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# Sex difference in atrial fibrillation recurrence after catheter ablation and antiarrhythmic drugs

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## ABSTRACT

**Objective** The risk of recurrence after atrial fibrillation (AF) catheter ablation (AFCA) is higher in women than in men. However, it is unknown whether a sex difference exists in antiarrhythmic drug (AAD) responsiveness among patients with recurrence.

**Methods** Among 2999 consecutive patients (26.5% women, 58.3±10.9 years old, 68.1% paroxysmal AF) who underwent de novo AFCA, we compared and evaluated the sex differences in rhythm outcome in 1094 patients with recurrence and in 788 patients who subsequently underwent rhythm control with AAD.

**Results** During a follow-up of 48.2±34.9 months, 1094 patients (36.5%) had AF recurrence after AFCA, and 508 of 788 patients (64.5%) had AF recurrence under AAD. Although the rhythm outcome of a de novo AFCA was worse (log-rank p=0.041, HR 1.28, 95% CI 1.02 to 1.59), p=0.031) in women, AAD response after postprocedural recurrences was better in women than in men (log-rank p=0.003, HR 0.75, 95% CI 0.59 to 0.95, p=0.022), especially in women older than 60 years old (log-rank p=0.003). In 249 patients who underwent repeat procedure after AAD use, the pulmonary vein (PV) reconnection rate (62.7% vs 76.8%, p=0.048) was lower in women than in men but not the existence of extra-PV trigger (37.8% vs 25.4%, p=0.169).

**Conclusions** Although women showed worse rhythm outcomes than men after AFCA, the post-AFCA AAD response was better in elderly women than in men.

**Trial registration number** NCT02138695.

### WHAT IS ALREADY KNOWN ON THIS SUBJECT?

⇒ The risk of atrial fibrillation (AF) recurrence after catheter ablation is higher in women than in men. However, the sex differences in antiarrhythmic drug (AAD) response among patients with recurrence after AF ablation and the mechanisms related to AAD response are unknown.

### WHAT MIGHT THIS STUDY ADD?

⇒ The AAD response of patients with post-AF catheter ablation (AFCA) recurrence was significantly better in women than in men, particularly in those older than 60 years old. The rate of pulmonary vein reconnection was significantly lower in women than in men (62.7% vs 76.8%, p=0.048) during repeat ablation after AAD use, which might be the reason for the better AAD response in women than in men after post-AFCA recurrence.

### HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE?

⇒ Women show opposite responsiveness to catheter ablation and AAD therapy compared with men with AF. In practice, some patients with postprocedural AF recurrence cannot undergo repeat ablation due to a poor general condition, advanced age or patient rejection. AAD may be an alternative for such patients.

## INTRODUCTION

Sex differences are emerging as an important issue in various cardiovascular diseases. The prevalence of atrial fibrillation (AF) has reached 1.6% in the South Korean population and is continuously increasing.[1] The incidence of AF is notably higher in men, but the proportion of women with AF increases with age.[2] Women with AF have more severe symptoms, a lower quality of life and a higher risk of stroke and mortality than men.[3] Nevertheless, a lower proportion of women receive AF catheter ablation (AFCA) compared with men.[4] AFCA not only improves AF-related symptoms, it also has positive clinical effects on reducing heart failure mortality, hospitalisations and the incidence of cerebral infarctions, in addition to improving cognitive function in patients with AF.[5–7] However, AF is a progressive disease and recurs continuously during the long-term follow-up after AFCA.[8] Repeat ablation has been found to significantly improve the rhythm outcome for recurrent AF after AFCA.[9] Nevertheless, only select patients undergo repeat ablation procedures because of economic burden or personal preference after a post-AFCA recurrence. As the Korean medical insurance does not cover all repeat AFCAs, antiarrhythmic drugs (AADs) are often used as an alternative method when the burden of recurrent AF is not high or the associated symptoms are not significant. In recurrent AF after AFCA, a better AAD response is expected due to the significantly reduced AF burden and atrial critical mass achieved by the pulmonary vein (PV) isolation (PVI) during de novo AFCA.[10] Although rhythm outcomes of both de novo and repeat AFCAs are worse in women than in men,[11] the sex differences in the efficacy and safety of AAD, to our knowledge, have not yet been studied in patients with AF recurrence after AFCA. Therefore, this study aimed

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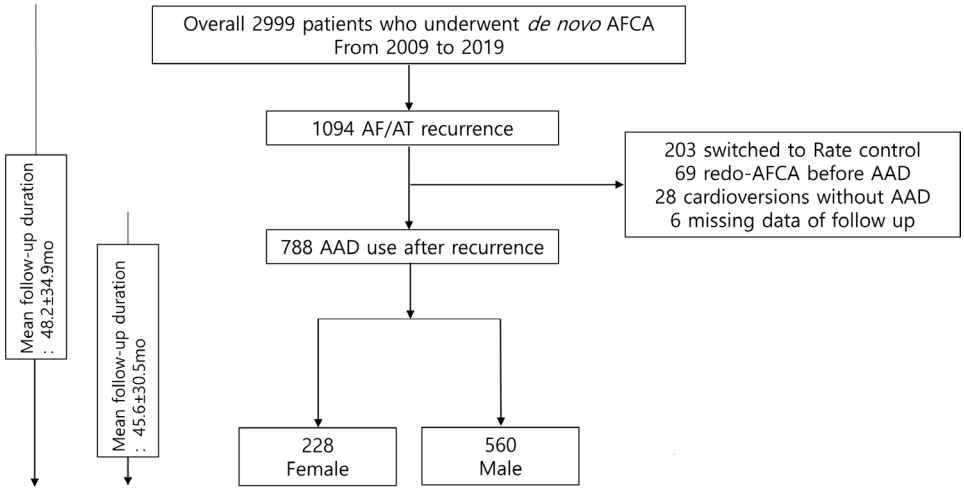


**Figure 1** Study design. AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AT, atrial tachycardia.

to evaluate the existence of a sex difference in AAD responsiveness among patients with recurrent AF after AFCA.

## METHODS

### Study population

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. We included 2999 patients, who underwent a de novo AFCA between 2009 and 2019, in the Yonsei AF ablation cohort. Of these, 1094 patients experienced clinical recurrences of AF after AFCA (figure 1). A total of 788 patients used AADs after the clinical recurrence. Patients who did not visit the outpatient clinic after clinical recurrence were excluded. We maintained rate control in patients with sinus node dysfunction, no significant symptoms or those who refused rhythm control. AF recurrence was defined as any episode of AF or atrial tachycardia lasting over 30 s.

### Electrophysiological mapping and catheter ablation

We performed electroanatomical mapping using a three-dimensional (3D) electroanatomical mapping system (NavX; Abbott Inc, Minnetonka, Minnesota, USA, or CARTO; Biosense Webster Inc, Diamond Bar, California, USA) merged with 3D spiral CT. To conduct circumferential PVI, we used an open-irrigated tip catheter (Celsius, Johnson & Johnson; Navistar ThermoCool, Biosense Webster; ThermoCool SF, Biosense Webster; ThermoCool SmartTouch, Biosense Webster; Coolflex, St. Jude Medical; FlexAbility, St. Jude Medical; and TactiCath, St. Jude Medical). After circumferential PVI, we confirmed electrical PVI and bidirectional block. Additional linear ablation, such as posteroinferior line, roof line, anterior line, left lateral isthmus line, right atrial ablation and/or complex fractionated electrograms, was performed at the operator's discretion. After completion of the circumferential PVI or extra-PV ablation, isoproterenol infusion (5–10 µg/min) was administered to map the extra-PV triggers. If mappable AF triggers or frequent premature atrial complex (PAC) were present, we carefully mapped and ablated the non-PV triggers.

### Postablation management and follow-up

The patients visited the outpatient clinic at 1, 3, 6 and 12 months and every 6 months thereafter or whenever symptoms occurred after the AFCA. According to the guidelines,[12] a rhythm follow-up was performed using ECGs and 24 hours Holter monitoring at 3, 6 and 12 months, every 6 months for 2 years, and then annually after the AFCA.[12] We identified the symptoms of the PAC and AF episodes and the percentage of PACs during Holter recordings. Moreover, we recommended ECG whenever patients had palpitation. We diagnosed clinical recurrence when an AF recurrence lasting over 30 s occurred following a 3-month blanking period.

### Management of AF recurrence

We prescribed AADs for rhythm control first for patients with AF recurrence, and then electrical cardioversion was performed unless sinus rhythm was restored. After the sinus rhythm was restored, patients using AADs underwent ECG recordings during every visit with regular 24 hours Holter monitoring in the outpatient clinic. The definition of AF recurrence after AAD use and that of AF recurrence after AFCA were the same. Repeat ablation was recommended if an atrial arrhythmia persisted during the AAD treatment or recurred after sinus rhythm conversion with AADs. Following repeat ablation, the management and follow-up schedule were the same as those after the de novo procedure.

### Statistical analysis

To compare the baseline variables, we used the Student's t-test for the continuous variables. The results of the analysis of variance are expressed as the mean±SD. Categorical variables were analysed using the Pearson's $\chi^2$ test or Fisher's exact test, with variables reported as numbers (percentage). We performed Cox regression analysis to identify the factors related to AF recurrence after de novo AFCA and AAD use. We evaluated the assumption of proportional hazard by using testing of Schoenfeld residuals. The risk of AF recurrence after de novo AFCA and AAD use was analysed using the Kaplan-Meier method. We used the median value to set the cut-off value for age. To adjust the selection bias between men and women, we conducted propensity score (PS) matching analyses. For de novo AFCA patients, we performed PS matching with a calliper 0.25 and without replacement in 1:1 ratio based on age, AF type, body surface area (BSA), left atrium (LA) diameter, left ventricular ejection fraction, the ratio of the early diastolic mitral inflow velocity to the early mitral annular velocity (E/Em) and heart failure. For the patients with AAD use, we used PS matching with a calliper 0.2 and without replacement in 1:1 ratio based on age, AF type, BSA, LA diameter, left ventricular

**Table 1** Baseline characteristics of patients with a de novo ablation

| | Overall (n=2999) | Female (n=794) | Male (n=2205) | P value |
|---|---|---|---|---|
| Age, years | 58.3±10.9 | 61.1±10.7 | 57.2±10.8 | <0.001 |
| Persistent AF (%) | 956 (31.9) | 218 (27.5) | 738 (33.5) | 0.002 |
| BSA | 1.8±0.2 | 1.6±0.1 | 1.9±0.2 | <0.001 |
| Comorbidities (%) | | | | |
| Heart failure | 352 (11.7) | 122 (15.4) | 230 (10.4) | <0.001 |
| Hypertension | 1381 (46.0) | 378 (47.6) | 1003 (45.5) | 0.324 |
| Diabetes | 453 (15.1) | 109 (13.7) | 344 (15.6) | 0.228 |
| Stroke or TIA | 337 (11.2) | 104 (13.1) | 233 (10.6) | 0.061 |
| Vascular disease | 316 (10.5) | 61 (7.7) | 255 (11.6) | 0.003 |
| $CHA_2DS_2VASc$ score | 1.7±1.5 | 2.6±1.5 | 1.4±1.4 | <0.001 |
| Non-gender $CHA_2DS_2VA$ score | 1.4±1.4 | 1.6±1.5 | 1.4±1.4 | <0.001 |
| Echocardiographic parameters | | | | |
| LA dimension, mm | 41.4±6.2 | 40.6±6.3 | 41.6±6.2 | <0.001 |
| LV ejection fraction, % | 63.1±8.4 | 64.8±8.0 | 62.5±8.4 | <0.001 |
| E/Em | 10.2±4.4 | 12.2±5.4 | 9.5±3.8 | <0.001 |
| LAA flow velocity, cm/s (n=1421) | 48.2±22.1 | 45.0±22.0 | 49.5±22.1 | 0.001 |
| LA voltage (n=2119) | 1.3±0.7 | 1.1±0.6 | 1.4±1.4 | <0.001 |
| Procedure time, min | 171.5±55.9 | 170.5±52.8 | 171.8±56.9 | 0.553 |
| Ablation time, s | 4429.5±1702.9 | 4235.4±1594.9 | 4499.4±1735.2 | <0.001 |
| Ablation lesions (%) | | | | |
| CPVI | 2999 (100) | 794 (100) | 2205 (100) | |
| CTI | 2651 (88.5) | 704 (88.9) | 1947 (88.4) | 0.771 |
| Empirical extra-PV LA ablation* | 932 (31.1) | 230 (29.0) | 702 (31.8) | 0.146 |
| Posterior box | 873 (29.1) | 217 (27.3) | 656 (29.8) | 0.214 |
| Anterior line | 633 (21.1) | 157 (19.8) | 476 (21.6) | 0.310 |
| Mitral isthmus line | 141 (4.7) | 38 (4.8) | 103 (4.7) | 0.982 |
| CFAE ablation | 140 (4.7) | 23 (2.9) | 117 (5.3) | 0.008 |
| Extra-PV trigger (n=1864) | 217 (11.6) | 86 (16.3) | 131 (9.8) | <0.001 |

Variables are presented as the mean±SD or count (percentage).
*Additional ablation lesions other than the pulmonary veins in the LA.
AF, atrial fibrillation; BSA, body surface area; CFAE, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LAA, left atrium appendage; LV, left ventricle; PV, pulmonary vein; TIA, transient ischaemic attack.

ejection fraction, E/Em, heart failure and empirical extra-PV ablation. Then, we compared the responses to de novo AFCA and AAD use between men and women, respectively. All statistical analyses were performed using SPSS (V.25; IBM Corp) for Windows and R (V.3.1.0; The R Foundation, www.R-project.org), with statistical significance set at a $p<0.05$.

## RESULTS

### Sex differences in the included population

Among the 2999 patients who underwent a de novo AFCA, 794 were women and 2205 were men (table 1). The women were older ($p<0.001$), had a lower BSA ($p<0.001$), lower proportions of a persistent type ($p=0.002$) and vascular disease ($p=0.003$), higher proportions of heart failure ($p<0.001$), smaller LA dimension ($p<0.001$), higher E/Em ($p<0.001$) and more frequent extra-PV triggers ($p<0.001$) compared with the men. Locations of extra-PV triggers are described in online supplemental table 1.

After the de novo AFCA, 1094 patients (36.5%) had recurrent AF. Online supplemental table 2 summarises the rhythm outcomes of de novo AFCA. AADs were maintained in 28.5% of patients at discharge and 38.2% of patients after 3 months of AFCA. Among 788 patients who received AADs after post-AFCA recurrence, the baseline characteristics of women compared with men were consistent with those at the time of the de novo AFCA (table 2). The time to recurrence after the de novo procedure was longer ($p=0.007$), the procedure time was shorter ($p=0.014$) and the proportion of empirical extra-PV LA ablation was lower ($p<0.001$) in women than in men (table 2). However, the incidence of extra-PV trigger during de novo AFCA did not differ between the sexes in this patient group ($p=0.217$).

### Sex difference in rhythm outcome after AFCA and AADs

The rhythm outcome of the overall de novo ablation population was poorer in women than in men during the follow-up of 48.2±34.9 months (log-rank $p=0.041$, figure 2A; off-AAD log-rank $p=0.004$; online supplemental figure 1A), but AAD response after recurrence was significantly better in women than in men (follow-up 45.6±30.5 months, log-rank $p=0.003$, figure 2B). In Cox regression analyses for AF recurrence after AFCA, female sex (HR 1.28, 95% CI 1.02 to 1.59, $p=0.031$), LA dimension (HR 1.23, 95% CI 1.11 to 1.36, $p<0.001$), extra-PV triggers (HR 1.75, 95% CI 1.39 to 2.20, $p<0.001$) and persistent AF (HR 1.40, 95% CI 1.15 to 1.71, $p=0.001$) were independently associated with AF recurrence after AFCA (table 3). In Cox regression analyses for AF recurrence after AAD among the patients with post-AFCA recurrence, being female (HR 0.75, 95% CI 0.59 to 0.96, $p=0.022$) and age (HR 0.83, 95% CI 0.76 to 0.92, $p<0.001$) had a protective effect (table 4). Therefore,

**Table 2** Baseline characteristics of patients with AAD use after AF recurrence

| | AAD user after recurrence (n=788) | Female (n=228) | Male (n=560) | P value |
|---|---|---|---|---|
| Age, years | 59.1±10.5 | 61.2±10.5 | 58.3±10.3 | <0.001 |
| Persistent AF (%) | 317 (40.2) | 68 (29.8) | 249 (44.5) | <0.001 |
| BSA | 1.8±0.2 | 1.7±0.1 | 1.9±0.2 | <0.001 |
| Total follow-up, mo | 45.6±30.5 | 42.6±27.2 | 46.8±31.7 | 0.063 |
| Time (recurrence ~de novo AFCA), mo | 21.9±22.3 | 25.3±22.4 | 20.5±22.1 | 0.007 |
| Comorbidities (%) | | | | |
| Heart failure | 94 (11.9) | 39 (17.1) | 55 (9.8) | 0.006 |
| Hypertension | 387 (49.1) | 120 (52.6) | 267 (47.7) | 0.237 |
| Diabetes | 134 (17.0) | 35 (15.4) | 99 (17.7) | 0.494 |
| Stroke or TIA | 101 (12.8) | 32 (14.0) | 69 (12.3) | 0.593 |
| Vascular disease | 99 (12.6) | 24 (10.5) | 75 (13.4) | 0.326 |
| Non-gender $CHA_2DS_2VASc$ score | 1.5±1.4 | 1.7±1.5 | 1.5±1.4 | 0.029 |
| Echocardiographic parameters | | | | |
| LA dimension, mm | 42.5±6.3 | 40.9±6.0 | 43.2±6.3 | <0.001 |
| LV ejection fraction, % | 62.6±8.3 | 63.7±8.1 | 62.2±8.3 | 0.015 |
| E/Em | 10.4±4.3 | 12.2±5.2 | 9.7±3.6 | <0.001 |
| Procedure time, min | 186.4±59.3 | 178.8±51.9 | 189.5±61.8 | 0.014 |
| Ablation time, s | 4925.8±1806.0 | 4580.1±1561.8 | 5065.7±1879.2 | <0.001 |
| Ablation lesions (%) | | | | |
| CPVI | 788 (100.0) | 228 (100.0) | 560 (100.0) | |
| CTI | 716 (91.1) | 204 (89.9) | 512 (91.6) | 0.528 |
| Empirical extra-PV LA ablation* | 329 (41.8) | 71 (31.1) | 258 (46.1) | <0.001 |
| Extra-PV trigger | 72 (14.9) | 29 (18.0) | 43 (13.3) | 0.217 |
| AAD use after recurrence (%) | | | | 0.944 |
| Class IC | 294 (37.3) | 86 (37.7) | 208 (37.1) | |
| Class III | 494 (62.7) | 142 (62.3) | 352 (62.9) | |
| Amiodarone | 269 (34.1) | 63 (27.6) | 206 (36.8) | 0.018 |

Variables are presented as the mean±SD or count (percentage).
*Additional ablation lesions other than the pulmonary veins in the LA.
AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; BSA, body surface area; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LV, left ventricle; PV, pulmonary vein; TIA, transient ischaemic attack.

female sex was a risk factor for post-AFCA recurrence but a protective factor for AF recurrence under AADs.

### Age factors

We compared rhythm outcomes depending on the median age of 60 years. AF recurrence did not differ according to age after AFCA (log-rank p=0.700, figure 2C; off-AAD log-rank p=0.080; online supplemental figure 1B) but was significantly lower in patients above 60 years of age after AAD use than their counterparts (log-rank p=0.016, figure 2D). After grouping with regard to age and sex, women younger than 60 years showed significantly poorer rhythm outcomes after de novo AFCA (log-rank p=0.004, figure 3A), whereas women older than 60 years showed significantly better rhythm outcomes after AAD use (log-rank p=0.003, figure 3B).

### Sex difference in rhythm outcome after PS matching

To minimise the selection bias between men and women, we performed PS matching (online supplemental figure 2) in de novo AFCA patients (469 women and 469 men; online supplemental table 3) and patients with AAD use (140 women and 140 men; online supplemental table 4), respectively. After the PS matching, the rhythm outcome of de novo AFCA was worse in women than in men (log-rank p=0.030; online supplemental figure 3A). However, the response to AAD after recurrence was better in women than in men (log-rank p=0.011; online supplemental figure 3B). Women younger than 60 years showed poor rhythm outcomes after de novo AFCA (log-rank p=0.026; online supplemental figure 4A), but women older than 60 years showed better AAD response than other groups (log-rank p=0.015; online supplemental figure 4B).

### AAD types, responsiveness and adverse effects

Although the proportions of class IC AAD prescribed at post-AFCA recurrence did not differ between women and men (table 2), AAD responses to class IC AAD were significantly better in women (log-rank p=0.009; online supplemental figure 5A) and in those over 60 years old (log-rank p=0.045; online supplemental figure 5C). Class III AAD responses did not differ depending on sex (log-rank p=0.075; online supplemental figure 5B) or age (log-rank p=0.071; online supplemental figure 5D).

Online supplemental table 5 summarises the duration and adverse effects of each AAD in women and men. The adverse effects of AADs did not differ between the two sexes. The most frequent adverse effects of AAD were sinus node dysfunction and thyroid dysfunction. By AAD type, amiodarone was more prescribed (p=0.018), and dronedarone was less prescribed (p=0.048) in women than in men.

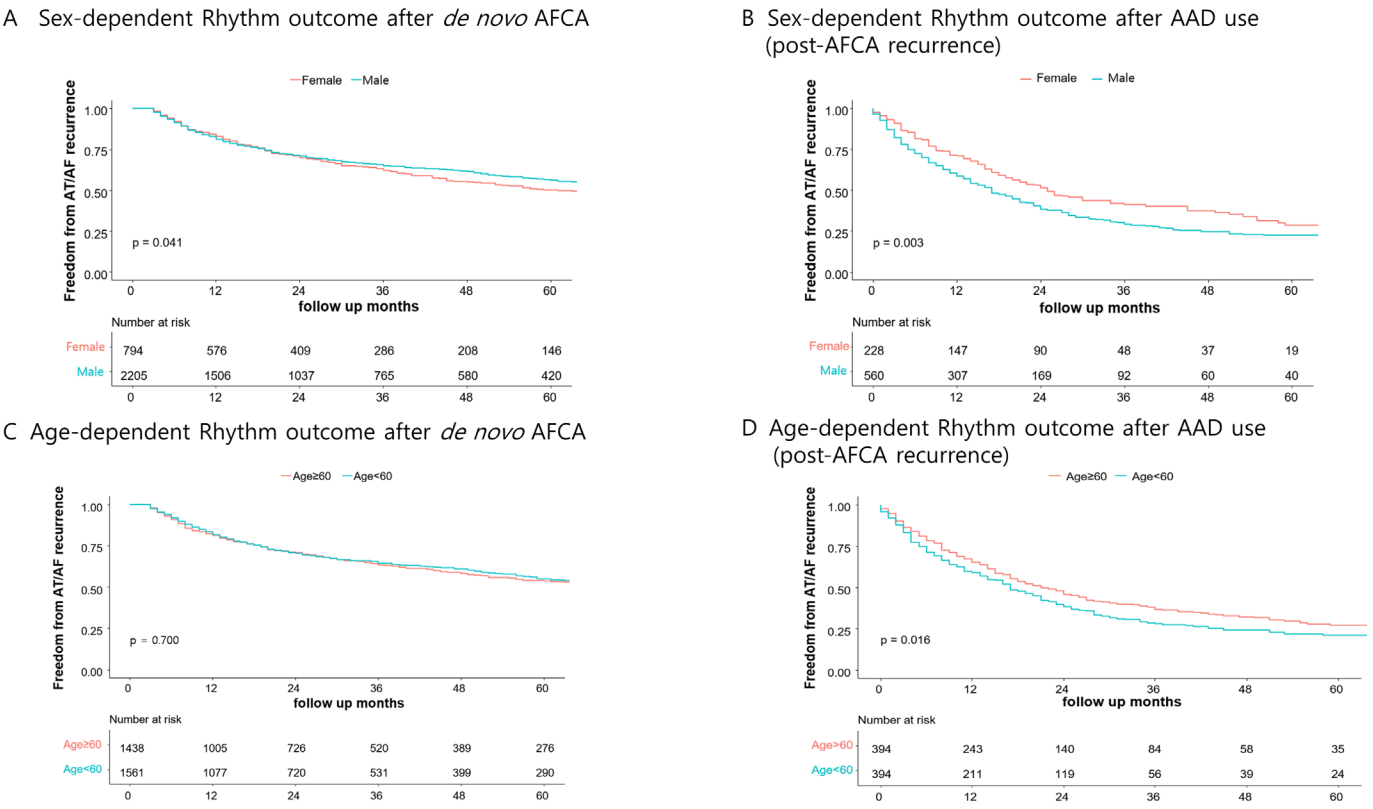


**Figure 2** Risk of AF recurrence according to the sex after the de novo AFCA (A) and AAD use in patients with AF recurrence after AFCA (B) and according to the age after de novo AFCA (C) and AAD use in patients with AF recurrence after AFCA (D). AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AT, atrial tachycardia.

### Redo-mapping findings

In 249 patients who underwent repeat procedures 34.7±26.7 months after the de novo procedure because of repeated recurrence after AAD use, the proportions of repeat ablations were 25.9% (59/228) in women and 33.9% (190/560) in men. The PV reconnection rate was significantly lower in women than in men (62.7% vs 76.8%, p=0.048), but there was no significant difference in the existence of extra-PV triggers (37.8% vs 25.4%, p=0.169, table 5).

**Table 3** Cox regression analysis of AF recurrence after de novo AFCA

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age* | 1.03 (0.97 to 1.09) | 0.389 | 1.03 (0.94 to 1.14) | 0.506 |
| Female | 1.14 (1.00 to 1.30) | 0.043 | 1.28 (1.02 to 1.59) | 0.031 |
| Persistent AF | 1.66 (1.47 to 1.87) | <0.001 | 1.40 (1.15 to 1.71) | 0.001 |
| BSA* | 0.98 (0.92 to 1.05) | 0.587 | 0.94 (0.83 to 1.07) | 0.339 |
| LA dimension, mm* | 1.28 (1.21 to 1.36) | <0.001 | 1.23 (1.11 to 1.36) | <0.001 |
| LV ejection fraction, %* | 0.94 (0.89 to 0.99) | 0.028 | | |
| E/Em* | 1.05 (0.99 to 1.12) | 0.079 | 0.92 (0.83 to 1.01) | 0.084 |
| Heart failure | 1.30 (1.09 to 1.55) | 0.004 | 1.00 (0.77 to 1.31) | 0.991 |
| Hypertension | 1.06 (0.94 to 1.20) | 0.311 | | |
| Diabetes | 1.08 (0.92 to 1.27) | 0.353 | | |
| Stroke or TIA | 1.14 (0.95 to 1.36) | 0.159 | | |
| Vascular disease | 1.05 (0.88 to 1.26) | 0.609 | 1.08 (0.85 to 1.37) | 0.540 |
| Ablation time* | 1.11 (1.05 to 1.18) | 0.001 | 1.09 (0.96 to 1.22) | 0.181 |
| Empirical extra-PV LA ablation† | 1.39 (1.23 to 1.57) | <0.001 | 1.12 (0.91 to 1.37) | 0.302 |
| Extra-PV triggers (n=1864) | 1.78 (1.44 to 2.21) | <0.001 | 1.75 (1.39 to 2.20) | <0.001 |

*Numerical data were divided by SD.
†Additional ablation lesions other than the pulmonary veins in the LA.
AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; BSA, body surface area; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrial; LV, left ventricular; PV, pulmonary vein; TIA, transient ischaemic attack.

## DISCUSSION

### Main findings

In this single-centre retrospective cohort study with a regular rhythm follow-up protocol, we found that the AAD response after post-AFCA recurrence was significantly better in women than in men, particularly older than 60 years of age using class IC AAD. This was in contrast with the outcome of the de novo AFCA, which showed worse rhythm outcomes in women than in men. Therefore, women show opposite responsiveness to catheter ablation and AAD therapy compared with men with AF.

### Sex differences in AF

The prevalence of AF is higher in men, but this progressive degenerative disease increases significantly in older women.[2] AF in older women is particularly affected by haemodynamic factors. Central aortic pressure significantly increases in women with ageing, inducing left ventricular hypertrophy and diastolic dysfunction, generating an AF vulnerable condition.[13 14] Aged women are more vulnerable to AF development and progression, and accompanying atrial structural remodelling and reduced LA appendage function are associated with a higher risk of stroke.[15] In this study, although the LA size was smaller and the proportion of paroxysmal AF was

**Table 4** Cox regression analysis of AF recurrence after AAD use

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age* | 0.89 (0.82 to 0.97) | 0.005 | 0.83 (0.76 to 0.92) | <0.001 |
| Female | 0.74 (0.61 to 0.91) | 0.003 | 0.75 (0.59 to 0.96) | 0.022 |
| Persistent AF | 1.24 (1.04 to 1.47) | 0.018 | 1.10 (0.87 to 1.38) | 0.430 |
| BSA* | 1.09 (1.00 to 1.19) | 0.047 | 0.96 (0.86 to 1.08) | 0.477 |
| LA dimension, mm* | 1.07 (0.98 to 1.16) | 0.131 | 1.00 (0.90 to 1.11) | 0.958 |
| LV ejection fraction, %†* | 0.89 (0.82 to 0.96) | 0.004 | | |
| E/Em* | 1.02 (0.93 to 1.11) | 0.740 | 1.07 (0.96 to 1.18) | 0.211 |
| Heart failure | 1.37 (1.05 to 1.78) | 0.019 | 1.34 (0.99 to 1.81) | 0.057 |
| Hypertension | 0.88 (0.74 to 1.05) | 0.158 | | |
| Diabetes | 0.97 (0.77 to 1.22) | 0.778 | | |
| Stroke or TIA | 0.91 (0.69 to 1.19) | 0.472 | | |
| Vascular disease | 0.76 (0.58 to 1.00) | 0.052 | | |
| Procedure time* | 1.11 (1.01 to 1.21) | 0.023 | 1.09 (0.99 to 1.21) | 0.095 |
| Ablation time* | 1.09 (1.00 to 1.18) | 0.063 | | |
| Empirical extra-PV LA ablation* | 1.17 (0.98 to 1.40) | 0.075 | 0.98 (0.77 to 1.25) | 0.891 |
| Extra-PV triggers | 1.13 (0.83 to 1.53) | 0.448 | | |
| Class III AAD | 1.21 (1.01 to 1.45) | 0.042 | 1.19 (0.98 to 1.44) | 0.083 |
| AMD‡ | 1.23 (1.00 to 1.50) | 0.047 | | |

*Numerical data were divided by SD.
†Additional ablation lesions other than the pulmonary veins in the LA.
‡Cox regression analysis was done for the class Ic AAD group versus amiodarone group.
AAD, antiarrhythmic drug; AF, atrial fibrillation; AMD, amiodarone; BSA, body surface area; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrial; LV, left ventricular; PV, pulmonary vein; TIA, transient ischaemic attack.

**Table 5** Procedural characteristics of repeat AFCA

| | Repeat AFCA after AAD use (n=249) | Female (n=59) | Male (n=190) | P value |
|---|---|---|---|---|
| PV reconnection (%) | 183 (73.5) | 37 (62.7) | 146 (76.8) | 0.048 |
| 1 | 51 (20.5) | 15 (25.4) | 36 (18.9) | |
| 2 | 56 (22.5) | 10 (16.9) | 46 (24.2) | |
| 3 | 37 (14.9) | 6 (10.2) | 31 (16.3) | |
| 4 | 39 (15.7) | 6 (10.2) | 33 (17.4) | |
| Extra-PV triggers (%), n=167 | 48 (28.7) | 17 (37.8) | 31 (25.4) | 0.169 |

Variables are presented as count (percentage).
AAD, antiarrhythmic drug; AFCA, atrial fibrillation catheter ablation; PV, pulmonary vein.

higher in women than in men, the rhythm outcome of de novo AFCA was worse in women than in men, consistent to the previous studies.[11 16] However, there has been no study on sex differences in AAD response in patients with post-ablation AF recurrence. In this study, although the recurrence rate after AFCA was high in women, the response to AAD was superior in women, especially in older aged women, than in men.

## Mechanisms of AF recurrence and the AAD response after AFCA

Despite the diverse and positive clinical effects of AFCA,[5–7] continuous AF recurrence after the procedure remains an unsolved issue. There are several potential mechanisms for AF recurrence after AFCA: first, insufficient ablation[17] or PV reconnection[18]; second, atrial remodelling and extra-PV triggers[19]; third, inflammation and atrial substrate progression[20]; and fourth, autonomic neural imbalance.[21] Durable PVI is an essential issue in AFCA, and updated catheter technology improved durable PVI by the ablation index-guided PVI.[22] EAST-AFNET4 trial[23] proved the importance of the early rhythm control. Shorter AF duration was associated with better rhythm outcomes of AFCA in our cohort.[24] Integrated AF management of other risk factors, such as hypertension, diabetes mellitus, obesity, obstructive sleep apnoea, dyslipidaemia and physical factors, also improves cardiovascular outcomes.[25]

AAD response is better in patients with recurrent AF after AFCA than in those without intervention.[10] Moreover, fewer PV reconnections result in a better response to AADs.[26] Prolongation of action potential duration, reduced resting membrane potential or reduced conduction velocity by AAD

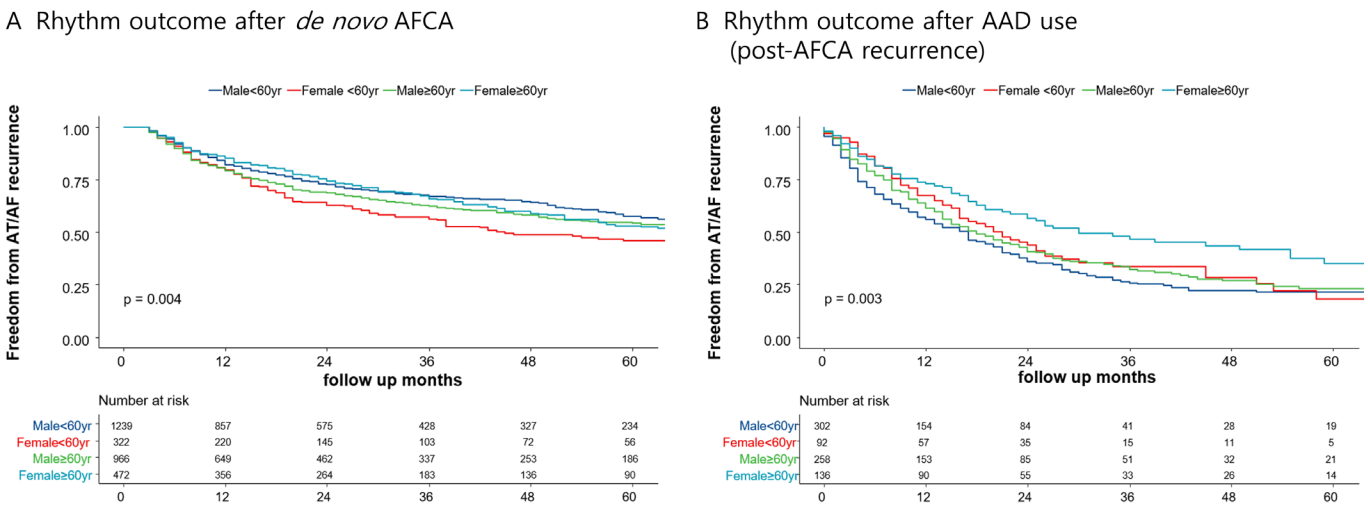


**Figure 3** Risk of AF recurrence after de novo AFCA (A) and AAD use (B) according to age and sex. AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AT, atrial tachycardia.

has an anti-AF effect on the gaps of PV reconnection, delayed conducting substrate or extra-PV triggers.

Female AF patients have a thinner antral wall thickness, more frequent extra-PV triggers and longer time to recurrence after de novo AFCA than male patients.[11 27 28] Women also show a lower PV reconnection rate and more common extra-PV triggers at repeat procedures after AF recurrence.[11 29] In our study, the PV reconnection rate was lower in women than in men during the repeat procedures after AAD use. Considering these facts, we can suggest a few reasons for superior AAD response after ablation in women than in men. First, the lower rate of PV reconnections in women indicates that progressive substrate remodelling and extra-PV triggers could be the main cause of recurrence in women. Therefore, women had a better response to AAD than men. Extra-PV triggers might be related to spontaneous calcium release,[30] so that AAD with beta-blocker activity might be more effective in women. Second, AAD appropriately controls extra-PV substrates or triggers that are more commonly found in women with relatively thin antral walls and well-maintained PVI. Third, the AAD blood concentration was potentially higher in women, who have a relatively lower BSA, than in men, even at the same AAD dose. Therefore, the effect of AAD on rhythm control was superior in women than in men, especially in those older than 60 years old, who experienced AF recurrence after catheter ablation.

### Clinical significance

Our study is clinically meaningful in that it identified the sex difference in AAD response among patients with post-AFCA recurrence and followed up for an extended period. Women, especially those above 60 years of age, showed better AAD response than men in this patient group. Lower rate of PV reconnections, more extra-PV triggers, more atrial remodelling associated with diastolic dysfunction and lower LA voltage could explain the mechanisms of the opposite response to ablation and AAD response in women and men with AF.

### Limitations

Despite these findings, this study had several limitations. First, this was a retrospective, non-randomised comparison study, and selection bias regarding the treatment could have been involved. We used PS matching to adjust some variables between the female and male groups. Second, this study was conducted at a single centre and included a relatively small number of patients; hence, the findings from this study cannot be generalised to all patients with AF. Third, the ablation lesion set was not controlled for de novo AFCA. Fourth, the type and dose of AAD were also not regulated. However, most patients used an optimal amount of AAD, and this could reduce this bias. Fifth, although we conducted a regular-based Holter follow-up, we could not evaluate the real AF burden. Sixth, with the nature of AF progression, later rhythm control might affect the rhythm outcomes. However, we could not match the index time because it was hard to determine the actual AF duration. Lastly, since patients who underwent repeat ablation were a part of patients with recurrence, it may be limited in explaining the sex difference in AAD response in recurrent patients after AFCA.

## CONCLUSION

Although women showed worse rhythm outcomes than men after AFCA, the post-AFCA AAD response was better in older women than in men.

**Correction notice** This article has been corrected since it was first published to correct a typo in Table 1.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by The study protocol adhered to the principles of the Declaration of Helsinki was approved by the Institutional Review Board of the Yonsei University Health System (4-2014-0104). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Data, analytic methods and study materials are available on reasonable request to other researchers who want to reproduce the results or replicated the procedure.



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**Supplementary Table 1. Locations of extra-PV triggers during de novo AFCA**

| | Overall (n=1864) | Female (n=528) | Male (n=1336) | P value |
|---|---|---|---|---|
| Extra-PV trigger | 217 (11.6) | 86 (16.3) | 131 (9.8) | <0.001 |
| Unmappable | 16 (7.4) | 7 (8.1) | 9 (6.9) | |
| SVC | 41 (18.9) | 21 (24.4) | 20 (15.3) | |
| RA | 29 (13.4) | 11 (12.8) | 18 (13.7) | |
| Interatrial septum | 59 (27.2) | 23 (26.7) | 36 (27.5) | |
| Coronary sinus | 36 (16.6) | 12 (14.0) | 24 (18.3) | |
| LA | 25 (11.5) | 7 (8.1) | 18 (13.7) | |
| LOM | 11 (5.1) | 5 (5.8) | 6 (4.6) | |

AFCA, atrial fibrillation catheter ablation; LA, left atrium; LOM, ligament of Marshall; PV, pulmonary vein; RA, right atrium; SVC, superior vena cava.

**Supplementary Table 2. Clinical rhythm outcomes after de novo AFCA**

| | Overall (n=2999) | Female (n=794) | Male (n=2205) | P value |
|---|---|---|---|---|
| Follow-up months | 48.2 ± 34.9 | 50.1 ± 34.2 | 47.6 ± 35.1 | 0.081 |
| Post-ABL medication | | | | |
| ACEi, or ARB, n (%) | 1024 (34.2) | 267 (33.7) | 757 (34.4) | 0.745 |
| Beta blocker, n (%) | 1122 (37.5) | 281 (35.4) | 841 (38.2) | 0.180 |
| Statin, n (%) | 936 (31.3) | 272 (34.3) | 664 (30.2) | 0.035 |
| AAD Use | | | | |
| AADs at discharge, n (%) | 853 (28.5) | 240 (30.3) | 613 (27.8) | 0.203 |
| AADs after 3 months, n (%) | 1144 (38.2) | 338 (42.6) | 806 (36.6) | 0.003 |
| AADs at final follow-up, n (%) | 981 (32.7) | 313 (39.4) | 668 (30.3) | <0.001 |
| Early recurrence, n (%) | 972 (32.4) | 269 (33.9) | 703 (31.9) | 0.324 |
| Recurrence type AF, n (% in early recur) | 665 (68.6) | 176 (65.7) | 489 (69.8) | 0.251 |
| Recurrence type AT, n (% in early recur) | 304 (31.4) | 92 (34.3) | 212 (30.2) | 0.251 |
| Clinical recurrence, n (%) | 1094 (36.5) | 326 (41.1) | 768 (34.8) | 0.002 |
| AF recurrence, n (% in recur/% in overall) | 790 (72.2/26.3) | 233 (71.5/29.3) | 557 (72.5/25.3) | 0.778 |
| AT recurrence, n (% in recur/% in overall) | 304 (27.8/10.1) | 93 (28.5/11.7) | 211 (27.5/9.6) | 0.778 |
| Cardioversion, n (% in recur/% in overall) | 310 (28.3/10.3) | 77 (23.6/9.7) | 233 (30.3/10.6) | 0.029 |

AAD antiarrhythmic drug; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; ARB, angiotensin receptor blocker; AT, atrial tachycardia.

**Supplementary Table 3. Baseline characteristics of patients with a de novo ablation before and after propensity score matching**

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall (n=2999) | Female (n=794) | Male (n=2205) | P value | Overall (n=938) | Female (n=469) | Male (n=469) | P value |
| Age, years | 58.3 ± 10.9 | 61.1 ± 10.7 | 57.2 ± 10.8 | <0.001 | 61.7 ± 10.0 | 61.7 ± 9.9 | 61.8 ± 10.2 | 0.930 |
| Persistent AF (%) | 956 (31.9) | 218 (27.5) | 738 (33.5) | 0.002 | 251 (26.8) | 122 (26.0) | 129 (27.5) | 0.658 |
| BSA | 1.8 ± 0.2 | 1.6 ± 0.1 | 1.9 ± 0.2 | <0.001 | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.1 | 0.065 |
| Comorbidities (%) | | | | | | | | |
| Heart failure | 352 (11.7) | 122 (15.4) | 230 (10.4) | <0.001 | 93 ( 9.9) | 52 (11.1) | 41 ( 8.7) | 0.275 |
| Hypertension | 1381 (46.0) | 378 (47.6) | 1003 (45.5) | 0.324 | 453 (48.3) | 242 (51.6) | 211 (45.0) | 0.050 |
| Diabetes | 453 (15.1) | 109 (13.7) | 344 (15.6) | 0.228 | 149 (15.9) | 72 (15.4) | 77 (16.4) | 0.721 |
| Stroke or TIA | 337 (11.2) | 104 (13.1) | 233 (10.6) | 0.061 | 113 (12.0) | 54 (11.5) | 59 (12.6) | 0.688 |
| Vascular disease | 316 (10.5) | 61 ( 7.7) | 255 (11.6) | 0.003 | 101 (10.8) | 36 ( 7.7) | 65 (13.9) | 0.003 |
| $CHA_2DS_2VASc$ score | 1.7 ± 1.5 | 2.6 ± 1.5 | 1.4 ± 1.4 | <0.001 | 2.1 ± 1.5 | 2.6 ± 1.5 | 1.6 ± 1.5 | <0.001 |
| Non-Gender $CHA_2DS_2VA$ score | 1.4 ± 1.4 | 1.6 ± 1.5 | 1.4 ± 1.4 | <0.001 | 1.6 ± 1.5 | 1.6 ± 1.5 | 1.6 ± 1.5 | 0.755 |
| Echocardiographic parameters | | | | | | | | |
| LA dimension, mm | 41.4 ± 6.2 | 40.6 ± 6.3 | 41.6 ± 6.2 | <0.001 | 40.4 ± 6.0 | 40.4 ± 5.7 | 40.5 ± 6.3 | 0.911 |
| LV ejection fraction, % | 63.1 ± 8.4 | 64.8 ± 8.0 | 62.5 ± 8.4 | <0.001 | 64.5 ± 7.6 | 64.4 ± 7.3 | 64.7 ± 7.9 | 0.460 |
| E/Em | 10.2 ± 4.4 | 12.2 ± 5.4 | 9.5 ± 3.8 | <0.001 | 11.1 ± 4.7 | 11.2 ± 4.0 | 11.1 ± 5.3 | 0.855 |
| LAA flow velocity, cm/s (n=1421) | 48.2 ± 22.1 | 45.0 ± 22.0 | 49.5 ± 22.1 | 0.001 | 47.5 ± 21.4 | 46.7 ± 20.8 | 48.1 ± 22.0 | 0.492 |
| LA voltage (n=2119) | 1.3 ± 0.7 | 1.1 ± 0.6 | 1.4 ± 1.4 | <0.001 | 1.3 ± 0.6 | 1.2 ± 0.6 | 1.4 ± 0.6 | 0.005 |
| Procedure time, min | 171.5 ± 55.9 | 170.5 ± 52.8 | 171.8 ± 56.9 | 0.553 | 171.0 ± 53.5 | 168.6 ± 51.5 | 173.3 ± 55.3 | 0.175 |
| Ablation time, s | 4429.5 ± 1702.9 | 4235.4 ± 1594.9 | 4499.4 ± 1735.2 | <0.001 | 4348.0 ± 1602.6 | 4212.0 ± 1547.2 | 4484.0 ± 1646.5 | 0.009 |
| Ablation lesions (%) | | | | | | | | |
| CPVI | 2999 (100) | 794 (100) | 2201 (100) | | 938 (100.0) | 469 (100.0) | 469 (100.0) | |
| CTI | 2651 (88.5) | 704 (88.9) | 1947 (88.4) | 0.771 | 839 (89.6) | 414 (88.7) | 425 (90.6) | 0.379 |
| Empirical extra-PV LA ablation* | 932 (31.1) | 230 (29.0) | 702 (31.8) | 0.146 | 259 (27.6) | 119 (25.4) | 140 (29.9) | 0.144 |
| Posterior box | 873 (29.1) | 217 (27.3) | 656 (29.8) | 0.214 | 239 (25.5) | 111 (23.7) | 128 (27.3) | 0.231 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Anterior line | 633 (21.1) | 157 (19.8) | 476 (21.6) | 0.310 | 166 (17.7) | 75 (16.1) | 91 (19.4) | 0.210 |
| Mitral isthmus line | 141 (4.7) | 38 (4.8) | 103 (4.7) | 0.982 | 38 ( 4.1) | 17 ( 3.6) | 21 ( 4.5) | 0.615 |
| CFAE ablation | 140 (4.7) | 23 (2.9) | 117 (5.3) | 0.008 | 41 ( 4.4) | 16 ( 3.4) | 25 ( 5.3) | 0.204 |
| Extra-PV trigger (n=1864) | 217 (11.6) | 86 (16.3) | 131 (9.8) | <0.001 | 80 (12.5) | 46 (14.5) | 34 (10.5) | 0.160 |

AF, atrial fibrillation; BSA, body surface area; CFAE, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LAA, left atrium appendage; LV, left ventricle; PV, pulmonary vein; TIA, transient ischemic attack.

* Additional ablation lesions other than the pulmonary veins in the LA.

Variables are presented as the mean ± standard deviation or count (percentage)

**Supplementary Table 4. Baseline characteristics of patients with AAD use after AF recurrence before and after propensity score matching**

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | AAD user after recurrence (n=788) | Female (n=228) | Male (n=560) | P value | AAD user after recurrence (n=280) | Female (n=140) | Male (n=140) | P value |
| Age, years | 59.1 ± 10.5 | 61.2 ± 10.5 | 58.3 ± 10.3 | <0.001 | 62.2 ± 9.6 | 62.1 ± 9.1 | 62.3 ± 10.2 | 0.892 |
| Persistent AF (%) | 317 (40.2) | 68 (29.8) | 249 (44.5) | <0.001 | 89 (31.8) | 46 (32.9) | 43 (30.7) | 0.797 |
| BSA | 1.8 ± 0.2 | 1.7 ± 0.1 | 1.9 ± 0.2 | <0.001 | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.1 | 0.519 |
| Total follow up, mo | 45.6 ± 30.5 | 42.6 ± 27.2 | 46.8 ± 31.7 | 0.063 | 45.8 ± 28.5 | 44.1 ± 27.0 | 47.5 ± 30.0 | 0.320 |
| Time (recurrence ~ *de novo* AFCA), mo | 21.9 ± 22.3 | 25.3 ± 22.4 | 20.5 ± 22.1 | 0.007 | 23.8 ± 23.6 | 25.5 ± 23.7 | 22.0 ± 23.4 | 0.222 |
| Comorbidities (%) | | | | | | | | |
| Heart failure | 94 (11.9) | 39 (17.1) | 55 (9.8) | 0.006 | 32 (11.4) | 17 (12.1) | 15 (10.7) | 0.851 |
| Hypertension | 387 (49.1) | 120 (52.6) | 267 (47.7) | 0.237 | 140 (50.0) | 80 (57.1) | 60 (42.9) | 0.023 |
| Diabetes | 134 (17.0) | 35 (15.4) | 99 (17.7) | 0.494 | 52 (18.6) | 24 (17.1) | 28 (20.0) | 0.645 |
| Stroke or TIA | 101 (12.8) | 32 (14.0) | 69 (12.3) | 0.593 | 37 (13.2) | 19 (13.6) | 18 (12.9) | 1.000 |
| Vascular disease | 99 (12.6) | 24 (10.5) | 75 (13.4) | 0.326 | 41 (14.6) | 17 (12.1) | 24 (17.1) | 0.310 |
| Non-gender $CHA_2DS_2VASc$ score | 1.5 ± 1.4 | 1.7 ± 1.5 | 1.5 ± 1.4 | 0.029 | 1.8 ± 1.5 | 1.8 ± 1.5 | 1.7 ± 1.5 | 0.872 |
| Echocardiographic parameters | | | | | | | | |
| LA dimension, mm | 42.5 ± 6.3 | 40.9 ± 6.0 | 43.2 ± 6.3 | <0.001 | 41.3 ± 5.8 | 41.3 ± 5.4 | 41.2 ± 6.1 | 0.925 |
| LV ejection fraction, % | 62.6 ± 8.3 | 63.7 ± 8.1 | 62.2 ± 8.3 | 0.015 | 63.9 ± 7.7 | 64.1 ± 7.8 | 63.6 ± 7.7 | 0.564 |
| E/Em | 10.4 ± 4.3 | 12.2 ± 5.2 | 9.7 ± 3.6 | <0.001 | 11.1 ± 4.1 | 10.9 ± 3.3 | 11.3 ± 4.7 | 0.364 |
| Procedure time, min | 186.4 ± 59.3 | 178.8 ± 51.9 | 189.5 ± 61.8 | 0.014 | 181.0 ± 50.3 | 181.4 ± 46.0 | 180.6 ± 54.4 | 0.898 |
| Ablation time, s | 4925.8 ± 1806.0 | 4580.1 ± 1561.8 | 5065.7 ± 1879.2 | <0.001 | 4745.1 ± 1541.0 | 4786.2 ± 1415.1 | 4704.6 ± 1659.8 | 0.660 |
| Ablation lesions (%) | | | | | | | | |
| CPVI | 788 (100.0) | 228 (100.0) | 560 (100.0) | | 280 (100.0) | 140 (100.0) | 140 (100.0) | |
| CTI | 716 (91.1) | 204 (89.9) | 512 (91.6) | 0.528 | 258 (92.5) | 128 (92.1) | 130 (92.9) | 0.986 |
| Empirical extra-PV LA ablation* | 329 (41.8) | 71 (31.1) | 258 (46.1) | <0.001 | 95 (33.9) | 46 (32.9) | 49 (35.0) | 0.801 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Extra-PV trigger | 72 (14.9) | 29 (18.0) | 43 (13.3) | 0.217 | 30 (15.2) | 16 (14.8) | 14 (15.7) | 1.000 |
| AAD use after recurrence (%) | | | | 0.944 | | | | 1.000 |
| Class IC | 294 (37.3) | 86 (37.7) | 208 (37.1) | | 98 (35.0 | 49 (35.0) | 49 (35.0) | |
| Class III | 494 (62.7) | 142 (62.3) | 352 (62.9) | | 182 (65.0) | 91 (65.0) | 91 (65.0) | |
| Amiodarone | 269 (34.1) | 63 (27.6) | 206 (36.8) | 0.018 | 88 (31.4) | 39 (27.9) | 49 (35.0) | 0.247 |

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; BSA, body surface area; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LV, left ventricle; PV, pulmonary vein; TIA, transient ischemic attack.

* Additional ablation lesions other than the pulmonary veins in the LA.

Variables are presented as the mean ± standard deviation or count (percentage)

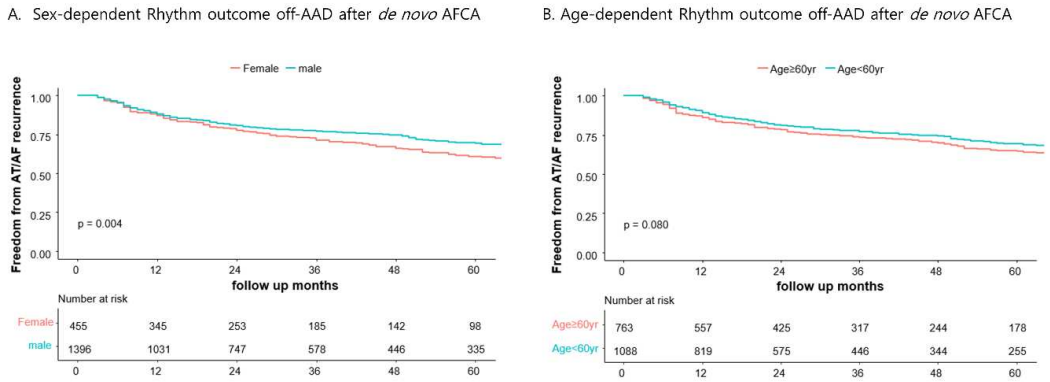
**Supplementary Table 5. Adverse effects and types of AADs**

| | Overall (n=788) | Female (n=228) | Male (n=560) | P value |
|---|---|---|---|---|
| Side effects of AADs | 107 (13.6) | 33 (14.5) | 74 (13.2) | 0.724 |
| Thyroid dysfunction | 44 (5.6) | 11 (4.8) | 33 (5.9) | |
| Liver function test abnormality | 14 (1.8) | 3 (1.3) | 11 (2.0) | |
| QT prolongation | 1 (0.1) | 0 (0) | 1 (0.2) | |
| Sinus node dysfunction | 35 (4.4) | 13 (5.7) | 22 (3.9) | |
| Interstitial pulmonary fibrosis | 2 (0.3) | 1 (0.4) | 1 (0.2) | |
| Others* | 11 (1.4) | 5 (2.2) | 6 (1.1) | |
| Duration of AAD use, mo | 23.6 ± 23.7 | 24.1 ± 20.8 | 23.4 ± 24.8 | 0.702 |
| Flecainide (%) | 256 (31.6) | 75 (32.9) | 181 (32.3) | 0.943 |
| Propafenone (%) | 31 (3.8) | 10 (4.4) | 21 (3.8) | 0.830 |
| Pilsicainide (%) | 5 (0.6) | 1 (0.4) | 4 (0.7) | 1.000 |
| Amiodarone (%) | 269 (34.1) | 63 (27.6) | 206 (36.8) | 0.018 |
| Dronedarone (%) | 157 (19.4) | 56 (24.6) | 101 (18.0) | 0.048 |
| Soltalol (%) | 70 (8.7) | 24 (10.5) | 46 (8.2) | 0.370 |

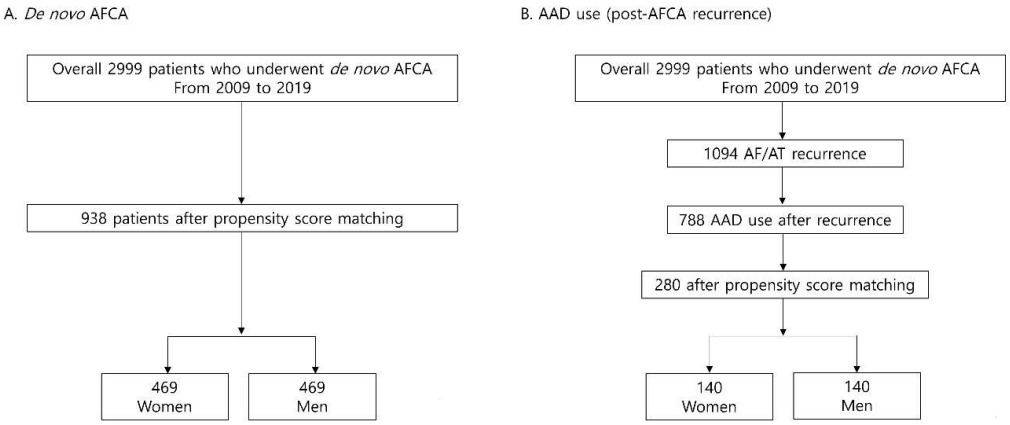
AAD, antiarrhythmic drug.

* Dyspnea, bradycardia, urticarial, edema.

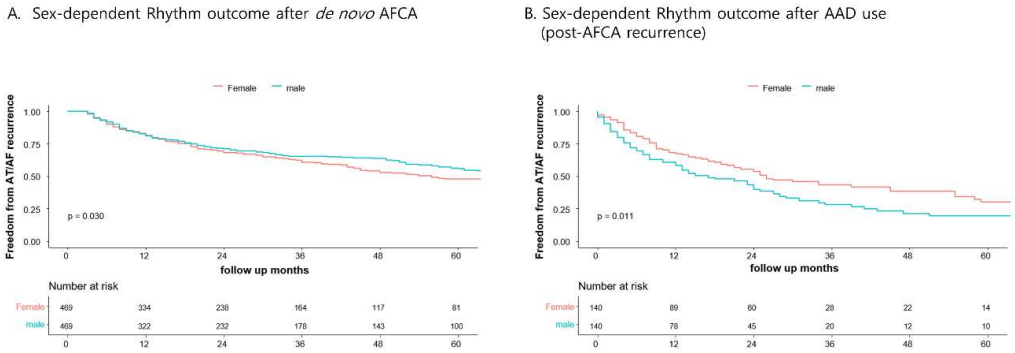
**Supplementary Figure 1. Risk of AF recurrence without AAD according to the sex after the d*e novo* AFCA (A) and according to age after d*e novo* AFCA (B).** AAD, antiarrhythmic drug; AT, atrial tachycardia; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation.



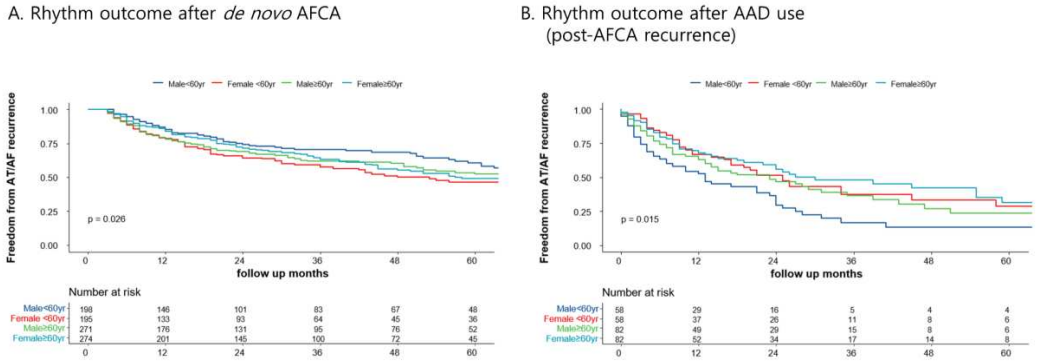
**Supplementary Figure 2. Propensity score matching in each group.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



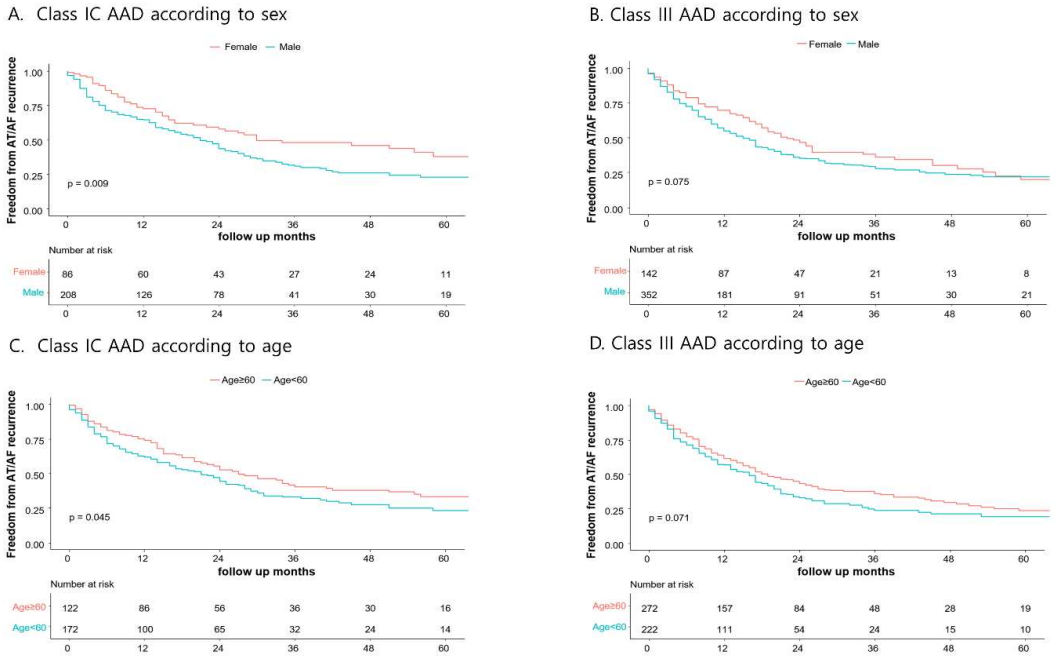
**Supplementary Figure 3. AF recurrence according to the sex after the de novo AFCA (A) and AAD use in patients with AF recurrence after AFCA (B) and according to the age after de novo AFCA.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



**Supplementary Figure 4. AF recurrence after De novo AFCA (A) and AAD use (B) according to the age and sex.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



**Supplementary Figure 5. Risk of AF recurrence after AAD use according to the sex in the group with Class IC AADs (A) and Class III AADs (B) and the age in the group with Class I AADs (C) and Class III AADs (D).** AAD, antiarrhythmic drug; AF, atrial fibrillation.



**Supplementary Table 1. Locations of extra-PV triggers during de novo AFCA**

| | Overall (n=1864) | Female (n=528) | Male (n=1336) | P value |
|---|---|---|---|---|
| Extra-PV trigger | 217 (11.6) | 86 (16.3) | 131 (9.8) | <0.001 |
| Unmappable | 16 (7.4) | 7 (8.1) | 9 (6.9) | |
| SVC | 41 (18.9) | 21 (24.4) | 20 (15.3) | |
| RA | 29 (13.4) | 11 (12.8) | 18 (13.7) | |
| Interatrial septum | 59 (27.2) | 23 (26.7) | 36 (27.5) | |
| Coronary sinus | 36 (16.6) | 12 (14.0) | 24 (18.3) | |
| LA | 25 (11.5) | 7 (8.1) | 18 (13.7) | |
| LOM | 11 (5.1) | 5 (5.8) | 6 (4.6) | |

AFCA, atrial fibrillation catheter ablation; LA, left atrium; LOM, ligament of Marshall; PV, pulmonary vein; RA, right atrium; SVC, superior vena cava.

**Supplementary Table 2. Clinical rhythm outcomes after de novo AFCA**

| | Overall (n=2999) | Female (n=794) | Male (n=2205) | P value |
|---|---|---|---|---|
| Follow-up months | 48.2 ± 34.9 | 50.1 ± 34.2 | 47.6 ± 35.1 | 0.081 |
| Post-ABL medication | | | | |
| ACEi, or ARB, n (%) | 1024 (34.2) | 267 (33.7) | 757 (34.4) | 0.745 |
| Beta blocker, n (%) | 1122 (37.5) | 281 (35.4) | 841 (38.2) | 0.180 |
| Statin, n (%) | 936 (31.3) | 272 (34.3) | 664 (30.2) | 0.035 |
| AAD Use | | | | |
| AADs at discharge, n (%) | 853 (28.5) | 240 (30.3) | 613 (27.8) | 0.203 |
| AADs after 3 months, n (%) | 1144 (38.2) | 338 (42.6) | 806 (36.6) | 0.003 |
| AADs at final follow-up, n (%) | 981 (32.7) | 313 (39.4) | 668 (30.3) | <0.001 |
| Early recurrence, n (%) | 972 (32.4) | 269 (33.9) | 703 (31.9) | 0.324 |
| Recurrence type AF, n (% in early recur) | 665 (68.6) | 176 (65.7) | 489 (69.8) | 0.251 |
| Recurrence type AT, n (% in early recur) | 304 (31.4) | 92 (34.3) | 212 (30.2) | 0.251 |
| Clinical recurrence, n (%) | 1094 (36.5) | 326 (41.1) | 768 (34.8) | 0.002 |
| AF recurrence, n (% in recur/% in overall) | 790 (72.2/26.3) | 233 (71.5/29.3) | 557 (72.5/25.3) | 0.778 |
| AT recurrence, n (% in recur/% in overall) | 304 (27.8/10.1) | 93 (28.5/11.7) | 211 (27.5/9.6) | 0.778 |
| Cardioversion, n (% in recur/% in overall) | 310 (28.3/10.3) | 77 (23.6/9.7) | 233 (30.3/10.6) | 0.029 |

AAD antiarrhythmic drug; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; ARB, angiotensin receptor blocker; AT, atrial tachycardia.

**Supplementary Table 3. Baseline characteristics of patients with a de novo ablation before and after propensity score matching**

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall (n=2999) | Female (n=794) | Male (n=2205) | P value | Overall (n=938) | Female (n=469) | Male (n=469) | P value |
| Age, years | 58.3 ± 10.9 | 61.1 ± 10.7 | 57.2 ± 10.8 | <0.001 | 61.7 ± 10.0 | 61.7 ± 9.9 | 61.8 ± 10.2 | 0.930 |
| Persistent AF (%) | 956 (31.9) | 218 (27.5) | 738 (33.5) | 0.002 | 251 (26.8) | 122 (26.0) | 129 (27.5) | 0.658 |
| BSA | 1.8 ± 0.2 | 1.6 ± 0.1 | 1.9 ± 0.2 | <0.001 | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.1 | 0.065 |
| Comorbidities (%) | | | | | | | | |
| Heart failure | 352 (11.7) | 122 (15.4) | 230 (10.4) | <0.001 | 93 ( 9.9) | 52 (11.1) | 41 ( 8.7) | 0.275 |
| Hypertension | 1381 (46.0) | 378 (47.6) | 1003 (45.5) | 0.324 | 453 (48.3) | 242 (51.6) | 211 (45.0) | 0.050 |
| Diabetes | 453 (15.1) | 109 (13.7) | 344 (15.6) | 0.228 | 149 (15.9) | 72 (15.4) | 77 (16.4) | 0.721 |
| Stroke or TIA | 337 (11.2) | 104 (13.1) | 233 (10.6) | 0.061 | 113 (12.0) | 54 (11.5) | 59 (12.6) | 0.688 |
| Vascular disease | 316 (10.5) | 61 ( 7.7) | 255 (11.6) | 0.003 | 101 (10.8) | 36 ( 7.7) | 65 (13.9) | 0.003 |
| $CHA_2DS_2VASc$ score | 1.7 ± 1.5 | 2.6 ± 1.5 | 1.4 ± 1.4 | <0.001 | 2.1 ± 1.5 | 2.6 ± 1.5 | 1.6 ± 1.5 | <0.001 |
| Non-Gender $CHA_2DS_2VA$ score | 1.4 ± 1.4 | 1.6 ± 1.5 | 1.4 ± 1.4 | <0.001 | 1.6 ± 1.5 | 1.6 ± 1.5 | 1.6 ± 1.5 | 0.755 |
| Echocardiographic parameters | | | | | | | | |
| LA dimension, mm | 41.4 ± 6.2 | 40.6 ± 6.3 | 41.6 ± 6.2 | <0.001 | 40.4 ± 6.0 | 40.4 ± 5.7 | 40.5 ± 6.3 | 0.911 |
| LV ejection fraction, % | 63.1 ± 8.4 | 64.8 ± 8.0 | 62.5 ± 8.4 | <0.001 | 64.5 ± 7.6 | 64.4 ± 7.3 | 64.7 ± 7.9 | 0.460 |
| E/Em | 10.2 ± 4.4 | 12.2 ± 5.4 | 9.5 ± 3.8 | <0.001 | 11.1 ± 4.7 | 11.2 ± 4.0 | 11.1 ± 5.3 | 0.855 |
| LAA flow velocity, cm/s (n=1421) | 48.2 ± 22.1 | 45.0 ± 22.0 | 49.5 ± 22.1 | 0.001 | 47.5 ± 21.4 | 46.7 ± 20.8 | 48.1 ± 22.0 | 0.492 |
| LA voltage (n=2119) | 1.3 ± 0.7 | 1.1 ± 0.6 | 1.4 ± 1.4 | <0.001 | 1.3 ± 0.6 | 1.2 ± 0.6 | 1.4 ± 0.6 | 0.005 |
| Procedure time, min | 171.5 ± 55.9 | 170.5 ± 52.8 | 171.8 ± 56.9 | 0.553 | 171.0 ± 53.5 | 168.6 ± 51.5 | 173.3 ± 55.3 | 0.175 |
| Ablation time, s | 4429.5 ± 1702.9 | 4235.4 ± 1594.9 | 4499.4 ± 1735.2 | <0.001 | 4348.0 ± 1602.6 | 4212.0 ± 1547.2 | 4484.0 ± 1646.5 | 0.009 |
| Ablation lesions (%) | | | | | | | | |
| CPVI | 2999 (100) | 794 (100) | 2201 (100) | | 938 (100.0) | 469 (100.0) | 469 (100.0) | |
| CTI | 2651 (88.5) | 704 (88.9) | 1947 (88.4) | 0.771 | 839 (89.6) | 414 (88.7) | 425 (90.6) | 0.379 |
| Empirical extra-PV LA ablation* | 932 (31.1) | 230 (29.0) | 702 (31.8) | 0.146 | 259 (27.6) | 119 (25.4) | 140 (29.9) | 0.144 |
| Posterior box | 873 (29.1) | 217 (27.3) | 656 (29.8) | 0.214 | 239 (25.5) | 111 (23.7) | 128 (27.3) | 0.231 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Anterior line | 633 (21.1) | 157 (19.8) | 476 (21.6) | 0.310 | 166 (17.7) | 75 (16.1) | 91 (19.4) | 0.210 |
| Mitral isthmus line | 141 (4.7) | 38 (4.8) | 103 (4.7) | 0.982 | 38 ( 4.1) | 17 ( 3.6) | 21 ( 4.5) | 0.615 |
| CFAE ablation | 140 (4.7) | 23 (2.9) | 117 (5.3) | 0.008 | 41 ( 4.4) | 16 ( 3.4) | 25 ( 5.3) | 0.204 |
| Extra-PV trigger (n=1864) | 217 (11.6) | 86 (16.3) | 131 (9.8) | <0.001 | 80 (12.5) | 46 (14.5) | 34 (10.5) | 0.160 |

AF, atrial fibrillation; BSA, body surface area; CFAE, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LAA, left atrium appendage; LV, left ventricle; PV, pulmonary vein; TIA, transient ischemic attack.

* Additional ablation lesions other than the pulmonary veins in the LA.

Variables are presented as the mean ± standard deviation or count (percentage)

**Supplementary Table 4. Baseline characteristics of patients with AAD use after AF recurrence before and after propensity score matching**

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | AAD user after recurrence (n=788) | Female (n=228) | Male (n=560) | P value | AAD user after recurrence (n=280) | Female (n=140) | Male (n=140) | P value |
| Age, years | 59.1 ± 10.5 | 61.2 ± 10.5 | 58.3 ± 10.3 | <0.001 | 62.2 ± 9.6 | 62.1 ± 9.1 | 62.3 ± 10.2 | 0.892 |
| Persistent AF (%) | 317 (40.2) | 68 (29.8) | 249 (44.5) | <0.001 | 89 (31.8) | 46 (32.9) | 43 (30.7) | 0.797 |
| BSA | 1.8 ± 0.2 | 1.7 ± 0.1 | 1.9 ± 0.2 | <0.001 | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.1 | 0.519 |
| Total follow up, mo | 45.6 ± 30.5 | 42.6 ± 27.2 | 46.8 ± 31.7 | 0.063 | 45.8 ± 28.5 | 44.1 ± 27.0 | 47.5 ± 30.0 | 0.320 |
| Time (recurrence ~ *de novo* AFCA), mo | 21.9 ± 22.3 | 25.3 ± 22.4 | 20.5 ± 22.1 | 0.007 | 23.8 ± 23.6 | 25.5 ± 23.7 | 22.0 ± 23.4 | 0.222 |
| Comorbidities (%) | | | | | | | | |
| Heart failure | 94 (11.9) | 39 (17.1) | 55 (9.8) | 0.006 | 32 (11.4) | 17 (12.1) | 15 (10.7) | 0.851 |
| Hypertension | 387 (49.1) | 120 (52.6) | 267 (47.7) | 0.237 | 140 (50.0) | 80 (57.1) | 60 (42.9) | 0.023 |
| Diabetes | 134 (17.0) | 35 (15.4) | 99 (17.7) | 0.494 | 52 (18.6) | 24 (17.1) | 28 (20.0) | 0.645 |
| Stroke or TIA | 101 (12.8) | 32 (14.0) | 69 (12.3) | 0.593 | 37 (13.2) | 19 (13.6) | 18 (12.9) | 1.000 |
| Vascular disease | 99 (12.6) | 24 (10.5) | 75 (13.4) | 0.326 | 41 (14.6) | 17 (12.1) | 24 (17.1) | 0.310 |
| Non-gender $CHA_2DS_2VASc$ score | 1.5 ± 1.4 | 1.7 ± 1.5 | 1.5 ± 1.4 | 0.029 | 1.8 ± 1.5 | 1.8 ± 1.5 | 1.7 ± 1.5 | 0.872 |
| Echocardiographic parameters | | | | | | | | |
| LA dimension, mm | 42.5 ± 6.3 | 40.9 ± 6.0 | 43.2 ± 6.3 | <0.001 | 41.3 ± 5.8 | 41.3 ± 5.4 | 41.2 ± 6.1 | 0.925 |
| LV ejection fraction, % | 62.6 ± 8.3 | 63.7 ± 8.1 | 62.2 ± 8.3 | 0.015 | 63.9 ± 7.7 | 64.1 ± 7.8 | 63.6 ± 7.7 | 0.564 |
| E/Em | 10.4 ± 4.3 | 12.2 ± 5.2 | 9.7 ± 3.6 | <0.001 | 11.1 ± 4.1 | 10.9 ± 3.3 | 11.3 ± 4.7 | 0.364 |
| Procedure time, min | 186.4 ± 59.3 | 178.8 ± 51.9 | 189.5 ± 61.8 | 0.014 | 181.0 ± 50.3 | 181.4 ± 46.0 | 180.6 ± 54.4 | 0.898 |
| Ablation time, s | 4925.8 ± 1806.0 | 4580.1 ± 1561.8 | 5065.7 ± 1879.2 | <0.001 | 4745.1 ± 1541.0 | 4786.2 ± 1415.1 | 4704.6 ± 1659.8 | 0.660 |
| Ablation lesions (%) | | | | | | | | |
| CPVI | 788 (100.0) | 228 (100.0) | 560 (100.0) | | 280 (100.0) | 140 (100.0) | 140 (100.0) | |
| CTI | 716 (91.1) | 204 (89.9) | 512 (91.6) | 0.528 | 258 (92.5) | 128 (92.1) | 130 (92.9) | 0.986 |
| Empirical extra-PV LA ablation* | 329 (41.8) | 71 (31.1) | 258 (46.1) | <0.001 | 95 (33.9) | 46 (32.9) | 49 (35.0) | 0.801 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Extra-PV trigger | 72 (14.9) | 29 (18.0) | 43 (13.3) | 0.217 | 30 (15.2) | 16 (14.8) | 14 (15.7) | 1.000 |
| AAD use after recurrence (%) | | | | 0.944 | | | | 1.000 |
| Class IC | 294 (37.3) | 86 (37.7) | 208 (37.1) | | 98 (35.0 | 49 (35.0) | 49 (35.0) | |
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| Amiodarone | 269 (34.1) | 63 (27.6) | 206 (36.8) | 0.018 | 88 (31.4) | 39 (27.9) | 49 (35.0) | 0.247 |

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; BSA, body surface area; CPVI, circumferential pulmonary vein isolation; CTI, carvotricuspid isthmus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early mitral annular velocity (Em); LA, left atrium; LV, left ventricle; PV, pulmonary vein; TIA, transient ischemic attack.

* Additional ablation lesions other than the pulmonary veins in the LA.

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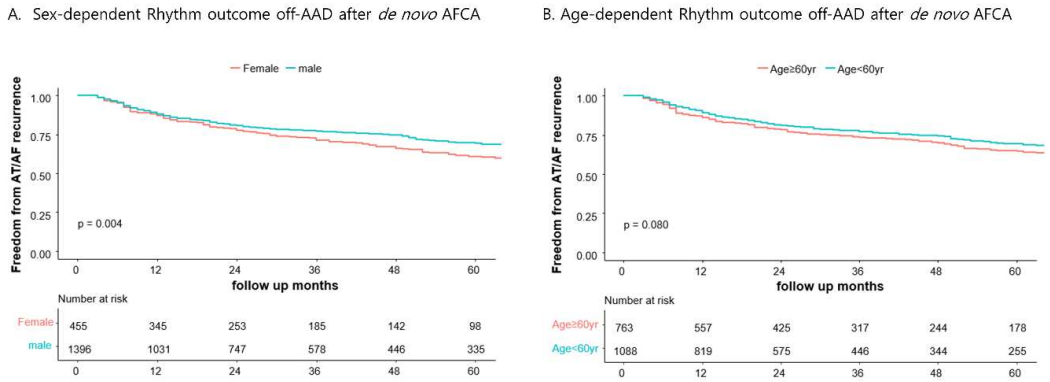
**Supplementary Table 5. Adverse effects and types of AADs**

| | Overall (n=788) | Female (n=228) | Male (n=560) | P value |
|---|---|---|---|---|
| Side effects of AADs | 107 (13.6) | 33 (14.5) | 74 (13.2) | 0.724 |
| Thyroid dysfunction | 44 (5.6) | 11 (4.8) | 33 (5.9) | |
| Liver function test abnormality | 14 (1.8) | 3 (1.3) | 11 (2.0) | |
| QT prolongation | 1 (0.1) | 0 (0) | 1 (0.2) | |
| Sinus node dysfunction | 35 (4.4) | 13 (5.7) | 22 (3.9) | |
| Interstitial pulmonary fibrosis | 2 (0.3) | 1 (0.4) | 1 (0.2) | |
| Others* | 11 (1.4) | 5 (2.2) | 6 (1.1) | |
| Duration of AAD use, mo | 23.6 ± 23.7 | 24.1 ± 20.8 | 23.4 ± 24.8 | 0.702 |
| Flecainide (%) | 256 (31.6) | 75 (32.9) | 181 (32.3) | 0.943 |
| Propafenone (%) | 31 (3.8) | 10 (4.4) | 21 (3.8) | 0.830 |
| Pilsicainide (%) | 5 (0.6) | 1 (0.4) | 4 (0.7) | 1.000 |
| Amiodarone (%) | 269 (34.1) | 63 (27.6) | 206 (36.8) | 0.018 |
| Dronedarone (%) | 157 (19.4) | 56 (24.6) | 101 (18.0) | 0.048 |
| Soltalol (%) | 70 (8.7) | 24 (10.5) | 46 (8.2) | 0.370 |

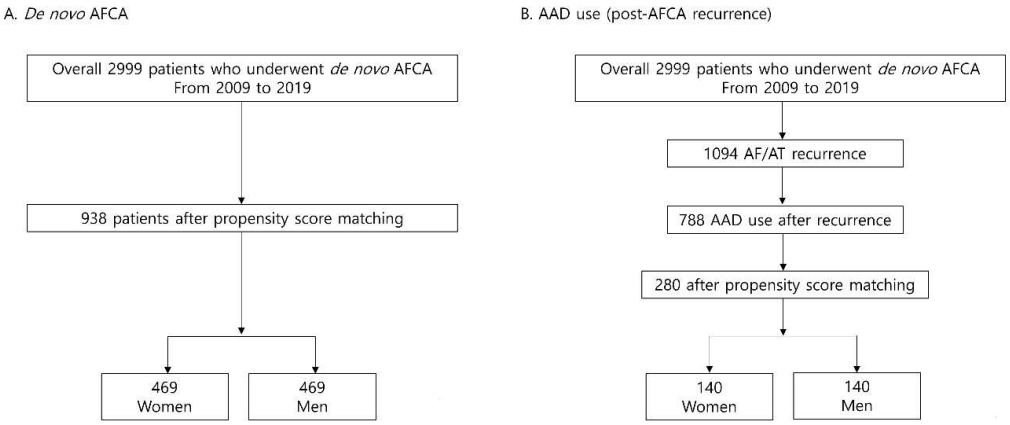
AAD, antiarrhythmic drug.

* Dyspnea, bradycardia, urticarial, edema.

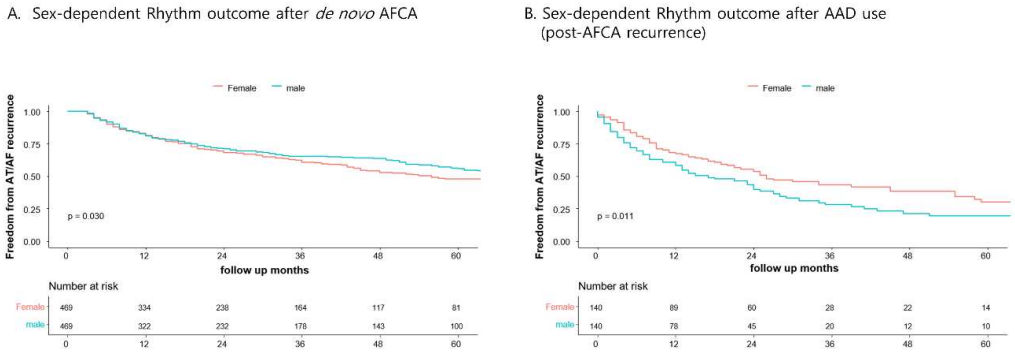
**Supplementary Figure 1. Risk of AF recurrence without AAD according to the sex after the d*e novo* AFCA (A) and according to age after d*e novo* AFCA (B).** AAD, antiarrhythmic drug; AT, atrial tachycardia; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation.



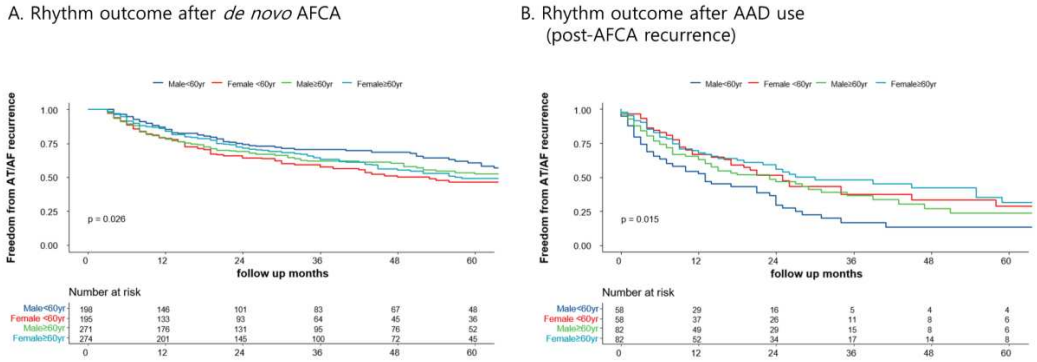
**Supplementary Figure 2. Propensity score matching in each group.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



**Supplementary Figure 3. AF recurrence according to the sex after the de novo AFCA (A) and AAD use in patients with AF recurrence after AFCA (B) and according to the age after de novo AFCA.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



**Supplementary Figure 4. AF recurrence after De novo AFCA (A) and AAD use (B) according to the age and sex.** AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; AAD, antiarrhythmic drug.



**Supplementary Figure 5. Risk of AF recurrence after AAD use according to the sex in the group with Class IC AADs (A) and Class III AADs (B) and the age in the group with Class I AADs (C) and Class III AADs (D).** AAD, antiarrhythmic drug; AF, atrial fibrillation.