



## Long-term results of single-procedure catheter ablation for atrial fibrillation in pre- and post-menopausal women

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### Abstract

**Objectives** To address whether menopause affects outcome of catheter ablation (CA) for atrial fibrillation (AF) by comparing the safety and long-term outcome of a single-procedure in pre- and post-menopausal women. **Methods** A total of 743 female patients who underwent a single CA procedure of drug-refractory AF were retrospectively analyzed. The differences in clinical presentation and outcomes of CA for AF between the pre-menopausal women (PreM group, 94 patients, 12.7%) and the post-menopausal women (PostM group, 649 patients, 87.3%) were assessed. **Results** The patients in the PreM group were younger ( $P < 0.001$ ) and less likely to have hypertension ( $P < 0.001$ ) and diabetes ( $P = 0.005$ ) than those in the PostM group. The two groups were similar with regards to the proportion of concomitant mitral valve regurgitation coronary artery disease, left atrium dimensions, and left ventricular ejection fraction. The overall rate of complications related to AF ablation was similar in both groups ( $P = 0.385$ ). After 43 (16–108) months of follow-up, the success rate of ablation was 54.3% in the PreM group and 54.2% in the PostM group ( $P = 0.842$ ). The overall freedom from atrial tachyarrhythmia recurrence was similar in both groups. Menopause was not found to be an independent predictive factor of the recurrence of atrial tachyarrhythmia. **Conclusions** The long-term outcomes of single-procedure CA for AF are similar in pre- and post-menopausal women. Results indicated that CA of AF appears to be as safe and effective in pre-menopausal women as in post-menopausal women.

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**Keywords:** Atrial fibrillation; Catheter ablation; Follow-up; Menopausal woman

## 1 Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by disorganized electrical activity in the atrium, leading to loss of effective atrial contraction. Catheter ablation (CA) of AF has emerged as an important way of managing drug-refractory symptomatic paroxysmal and persistent AF.<sup>[1]</sup> AF is well known to be male-dominant. Female sex hormones maybe involved, since very few pre-menopausal women experience AF. Sex hormones and gender differences are associated with the occurrence of AF, which is more frequently in men than in women.<sup>[2]</sup> The gender difference in AF is well known not only in terms of prevalence, it has also been observed in the clinical characteristics and complications caused by AF.<sup>[3]</sup> Some reports

have demonstrated that women have a higher heart rate and longer duration of paroxysmal AF and more frequent recurrence of the arrhythmia after cardioversion.<sup>[4,5]</sup> These gender differences in AF patients may be attributable to female sex hormones, but the role of sex hormones in the predisposition to AF has not been well studied. It is unclear how sex hormones relate to differences in arrhythmia incidence between men and women, noting that pre-menopausal women have higher values of female hormones compared with men.<sup>[6]</sup>

AF is the most common chronic arrhythmia in women, with a prevalence that steadily increases from 0.1% in women < 55 years of age to 9.1% in those 85 years or older. Old women are more susceptible to AF and have an increased risk of AF-related complications than young women, and this is probably attributable to the absence of the female hormones.<sup>[7]</sup> Pre-menopausal women generally have higher resting heart rates, longer QT intervals, and lower atrial effective refractory periods compared with post-menopausal women.<sup>[8]</sup> However, no objective evidence or data have shown whether the absence of female hormones can affect the outcomes of CA for AF in female patients. We speculate

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that pre-menopausal women probably have a higher success rate of CA than post-menopausal women because of the effect of female hormones. The aim of the present study was to address this question by comparing the long-term results of CA for symptomatic drug-refractory AF in pre- and post-menopausal women.

## 2 Methods

### 2.1 Study population

“Menopause” was here defined as an absence of menses for one year or more immediately prior to the study. “Pre-menopause” was defined as the absence of menopause. The pre-menopausal group (PreM) consisted of women who declared that they had experienced menses during the year prior to the study. The post-menopausal group (PostM) included those women who had not had menses for more than one year prior to the beginning of the study.<sup>[9]</sup> The exclusion criteria were as follows: left ventricular ejection fraction (LVEF) < 35%, New York Heart Association functional classes III and IV, contraindications for anticoagulation, stroke, and transient ischemic attack (TIA) within three months, pulmonary embolism, previous AF ablation, recent myocardial infarction, and taking menstrual drugs. The patients in the PreM group did not undergo CA during menstruation. Between January 2005 and December 2011, 743 female patients who underwent CA at Beijing Anzhen Hospital for treatment of drug-refractory AF were retrospectively analyzed. The participants supplied detailed information regarding their menstrual status and medical history. The patients were divided into two groups, the PreM group (94 cases, 12.7%) and the PostM group (649 cases, 87.3%).

### 2.2 Ablation procedure

Each patient gave written informed consent before undergoing electrophysiological study and ablation. All patients underwent trans-esophageal echocardiography examination to rule out the presence of atrial thrombi. The left atrium (LA) was accessed by a trans-septal puncture. Intravenous heparin was infused to maintain an activated clotting time of at least 300 s after trans-septal puncture.

A decapolar or quadripolar catheter was advanced via the right femoral vein and positioned in the coronary sinus for atrial pacing and signal reference. Single trans-septal puncture was made under fluoroscopic guidance, and an 8 Fr sheath (SL1, St. Jude Medical, St. Paul, MN, USA) was advanced into the LA. Patients with paroxysmal AF underwent circumferential pulmonary vein ablation (CPVA) guided by Carto system (Biosense Webster Inc, Diamond

Bar, CA, USA) and verified using one circular catheter (Lasso<sup>TM</sup>, Biosense Webster Inc.).<sup>[10]</sup> For patients with persistent AF, CPVA was essential to AF ablation procedures and additional ablation lines were created along the left atrial roof, mitral isthmus, and cavotricuspid isthmus.<sup>[11,12]</sup> Cardioversion was performed if sinus rhythm could not be restored by the above ablation procedure. The endpoint of the procedure included electrical isolation of the pulmonary veins, bidirectional conduction blockage of additional lines, and non-inducibility of any sustained atrial tachyarrhythmia.<sup>[13,14]</sup>

### 2.3 Post-ablation management

Except where contraindicated, all patients received one antiarrhythmic drug (as considered clinically appropriate) for two months to prevent any early recurrence of AF. Treatment was discontinued if no AF recurred within this two-month period. Warfarin was reinitiated and low molecular weight heparin (LMWH) was used as a bridge to resumption of international normalized ratio (INR) 2–3. Oral warfarin was discontinued after 2 months if no AF recurrence was observed in patients with CHADS<sub>2</sub> (congestive heart failure, hypertension, age > 75 years old, diabetes mellitus, prior stroke and TIA) scores < 2. Upon cessation of oral anticoagulation, patients who had at least one cardiovascular risk factor, such as coronary artery disease, hypertension, diabetes mellitus, or smoking, were replaced with anti-platelet treatment (aspirin 100 mg/d).

### 2.4 Follow-up

All patients were scheduled for visits to the arrhythmia clinic at 3, 6, and 12 months after ablation and every six months thereafter. During each visit, those patients continued to be monitored by means of 24-h Holter. The patients contacted the hospital anytime they perceived symptoms that might be related to arrhythmia relapse. All patients were instructed to either obtain a 12-lead ECG or undergo 24-h Holter monitoring in the event of palpitations. Successful ablation was defined as maintenance of sinus rhythm without symptoms or a documented lack of symptoms of AF or AT. The rates of freedom from AF and AT with or without anti-arrhythmic drug therapy, cardiac re-admission, death, stroke, and complications were evaluated in the PreM and PostM groups and compared.

### 2.5 Statistical analysis

Statistical analysis was performed with SPSS for Windows (Microsoft, Redmond, WA, USA) version 13.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean ± SD or as medians. Non-continuous va-

riables, expressed as proportions, were compared using  $\chi^2$  analysis or Fisher's exact test. Comparisons between the two groups were performed with the Student's *t*-test. A Kaplan–Meier analysis with the log-rank test was used to determine the probability of freedom from atrial tachyarrhythmia recurrence. Cox regression analysis was used for the multivariate analysis test.  $P < 0.05$  was considered statistically significant.

### 3 Results

#### 3.1 Patient characteristics

Clinical characteristics of the 743 patients are shown in Table 1. Among the patients included in this study, there were more post-menopausal women ( $n = 649$ ; 87.3%) than pre-menopausal women ( $n = 94$ ; 12.7%). Paroxysmal AF was observed in 70 patients in the PreM group (74.5%) and 471 patients in the PostM group (72.6%),  $P = 0.532$ . The average age of all patients was  $61.6 \pm 10.0$  years. The patients in the PreM group were generally younger ( $43.3$  vs.  $64.2$  years old;  $P < 0.001$ ) and less likely to have hypertension (13.8% vs. 61.2%;  $P < 0.001$ ) and diabetes (2.1% vs. 14.0%;  $P = 0.005$ ) than those in PostM group.

**Table 1. Baseline clinical features of different female patients groups.**

Characteristics	Overall ( $n = 743$ )	PreM group ( $n = 94$ )	PostM group ( $n = 649$ )	<i>P</i> -value
Age, yrs	$61.6 \pm 10.1$	$43.5 \pm 7.0$	$64.2 \pm 7.4$	$< 0.001$
BMI, kg/m <sup>2</sup>	$25.2 \pm 3.7$	$24.5 \pm 3.3$	$25.2 \pm 3.7$	0.078
Comorbidities				
Hypertension	410 (55.2)	13 (13.8)	397 (61.2)	$< 0.001$
Diabetes	93 (12.5)	2 (2.1)	91 (14.0)	0.005
Previous stroke	57 (7.7)	3 (3.2)	54 (8.3)	0.218
Coronary artery disease	35 (4.7)	0 (0)	35 (5.4)	0.070
Mitral valve regurgitation	55 (7.4)	4 (4.3)	51 (7.9)	0.460
Echocardiographic measurements				
Left atrial diameter (long axis), mm	$38.8 \pm 6.3$	$36.0 \pm 6.5$	$38.9 \pm 6.2$	0.682
LVEF, %	$64.1 \pm 8.5$	$63.1 \pm 7.6$	$63.9 \pm 8.9$	0.725
Type of AF				
Paroxysmal	541 (72.8)	70 (74.5)	471 (72.6)	0.532
Persistent	202 (27.2)	24 (25.5)	178 (27.4)	0.532

Values are presented as mean  $\pm$  SD or  $n$  (%). AF: atrial fibrillation; BMI: body mass index; LVEF: left ventricular ejection fraction; PreM: pre-menopausal; PostM: post-menopausal.

#### 3.2 Ablation and follow-up outcome

Ablation procedures were performed in 743 patients (Ta-

ble 2). Between the PreM and PostM groups, there were no significant differences in radiofrequency delivery time ( $76.3 \pm 23.8$  min vs.  $75.4 \pm 22.4$  min,  $P = 0.539$ ), fluoroscopy time ( $40.5 \pm 22.3$  min vs.  $37.4 \pm 13.8$  min,  $P = 0.695$ ), and the mean total duration of the procedure ( $180.0 \pm 68.1$  min vs.  $174.6 \pm 67.1$  min,  $P = 0.764$ ). Pericardial tamponade occurred in three post-menopausal women (0.43%), was managed by percutaneous pericardiocentesis and discharged home without any sequelae. The outcomes of CA for the 743 patients are shown in Table 2.

All patients were followed up for a mean of  $46.8 \pm 21.6$  months (range 13–108 months). Neurological events (embolism and stroke) were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) in four patients, one in the PreM group and three patients in the PostM group (1.06% vs. 0.46%,  $P = 0.758$ ). The total rate of complications had no statistically significant differences

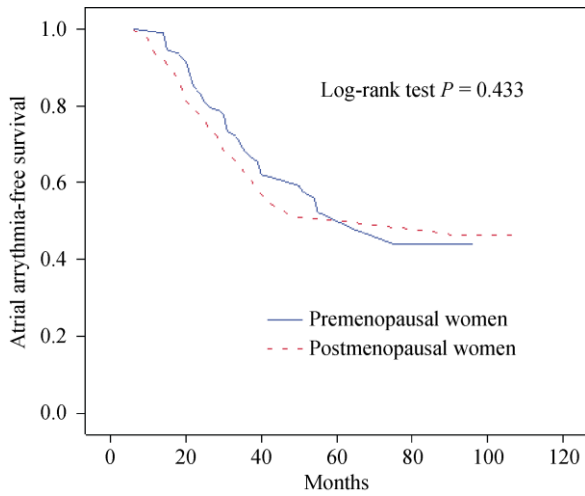
**Table 2. Procedural features and clinical outcome.**

Characteristics	Overall ( $n = 743$ )	PreM group ( $n = 94$ )	PostM group ( $n = 649$ )	<i>P</i> -value
Total procedure time, min	$175 \pm 67.2$	$180.0 \pm 68.1$	$174.6 \pm 67.1$	0.764
RF delivery time, min	$73.1 \pm 24.2$	$76.3 \pm 23.8$	$75.4 \pm 22.4$	0.539
Mean fluoroscopy time, min	$37.8 \pm 15.9$	$40.5 \pm 22.3$	$37.4 \pm 13.8$	0.695
Successful additional				
Linear ablation				
LA roofline block	222 (29.9)	30 (29.7)	192 (31.9)	0.627
Mitral isthmus block	247 (32.9)	32 (34.0)	215 (33.1)	0.331
Bidirectional CTI block	382 (51.4)	47 (50.0)	335 (51.6)	0.571
Complication type				
Pericardial tamponade	3 (0.40)	0 (0.00)	3 (0.43)	0.666
Embolism or stroke	4 (0.54)	1 (1.06)	3 (0.46)	0.758
PV stenosis	2 (0.27)	1 (1.06)	1 (0.15)	0.282
Total	9 (1.21)	2 (2.13)	7 (1.07)	0.385
Outcomes				
Follow-up (months, median)	43 (16–108)	40 (16–101)	47 (13–108)	0.927
Success rate without AAD	403 (54.2)	51 (54.3)	352 (54.2)	0.842
Atrial tachyarrhythmia recurrence	123 (16.6)	16 (17.0)	107 (16.5)	0.992
AF recurrence	217 (29.2)	27 (28.7)	190 (29.3)	0.994
Hospitalization	125 (16.8)	11 (11.7)	114 (17.6)	0.365

Values are presented as mean  $\pm$  SD or  $n$  (%). *P*-values are from  $\chi^2$  tests for the equality of proportions or *t*-tests for the equality of means. AAD: anti-arrhythmic drug; AF: atrial fibrillation; CTI: cavo-tricuspid isthmus; LA: left atrium; PreM: pre-menopausal; PostM: post-menopausal; PV: pulmonary veins; RF: radiofrequency.

between the PreM and PostM groups (7.9% vs. 4.3%,  $P = 0.460$ ). The overall success rate was 54.3% in the PreM group and 54.2% in the PostM group ( $P = 0.842$ ). The curves of freedom from AF and AT recurrence with and without antiarrhythmic drugs in the PreM and PostM groups are shown in Figure 1. The cumulative maintenance of sinus rhythm did not prove significantly different between the PreM and PostM groups ( $P = 0.433$ ).

The characteristics of the groups in which recurrence did and did not occur are shown in Table 3. There were no



**Figure 1.** Kaplan–Meier estimation of the time to atrial tachyarrhythmia after ablation in both groups.

**Table 3.** Characteristics of groups free of recurrence and not free of recurrence.

Variables	Recurrence (n = 403)	No-recurrence (n = 346)	P-value
Age, yrs	60.5 ± 7.1	61.3 ± 8.3	0.558
Women(Pre-menopause)	51 (12.7)	43 (12.4)	0.508
BMI	24.4 ± 3.2	25.2 ± 3.5	0.083
Type of AF			
Paroxysmal	276 (69.5)	271 (79.3)	0.002
Persistent	127 (31.5)	75 (21.7)	0.002
Hypertension	199 (49.5)	175 (50.7)	0.661
Diabetes mellitus	51 (12.7)	43 (12.5)	0.960
Stroke	38 (9.5)	29 (8.4)	0.214
Left atrial diameter (long axis), mm	41.8 ± 6.8	37.9 ± 5.6	< 0.001
LVEF	63.6 ± 7.8	63.2 ± 7.3	0.849
Medications			
β-block	125 (31.2)	98 (28.3)	0.058
ACE/ARB	139 (34.4)	113 (32.6)	0.421
Statins	79 (19.4)	64 (18.5)	0.780

Values are presented as mean ±SD or n (%). ACE: angiotensin-converting enzyme; AF: atrial fibrillation; ARB: angiotensin II receptors blockers; ParAF: Paroxysmal AF; PerAF: Persistent AF; LVEF: left ventricular ejection fraction.

significant differences in age, gender, BMI, concomitant disease (hypertension, diabetes mellitus, chronic heart failure, or stroke), or LVEF between the groups with and without AF recurrence. There were also no significant differences in medications used and in the rate of pulmonary veins isolation (PVI) between the two groups. However, patients in the recurrent group had a higher proportion of persistent AF (31.5% vs. 21.7%;  $P = 0.002$ ) and larger left atria ( $41.8 \pm 6.8$  vs.  $37.9 \pm 5.6$ ;  $P < 0.001$ ) than those in the non-recurrent group. In the multivariate Cox regression analysis, the only variable found to be an independent predictor of arrhythmia recurrence was left atrial diameter [hazard ratio (HR): 1.038, 95% confidence interval (CI): 1.023–1.050,  $P < 0.001$ ]. Menopause was not associated with a higher risk of AF recurrence (HR: 1.217, 95% CI: 0.929–1.591,  $P = 0.164$ ).

#### 4 Discussion

The present study provides a detailed analysis of the differences in clinical features and long-term outcomes of CA of AF between pre- and post-menopausal women. Results indicated CA of AF to be safe and effective in pre- and post-menopausal women.

The present data suggest post-menopausal women were older and had more advanced disease. They were also significantly more symptomatic than pre-menopausal women. One possible explanation is that symptoms are more likely to be attributed to stress, panic, or anxiety in older women than in younger ones. So less attention has been paid to early clinical signs and treatment strategies in pre-menopausal women than in post-menopausal ones. Studies have shown that women suffering from AF are significantly older and have a greater prevalence of structural heart disease than younger.<sup>[15]</sup> These characteristics may in part explain why fewer pre-menopausal women are referred for AF ablation procedures than post-menopausal women. In this study, the angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARB) and statins were prescribed in some patients with AF. This was in line with the observations that patients had related comorbidities, such as hypertension and diabetes. It could be argued that although those drugs were not antiarrhythmic in the conventional sense, they played a beneficial role in AF patients, as described in previous reports.<sup>[16]</sup> But as shown in Table 3, identical drugs were prescribed in the present study population between the group experiencing recurrence and the group free of recurrence. These drugs were not related to the recurrence of atrial tachyarrhythmia.

CA of AF has emerged as an important treatment for patients with drug-refractory, symptomatic AF. Some studies have shown that more women suffer from AF after menopause, when there is also a greater prevalence of structural heart disease.<sup>[17]</sup> Some recent studies have demonstrated gender-related differences in clinical presentation and management of patients with AF.<sup>[18,19]</sup> Forleo, *et al.*,<sup>[20]</sup> found that CA of AF provides a significant clinical benefit and appears to be as effective in women as in men. However, few studies have investigated the results of CA for AF in pre- and post-menopausal women with long-term follow up. In the present study, patients in the PreM group showed the same probability of maintaining sinus rhythm as the PostM group. After long-term follow-up, the actuarial absence of AF and the AT recurrence rate in the PreM group was the same as in the PostM group. Results showed CA to be safe and effective in pre- as in post-menopausal women. This could be confirmed by increasing the number of patients in the study.

Recently, evidence has shown that arrhythmia is different in male and female organisms and that it is especially high in pre-menopausal women.<sup>[21,22]</sup> These gender differences in AF patients might be induced by estrogen.<sup>[23,24]</sup> Serum estrogen levels in females decrease after menopause. Subsequently, post-menopausal women have lower levels of the sex hormone than pre-menopausal women. So the rate of AF in women increases after age 65, but young women seldom experience AF before menopause. This is probably related to the absence of the estrogen antiarrhythmic effect in older women.<sup>[25]</sup> One basic study had shown that the changes in estrogen levels affected not only women's physiological characteristics and basic function but also cardiac ion channel function.<sup>[26]</sup> The resistance to apoptosis mediated by estradiol can strengthen the effects of a blocked angiotensin receptor, which can prevent AF.<sup>[27]</sup> Estrogen has been reported to restore pathologically shortened atrial refractoriness by inhibiting intracellular calcium overload and delaying outward potassium current. The electrophysiological action of the hormone might inhibit atrial tachyarrhythmia.<sup>[28]</sup> Serum estrogen levels in women decrease after menopause,<sup>[29]</sup> which can explain why more women suffer from AF after menopause.

However, for the women who suffered AF, regardless of their estrogen levels, the mechanism of AF in all patients is the same. There are three major schools of thought to explain the mechanism of AF: multiple random propagating wavelets, focal electrical discharges, and localized re-entrant activity with fibrillatory conduction.<sup>[30]</sup> It is well accepted that the development of AF requires both a trigger and a susceptible substrate. The goals of AF ablation pro-

cedures are to prevent AF by either eliminating the trigger that initiates AF, or by altering the arrhythmogenic substrate.<sup>[31]</sup> In the present study, the mechanisms of AF and ablation strategy in both groups were exactly the same, which might explain why no different clinical outcomes were observed between the PreM and PostM groups after CA of AF. Therefore, although the prevalence of AF was different because of the different levels of the sex hormone between pre- and post-menopausal women, the results of this study indicated CA of AF to be safe and effective in both groups. Post-menopausal women were neither associated with less arrhythmia recurrence nor with a decreased risk of CA complications than pre-menopausal women.

One important limitation of the present study is that it is an observational and retrospective study. The study was not originally designed to prospectively evaluate the results of CA for AF in pre-menopausal female patients. For this reason, estrogen levels were not tested in either group. The manner in which the female hormone affects the long-term outcome of single-procedure CA for AF needs further investigation. Another possible limitation of this study is that the follow-up was performed mainly through telephone interviews, which means that asymptomatic AF recurrences could have been missed. Finally, a CT scan was not routinely performed in all patients after CA of AF, so the differences in pulmonary veins (PV) stenosis between the two groups could not be evaluated.

In conclusion, despite the probable effect of female hormones in the pre-menopausal women, the long-term outcomes of single-procedure CA for AF were similar between pre- and post-menopausal female patients. The results indicated CA of AF to be safe and effective in pre- as well as in post-menopausal women.

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