014	
Women	Rhythm control (N=2711)			Rate control (N=2711)						
	735	10175	7.22	813	10013	8.12	-0.90 (-1.66 to -0.13)	0.89 (0.81–0.98)	0.025	
AF treatment (6–12 months since the first diagnosis of AF)										0.007
Men	Rhythm control (N=158)			Rate control (N=158)						
	30	615	4.88	48	556	8.63	-3.75 (-6.76 to -0.75)	0.62 (0.39–0.98)	0.040	
Women	Rhythm control (N=109)			Rate control (N=109)						
	35	409	8.56	25	459	5.45	3.11 (-0.44 to 6.66)	1.59 (0.95–2.66)	0.077	

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Enrollment of patients taking AADs as the initial strategy of rhythm control showed consistent results (Table 10).

Table 10. The relative effect of anti–arrhythmic drugs over rate control on primary composite outcome in men and women according to timing of treatment initiation after overlap weighting

Primary composite outcome	Number of events	Person–years	IR	Number of events	Person–years	IR	Absolute rate difference per 100 person–years (95% CI)	Hazard rati * (95% CI)	P-value	P for interaction
AF treatment (<6 months since the first diagnosis of AF)										0.819
Men	Rhythm control (N=2119)			Rate control (N=2119)						
	461	7875	5.86	520	7567	6.87	-1.01 (-1.81 to -0.22)	0.87 (0.79–0.94)	0.001	
Women	Rhythm control (N=1910)			Rate control (N=1910)						
	516	7187	7.18	590	6946	8.49	-1.30 (-2.23 to -0.38)	0.85 (0.79–0.93)	<0.001	
AF treatment (6~12 months since the first diagnosis of AF)										0.023
Men	Rhythm control (N=130)			Rate control (N=130)						
	30	513	5.91	39	460	8.42	-2.50 (-5.89 to 0.88)	0.74 (0.54–1.03)	0.074	
Women	Rhythm control (N=99)			Rate control (N=99)						
	33	390	8.44	26	402	6.50	1.94 (-1.87 to 5.75)	1.32 (0.92–1.88)	0.137	

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

In the analyses of 24 falsification endpoints, the 95% CIs of the associations of rhythm control with each end-point covered 1 in 24 (100%) endpoints (Table 11).

Table 11. Risk of 24 falsification endpoints in weighted male and female patients undergoing rhythm control compared with rate control

	<6months				6–12 months			
	Men		Women		Men		Women	
Endpoints	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Influenza	0.76 (0.57–1.01)	0.054	0.83 (0.64–1.09)	0.180	0.57 (0.15–2.07)	0.389	1.64 (0.43–6.28)	0.470
Major fracture	0.98 (0.79–1.21)	0.838	1.08 (0.94–1.24)	0.257	0.76 (0.34–1.70)	0.510	0.78 (0.41–1.45)	0.428
Urinary tract infection	1.04 (0.94–1.14)	0.451	0.98 (0.92–1.06)	0.679	1.33 (0.97–1.84)	0.079	1.04 (0.77–1.41)	0.810
Syphilis	0.82 (0.49–1.35)	0.429	0.79 (0.48–1.29)	0.348	3.94 (0.46–34.01)	0.212	7.06 (0.81–61.74)	0.077
Viral enteritis	1.20 (0.80–1.82)	0.380	0.88 (0.61–1.27)	0.496	0.94 (0.27–3.25)	0.923	1.91 (0.47–7.73)	0.366
Warts	1.46 (0.85–2.50)	0.172	0.93 (0.52–1.66)	0.809	0.54 (0.09–3.21)	0.496	0.41 (0.04–4.85)	0.483
Acute hepatitis A	1.17 (0.63–2.16)	0.620	1.09 (0.59–2.01)	0.785	2.18 (0.27–17.44)	0.462	0.55 (0.10–3.02)	0.488
Stomach cancer	0.81 (0.64–1.04)	0.092	0.89 (0.63–1.27)	0.524	0.58 (0.25–1.34)	0.201	1.01 (0.22–4.58)	0.988
Lipoma	1.14 (0.80–1.64)	0.473	1.34 (0.86–2.09)	0.195	0.80 (0.22–2.89)	0.729	0.69 (0.12–3.84)	0.669
Carpal tunnel syndrome	1.30 (0.84–2.00)	0.240	0.93 (0.68–1.29)	0.674	0.74 (0.14–3.89)	0.720	0.52 (0.13–2.08)	0.358
Pterygium	1.08 (0.78–1.48)	0.651	1.15 (0.86–1.54)	0.354	0.90 (0.24–3.40)	0.877	1.05 (0.31–3.60)	0.940
Meniere's disease	1.15 (0.87–1.51)	0.328	1.06 (0.84–1.34)	0.633	1.51 (0.56–4.10)	0.416	2.87 (0.92–8.97)	0.069
Benign paroxysmal positional vertigo	1.16 (0.93–1.45)	0.197	1.11 (0.94–1.33)	0.224	1.13 (0.54–2.38)	0.748	0.80 (0.38–1.71)	0.570
Varicose veins of lower extremities	0.99 (0.70–1.38)	0.937	0.74 (0.50–1.11)	0.147	0.50 (0.14–1.78)	0.287	1.08 (0.26–4.46)	0.920
Acute appendicitis	1.41 (0.88–2.27)	0.154	1.15 (0.75–1.76)	0.536	0.42 (0.09–1.96)	0.272	0.80 (0.17–3.67)	0.770
Diverticulitis of intestine	1.35 (0.89–2.06)	0.160	1.04 (0.66–1.62)	0.873	0.52 (0.16–1.70)	0.279	0.51 (0.09–2.99)	0.456
Cellulitis	1.11 (0.99–1.23)	0.060	1.05 (0.93–1.17)	0.435	0.98 (0.65–1.48)	0.916	0.63 (0.40–1.01)	0.053
Urticaria	1.05 (0.96–1.15)	0.330	1.05 (0.96–1.15)	0.292	1.02 (0.72–1.44)	0.911	0.80 (0.56–1.16)	0.245
Ingrowing nail	1.33 (0.96–1.83)	0.083	1.12 (0.84–1.50)	0.423	0.43 (0.09–1.91)	0.265	1.18 (0.20–7.10)	0.855
Frozen shoulder	1.06 (0.94–1.20)	0.346	0.94 (0.84–1.05)	0.278	1.21 (0.73–1.99)	0.467	0.97 (0.61–1.56)	0.907
Osteomyelitis	0.79 (0.46–1.38)	0.415	0.76 (0.36–1.60)	0.468	3.16 (0.29–34.3)	0.345	6.78 (0.44–105.4)	0.171
Dysuria	1.02 (0.87–1.19)	0.828	0.94 (0.80–1.11)	0.448	0.92 (0.53–1.58)	0.753	0.67 (0.34–1.29)	0.230
Burns	1.15 (0.90–1.48)	0.270	0.78 (0.79–1.21)	0.839	2.05 (0.83–5.05)	0.121	0.86 (0.40–1.88)	0.712
Anaphylaxis/Allergic reaction	1.02 (0.73–1.43)	0.900	0.77 (0.54–1.12)	0.170	1.29 (0.33–5.12)	0.713	1.08 (0.26–4.50)	0.916

CI, confidence interval

IV. DISCUSSION

1. Main findings

The principal findings of this nationwide cohort study that categorized patients according to sex and the timing of treatment initiation were as follows. First, as treatment initiation was delayed, the relative effect of rhythm control over rate control on primary composite outcome was attenuated gradually in women while remained steadily until 12 months in men. Second, among patients who received AF treatment after 6 months from AF diagnosis, there were significant interactions between sex and relative effects of rhythm control over rate control on the primary composite outcome. Third, compared to rate control, rhythm control showed a trend towards an increased risk of the composite safety outcome in women, irrespective of timing of treatment initiation.

2. Sex differences in benefits and harms of rhythm control

AF is a common arrhythmic disease with a higher prevalence in men than in women; however, stroke and mortality risk are significantly higher in women than in men.[18,19] Sex differences in outcomes of rhythm control over rate control were investigated in subgroup analyses of previous trials. The AFFIRM trial showed that mortality rates between rhythm- and rate control did not differ by sex.[3] In comparison, the RACE trial showed that rhythm control was associated with a higher incidence of the primary outcome compared to rate control in women, not in men.[13] Recently, the EAST-AFNET 4 and Kim et al. reported that in comparison with usual care or rate control irrespective of sex, rhythm control initiated within 12 months from AF diagnosis lowered the risk of the first primary outcome (i.e., ischemic stroke, HF hospitalization, acute MI, and cardiovascular death).[6,8] However, the aforementioned trials did not show the relationship between the out-come of rhythm control and timing of AF treatment initiation in men and women, respectively.

3. Earlier rhythm control therapy is needed in women

The present study's findings show that the relative effects of rhythm control over rate

control on the primary composite outcome was reversed in women after 6 months from AF diagnosis. Significant interactions in the group that received AF treatment within 6–12 months from AF diagnosis mainly originated from the interaction between sex and relative effect of rhythm control over rate control on ischemic stroke. In a previous randomized controlled trial, which showed that rhythm control offered no advantage or significant disadvantage for ischemic stroke over rate control irrespective of sex, most patients already had AF for >2 years.[20] In the RACE trial, rhythm control led to more thromboembolic complications in women, whereas the opposite trend was observed in men. However, a recent large cohort study reported that rhythm control was associated with a reduced risk of ischemic stroke when it was prescribed within 7 days from AF diagnosis regardless of sex.[21] This finding also supported the results of this study in the group that received AF treatment <6 months from AF diagnosis.

Precise mechanisms of sex differences in outcomes of rhythm over rate control have not been fully elucidated yet. The possible explanation for the waning of relative efficacy of early rhythm-control therapy is that women are older than men at the initial treatment for AF. This finding is consistent with those of previous reports, although women's symptoms and quality of life were poorer than those of men. Further, they were referred later and were less likely to undergo rhythm control.[9-12] However, a significant interaction between sex and the primary composite outcome was still noted even after weighing age and comorbidities. Among patients treated with catheter ablation, women had a significantly smaller mean voltage, slow conduction velocity, and greater proportion of complex fractionated signals in the left atrium compared to men.[22] Since atrial remodeling progresses gradually over time, women may have a narrower window to obtain benefits from rhythm control because they already have more advanced atrial remodeling at the time of AF treatment initiation.

4. Increased safety outcome by rhythm control in women

In this study, compared with men, women had a higher risk of the composite safety

outcome and adverse event related to rhythm control. Previous studies have reported comparable results for adverse events related to rhythm control. One study demonstrated that AADs tended to increase risks of torsades de pointes and sick sinus syndrome more in women compared to men.[23] Additionally, as use of catheter ablation has been increased during the last few decades, female sex has become a predictor of in-hospital complications for any cardiac arrhythmia.[24] A large retrospective study reported that women tended to have higher risks of access site complications, cardiac tamponade and pericardial effusions, and postoperative bleeding requiring transfusions.[25-27] Therefore, even if rhythm control can be initiated at an earlier stage, the benefit of rhythm control in women with AF must be balanced against the risk of adverse event related to rhythm control.

5. Study limitations

This study has several limitations. First, a claims-based database was used; hence, it is not possible to evaluate the changes in AF burden before and after AF treatment, the target heart rate for rate control, and the number of patients who had reached the target heart rate. Moreover, AF diagnosis and treatment strategies were defined by ICD-10 or claim codes only; therefore, it was not possible to obtain the data regarding the AF type (paroxysmal vs. non-paroxysmal), and the presence of symptoms (symptomatic vs. asymptomatic); thus, the role of AF type and the symptom status as contributors to long-term outcomes remain unknown. Second, the findings from this observational study cannot establish causality due to unmeasured or residual confounding factors. In this study, the vast majority of patients received warfarin. Among patients treated with warfarin, the higher incidence of stroke in women could be related to a lower time in therapeutic range compared to men.[28,29] The frequency of warfarin use and labile international normalized ratio values also can explain the trend towards higher bleeding events in women in the rhythm control group.[28] Therefore, results in population treated with direct anticoagulants are additionally required. Moreover, uncontrolled lifestyle factors (such as obesity, alcohol intake, and exercise habit) might lead to the detrimental long-term outcomes in patients with AF, and it was not possible to

determine their effect. Third, radiofrequency ablation was performed as an initial rhythm control strategy in only 1.7% of men and 1.4% of women, which were significantly lower compared to the 7% in the EAST-AFNET 4 trial. The cause of this phenomenon was that the national health insurance had reimbursed the cost of treatment only to patients who were diagnosed as drug-refractory AF or could not maintain AADs due to drug-related side effects, tachycardia-bradycardia syndrome, or other conditions.[6] Considering the superiority of radiofrequency ablation over AADs for maintenance of sinus rhythm, the absence of a reasonable portion of patients treated with ablation might have significantly limited the impact of the outcomes of this study. In addition, the reduced benefit of "rhythm control therapy" in women might be attributable to AAD therapy issues rather than rhythm control strategy, as AADs carries higher risk of proarrhythmia and toxicity compared to both ablation and rate control therapy, particularly in women Therefore, further randomized trials are necessary to reflect the long-term efficacy of ablation strategy.[30,31] Fourth, the specific reasons for choosing rhythm control over rate control, and immediate over delayed initiation of treatment are difficult to be evaluated because these decisions vary by physicians. Accordingly, this ambiguity might have caused potential bias. Nevertheless, the results of the falsification analysis showed that systematic bias was less likely to exist, and sufficient overlap of propensity scores were identified between rhythm- and rate control groups, which proves the balance between the two therapies. Fifth, since we excluded patients with AF who did not undergo therapy or who had a history of AF treatment, the proportions of treatment strategies in this study may not reflect the preferences in real-world practice. Sixth, this study enrolled only high-risk patients with a mean CHA2DS2-VASc score of 3.3 using inclusion criteria similar to that of EAST-AFNET 4. Thus, further investigation is warranted to elucidate sex differences in effects of rhythm control over rate control in low-risk patients. Finally, in this study, the mean period between treatment initiation and AF diagnosis was 1.0 ± 2.2 month and only 5% of the patients were treated between 6 and 12 months after AF diagnosis. Therefore, repeated studies will be required to solidify the conclusion that sex differences influence the outcomes if AF treatment is

delayed.

V. CONCLUSION

Among patients who underwent rhythm or rate control within one year after AF diagnosis, lower risk tendency of primary composite outcome was shown in rhythm control than rate control in both sexes. However, as treatment initiation was delayed, the benefit of early rhythm control was attenuated gradually in women, while it was maintained in men. Therefore, in women, rhythm control might be taken into consideration at an earlier stage with a careful assessment of the balance between its benefit and risk of adverse event.

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ABSTRACT

심방 세동에 이환된 환자에 대한 맥박 수 조절 대비 조기 리듬 조절 치료 효과의 성별에 따른 차이

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내용

배경: 이 연구는 심방 세동 환자에 대해 맥박 수 조절 치료를 진행하는 것 대비 리듬 조절 치료를 조기 진행할 때의 상대적인 효과가 성별에 따라 달라지는 지에 대해 확인하고자 하였다. 방법: 본 연구자들은 국민건강보험 공단의 자료를 이용하여 심방 세동을 진단 받은 지 1년 이내에 이에 대한 치료를 진행한 환자들을 모집하였다. 주요 복합 결과는 심혈관계 질환에 의한 사망, 허혈성 뇌졸중의 발생, 심부전으로 인한 입원, 그리고 급성 심근 경색으로 구성되었다. 결과: 평균 4.9년의 추적 기간 동안, 여성에서는 맥박 수 조절 대비 리듬 조절 치료의 주요 복합 결과에 대한 이점이 심방 세동 진단 3개월 이내 통계적으로 유의하지 않게 되었으나 남성에서는 12개월 동안 리듬 조절 치료의 상대적인 이점이 유의하게 유지되는 경향을 보였다. 심방 세동 진단일로부터 6개월 이내 리듬 조절 치료를 시행한 경우, 두 성별에서 모두 맥박 수 조절 치료를 시행한 것 대비 더 낮은 주요 복합 결과의 위험성을 보였다 (남자: hazard ratio 0.86, 95% confidence interval 0.79–0.94; 여자: hazard ratio 0.85, 95% confidence interval 0.78–0.93; P for interaction = 0.844). 하지만, 6개월 이후 리듬 조절 치료를 시행하였을 때는, 남성에서는 맥박 수 조절 치료를 시행하는 것 대비 유의한 이점을 보였으나 여성에서는 두 치료 사이 주요 복합 결과에 대한 이점의 차이를 보이지 못했다 (남자: hazard ratio 0.72, 95% confidence interval 0.52–0.99; 여자: hazard ratio 1.32, 95% confidence interval 0.92–1.88; P for interaction = 0.018). 결론: 리듬 조절 치료를 시행한 경우, 주요 복합 결과의 위험도가 맥박 수 조절 치료 대비 더 낮은 경향을 보였으나,

여성에서는 더 이른 시점에서의 치료 개시가 필요함을 이 연구의 결과를 통해
알 수 있었다.

PUBLICATION LIST

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