Sex- Based Differences in Safety and Efficacy of Catheter Ablation for Atrial Fibrillation

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Abstract

Background: Studies have identified significant sex-based differences and disparities in the clinical presentation and treatment of atrial fibrillation (AF). Studies have shown women are less likely to be referred for catheter ablation, are older at the time of ablation, and are more likely to have recurrence after ablation. However, in most studies investigating AF ablation outcomes, the female cohorts were relatively small. The impact of gender on the outcome and safety of ablation procedures is still unclear. **Objective:** To investigate sex-based differences in outcomes and complications after AF catheter ablation, with a significant size female cohort **Method:** In this retrospective study, patients undergoing AF ablation from January 1, 2014, to March 31, 2021, were included. We investigated clinical characteristics, duration and progression of AF, number of EP appointments from diagnosis to ablation, procedural data, and procedure complications. **Results:** Total 1346 patients underwent first catheter ablation for AF during this period, including 896 (66.5%) male and 450 (33.4%) female patients. Female patients were older at the time of ablation (66.2y vs 62.4y; p<0.001). Women had higher CHA $_2$DS $_2$-VASc scores (3 vs 2; p<0.001) than men, expectedly, as the female sex warrants an additional point. 25.3% female patients had PersAF at the time of diagnosis vs 35.3% male patients (p<0.001). At the time of ablation, 31.8% female patients had PersAF as compared to 43.1% male patients (p<0.001), indicating progression of PAF to PersAF in both genders. Women tried more AADs than men before ablation (1.13 vs 0.98; p=0.002). Male and female patients had no statistically significant difference in (a) arrhythmia recurrence at 1-y post ablation (27.7% vs 30%; p=0.38) or (b) procedural complication rate (1.8% vs 3.1%; p=0.56). **Conclusion:** Female patients were older and had higher CHA $_2$DS $_2$-VASc scores compared to males at the time of AF ablation. Women tried more AADs than men prior to ablation. 1-y arrhythmia recurrence rates and procedural complications were similar in both genders. No sex- based differences were observed in safety and efficacy of ablation.

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Objective: To investigate sex-based differences in outcomes and complications after AF catheter ablation, with a significant size female cohort

Method: In this retrospective study, patients undergoing AF ablation from January 1, 2014, to March 31, 2021, were included. We investigated clinical characteristics, duration and progression of AF, number of EP appointments from diagnosis to ablation, procedural data, and procedure complications.

Results: Total 1346 patients underwent first catheter ablation for AF during this period, including 896 (66.5%) male and 450 (33.4%) female patients. Female patients were older at the time of ablation (66.2y vs 62.4y; p<0.001). Women had higher CHA_2DS_2-VASc scores (3 vs 2; p<0.001) than men, expectedly, as the female sex warrants an additional point. 25.3% female patients had PersAF at the time of diagnosis vs 35.3% male patients (p<0.001). At the time of ablation, 31.8% female patients had PersAF as compared to 43.1% male patients (p<0.001), indicating progression of PAF to PersAF in both genders. Women tried more AADs than men before ablation (1.13 vs 0.98; p=0.002). Male and female patients had no statistically significant difference in (a) arrhythmia recurrence at 1-y post ablation (27.7% vs 30%; p=0.38) or (b) procedural complication rate (1.8% vs 3.1%; p=0.56).

Conclusion: Female patients were older and had higher CHA_2DS_2-VASc scores compared to males at the time of AF ablation. Women tried more AADs than men prior to ablation. 1-y arrhythmia recurrence rates and procedural complications were similar in both genders. No sex- based differences were observed in safety and efficacy of ablation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world, associated with an increased risk of stroke, heart failure and mortality. Data shows a growing incidence and prevalence of AF (1,2,3). There are notable disparities in the presentation, progression, and management of AF in men and women.

Women with AF tend to experience more symptoms, poorer quality of life, and increased functional impairment compared to men (4,5). Although the lifetime prevalence of AF is similar between men and women (5), women are at an increased independent risk of stroke and cardiovascular death due to AF (6,7,8,). In a large population-based cohort, the Copenhagen City Heart study demonstrated a 4.6-fold increase in independent stroke risk and 2.5-fold increase in death risk for women with AF compared with men with AF (6).

Despite this, women are more likely to receive rate control rather than rhythm control treatments for AF (9,10,). Additionally, women are less likely to benefit from pharmacological rhythm control medication and are more likely to experience adverse effects (11,12,). In contrast, men are more likely to undergo procedures aimed at restoring sinus rhythm, such as electrical cardioversion and catheter ablation (9,10,). According to a recent study of the temporal trends in referrals for the first ablation procedure for AF, catheter ablations have increased almost sevenfold over the past ten years, but the proportion of women undergoing this procedure has not increased significantly (13).

Previous studies on the outcomes of AF catheter ablation have primarily focused on male patients, with women being underrepresented (14-17). These studies have shown that women are often older (14,15), have a longer history of AF (16), larger left atrial size, and more comorbidities at the time of ablation (5,15). There is no clear evidence on gender-based differences in the outcomes of AF ablation, with some studies suggesting higher recurrence rates in females (16,18,19) and others showing no differences (12,14). Furthermore, gender incongruities have also been described in procedure-related adverse outcomes, but this too remains unclear due to an underrepresentation of female patients in clinical trials. The aim of this study is to further investigate gender differences in the safety and outcomes of catheter ablation for AF patients with a significant female cohort in the study population.

Methods

Patient Population

We conducted a single-center, retrospective observational study of patients enrolled in a prospectively populated AF ablation database approved by the Johns Hopkins IRB. The study cohort is comprised of patients undergoing first catheter ablation from January 1, 2014, to March 31, 2021. Patient characteristics were systematically recorded, including demographic, clinical, and echocardiographic parameters. We also investigated duration and progression of AF, prescribed medication information, number of electrophysiologist appointments from diagnosis to ablation, AF types, and procedural data.

Peri-Procedural Anticoagulation and Imaging

Catheter ablation was performed with minimal interruption of anticoagulation. Warfarin was continued throughout the peri-operative period. DOAC therapy was either uninterrupted, or a single DOAC dose was held prior to ablation. After ablation, all patients received anticoagulation for a minimum of 3 months.

Unless clinically contraindicated, patients had either CT or transesophageal echocardiography (TEE) immediately prior to ablation in order to exclude LAA thrombus. Data collected during electroanatomic mapping (EAM) was merged with pre-acquired CT or MRI at the operator's discretion.

Ablation Procedure

Ablation was performed under general anesthesia in all patients. A detailed electro-anatomical map (EAM) using either CARTO or ESI mapping systems was performed in all patients after vascular and left atrial access, prior to and following ablation. Patients presenting in AF underwent cardioversion to sinus rhythm prior to EAM. In all cases, PVI was the primary ablative strategy and any additional non-PV targets (linear lesions; low-voltage areas) were ablated at the operator's discretion.

Ablation was performed using either an irrigated, contact force-sensing RF ablation system (Biosense Webster, etc., or Abbott/ESI) or a cryoballoon ablation catheter (Arctic Front Advance and Arctic Front, Medtronic Inc.). For patients undergoing RF ablation, target power delivery to the anterior and posterior LA walls was 35–45 and 25–35 W, respectively. Patients undergoing cryo-balloon ablation underwent fluoroscopic positioning of a 28- or 23mm cryo-balloon to achieve complete PV occlusion as assessed by contrast injection. A minimum of two freeze-thaw cycles (3 min duration) were applied to each vein, sufficient to achieve PV isolation as assessed by a multipolar mapping catheter.

An esophageal temperature probe was placed in all patients during ablation, with temporary cessation of lesion application if significant temperature deviation occurred. During cryoballoon ablation of right-sided pulmonary veins, phrenic nerve pacing was performed, and ablation was terminated if diaphragmatic contractions diminished.

In all cases, PV isolation was determined by demonstrating an entrance block to each vein during sinus rhythm on post-ablation EAM after a 20-minute waiting period. Exit block was demonstrated at the operator's discretion, as was occult PV reconnection during adenosine infusion.

Follow-up

Following ablation, all patients were either monitored in the Post-anesthesia Care Unit for 4h or admitted to the hospital for overnight observation. Routine follow-up (history, exam, and electrocardiography) was performed at the outpatient clinic or by a local cardiologist at 3, 6, and 12 months, and additionally, if prompted by symptoms. Mean follow-up duration was 12 months. During the post-blanking follow-up period, Holter or event monitors were arranged for patients who developed symptoms suggestive of AF. When available, pacemaker interrogation records and mobile technology rhythm devices (Apple Watch; Kardia) were also used for arrhythmia recurrence monitoring. Antiarrhythmic drug (AAD) therapy, if present at the time of ablation, was discontinued prior to the 3-month follow-up visit. Arrhythmia recurrence was defined on the basis of the 2017 Heart Rhythm Society consensus document as any AF/atrial tachycardia/atrial flutter sustained for more than 30 seconds recorded by a surface ECG or rhythm monitoring device after a 90-day blanking period. One-year outcomes were assessed in all patients, either at clinic follow-up, electronic health record review, or phone interview.

Statistical Analysis

Continuous data were analyzed using the student's t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Categorical data were analyzed using the $\chi 2$ test. Values are presented as mean ± standard deviation or median and interquartile range (Q1-Q3) according to distribution for continuous data and count and percentage for categorical data unless otherwise stated. The cumulative probability of survival free from atrial arrhythmia was displayed according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test. Follow-up for all patients was censored one year after ablation. A p-value of <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, New York) and STATA Version 13 (Stata Corp, College Station, TX).

Results

Patient Characteristics

A total of 1346 patients underwent first catheter ablation for AF during this period, including 896 (66.5%) male patients and 450 (33.4%) female patients. Table 1 shows comparison of baseline characteristics of men and women. The female patient group was older at the time of ablation (66.2y vs 62.4y; p<0.001] compared to male patients. Women had higher CHA_2DS_2-VASc scores (3 vs 2; p<0.001) than men at the time of ablation, expectedly, given that female gender in the current guidelines confers a CHA_2DS_2-VASc point. There was no statistically significant difference in two groups in terms of BMI, DM, HTN, hyperlipidemia, CHF, stroke history, or CKD. In our study population, women had smaller LA diameter as compared to men (4.3 vs 4.5cm; p=0.024), and slightly reduced left-ventricular ejection fraction (LVEF) values (55.9% vs 58.4%; p<0.001).

AF Characteristics

A comparison of AF history and procedural characteristics between genders is shown in Table 2. At the time of initial diagnosis, 25.3% patients in female group had persistent AF (PersAF) vs 35.3% patients in male group (p<0.001). The mean duration of AF, from initial diagnosis to ablation, was 44.4 months for the study population, and was similar for men and women (44.6 vs 44.1; p=0.91). At the time of ablation, 31.8% female patients had PersAF as compared to 43.1% patients in male group (p<0.001), suggesting progression of paroxysmal AF (PAF) to PersAF in both genders.

The number of electrophysiologist appointments by women during the period leading up to catheter ablation was similar to that of men (5.35 vs 4.95; p=0.37), but women tried more AADs than men before presenting for catheter ablation (1.13 vs 0.98; p=0.002). In the female group, 92.2% of patients received anticoagulation before the ablation procedure as compared to 88.6% patients in male group (p=0. 012).

Procedural Characteristics

There were no significant differences in ablation strategy in men and women. Radiofrequency ablation was

performed in 60.5% of males and 60.9% of females, whereas cryoballoon ablation was used in 33.1% of males and 31.8% of females. Combined cryoballoon and RF was used in 6.4% men and 7.3% women (p=0.74). Men underwent more cardioversions during ablation then women (34.2% vs 27.6%; p=0.014), likely due to greater prevalence of persistent AF.

Outcomes

There was no significant difference in 1-year arrhythmia recurrence rate between men and women (27.7% vs 30%; p=0.38). Redo ablation rates were similar between the two groups (11.7% vs 9.3%; p=0.19).

A total 29 out of 1350 patients developed procedure related complications (2.1%). Adverse events included vascular complications, phrenic nerve injury, neurological complications, and pericardial effusion (Table 3). There was no significant difference in procedure related complication rate between men and women (1.9% vs 3.1%; p=0.56).

Discussion

Main findings

We conducted a single center, retrospective analysis of 1346 patients undergoing index AF ablation, with a significant size female cohort in the study population, to investigate gender differences in outcomes and complications following catheter ablation of AF. We found that: diagnosis-to-ablation time for both groups was similar; although the number of EP appointments leading up to ablation was similar in men and women, women tried and failed more AADs than men prior to ablation; there were no gender-based differences in one-year arrhythmia recurrence rates; and procedure-related complication rates between men and women were similar.

Studies have shown that women with AF have a worse prognosis, including an increased risk of stroke, heart failure, and death, as well as more severe symptoms, a worse quality of life, and diminished functional capacity (5). Despite these facts, women are less likely to receive rhythm control through catheter ablation and cardioversion. Consequently, women often undergo ablation procedures at an older age and later in their disease course, often having experienced AF for a longer period with advanced cardiac remodeling resulting from the disease (5). While some studies suggest that females have a higher post-ablation arrhythmia recurrence rate than males, other studies like the CASTLE-AF trial did not show a gender difference in the effectiveness of ablation procedures. There remains ambiguity regarding gender-based differences in outcomes and complications related to AF ablation, partly because of the underrepresentation of women in these studies. Our study aimed to investigate gender-based disparities in the management of AF and as well as the outcome and complication rate of AF ablation procedures.

In contrast to most previous studies investigating gender impact on AF ablation, our study included a relatively large cohort of patients with a significantly higher proportion of female patients (n=450, 33.4% of total study patients). In accordance with existing studies, women were older at the time of ablation (66.2 vs 62.4 years; p<0.001). Compared to their male counterparts, women also tried and failed more anti-arrhythmic drugs before presenting for ablation procedure (1.13 vs 0.98; p=0.002). These results may indicate female patients' apprehension towards procedural intervention, referral bias, or some other delaying factor. In contrast to previous studies (6), however, we found no significant difference in the duration of AF between men and women from initial diagnosis to ablation (44.6 months versus 44.1 m; p=0.97). At the time of diagnosis, it was observed that 25.3% of female patients had PersAF compared to 35.3% of male patients (p<0.001). Similarly, at the time of ablation, 31.8% of female patients had PersAF as opposed to 43.1% of male patients (p<0.001), suggesting a similar rate of progression from paroxysmal to PersAF in both genders.

With regards to procedural success, we found no significant difference in AF recurrence at 1-year post-ablation between male and female patients (27.7% vs 30%; p=0.38). This is consistent with previous studies (4,12,14) that have reported equal rates of procedural success and low recurrence rates in both genders. We believe it is more likely that the procedural results are primarily influenced by the consistency in timing of

ablation from the time of diagnosis, regardless of gender. Timing of ablation is one of the major predictive factors of ablation outcomes due to advancement of atrial substrate. The study by Bunch et al. demonstrated that increasing time between diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes (20).

In prior research, it has been suggested that sex differences in outcomes can be partly explained by women having more advanced AF disease at the time of ablation (16). The prospective multicenter DECAAF study found a linear relationship between the degree of atrial fibrosis as identified by LGE-CMR and AF recurrence rates post-ablation (21) and another study by Chelu and colleagues correlated higher levels of atrial fibrosis with longer AF duration (22). Recent clinical trials EARLY- AF, CASTLE-AF, STOP-AF strongly advocate for early rhythm control using catheter ablation as a first line treatment for AF to reduce morbidity and mortality (23,24,25). With the growing evidence for early ablation, our study supports a uniform approach for all patients with regards to early ablation. Given a greater tendency to use antiarrhythmic drug therapy in women with AF, greater attention to counseling on therapeutic choices may be needed in this population (5).

In addition, no gender-related differences were observed in procedural complications, including vascular injury (7 males, 5 females; p=0.55), phrenic nerve injury (1 male, 1 female), pericardial effusion (6 males, 7 females; p=0.12), esophageal fistula (0 males, 0 females), or stroke/TIA (3 males, 1 female; p=0.71), supporting the recommendation that both men and women should be offered catheter ablation for atrial fibrillation on an equal basis. It should be acknowledged, however, that unlike most other studies in this area (15), our population did not demonstrate significant gender-based differences in the rates of comorbidities such as diabetes, hypertension, heart failure, chronic kidney disease, which may also be contribute to the lack of gender differences in procedural complications.

One of the key gender disparities in the management of AF is in the use of anticoagulation therapy. Studies have shown that women with AF are less likely to receive anticoagulation therapy compared to men, despite having similar or higher risk for stroke (3, 26). It is worth emphasizing, however, that women in our study were adequately treated with oral anticoagulants (92.2% females, 88.6% males; p=0.012), and that may partly explain the reduction in neurological adverse events.

Future directions

Despite a growing body of evidence supporting early catheter ablation for treatment of AF, gender disparities in AF care persist. To address gender disparities and improve the care of women with AF, several campaigns have been launched to raise awareness and educate both the general public and healthcare providers alike about gender equity in cardiac care. These include the AHA – Go Red for Women and other similar campaigns. Continued efforts to educate healthcare providers and the general public about the need for gender-specific treatment are essential to ensure that women with AF receive the care they need to manage this condition effectively.

Conclusions

One year arrhythmia recurrence rate and procedural complication rates were similar in men and women undergoing index AF ablation. These findings support equal and early treatments for all procedure candidates regardless of their gender.

Limitations

Due to the single-center, retrospective, observational nature of this study, it has several inherent limitations. There is a possibility of selection bias. Second, a lack of continuous ECG monitoring after ablation could have resulted in the underestimation of arrhythmia recurrence. That, and the limited (12m) follow-up period of our study, could result in under-reporting of AF recurrence. Due to retrospective nature of study, it is not possible to determine the extent of fibrosis. Additionally, it should be noted that, despite the clear duration from initial diagnosis to ablation, it is not possible to determine the duration of time patients suffered from arrhythmia prior to diagnosis. In the present study, data regarding the frequency of ablation

of non-pulmonary vein foci was not included. Greater diligence in targeting these foci may have contributed to improved gender equity in procedural effectiveness.

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Conflict of Interest

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Table 1. Patient characteristics in male and female groups.

Characteristic	Total (1346)	Male (N=896) 66.5%	Female (N=450) 33.5%	p-value
Age	63.7	62.4	66.2	**<0.001**
Race				0.43
White	1,239 (92.1%)	832 (92.9%)	407 (90.4%)	
African American	57 (4.2%)	33 (3.7%)	24 (5.3%)	
Asian	18 (1.3%)	10 (1.1%)	8 (1.8%)	
Hispanic	6 (0.4%)	3 (0.3%)	3 (0.7%)	
Other	25 (1.9%)	17 (1.9%)	8 (1.8%)	
BMI	32.01	32.24	31.51	0.52
CHADSVASC	2 (1-3)	2 (1-3)	3 (2-4)	**<0.001**
DM	185 (13.7%)	132 (14.7%)	53 (11.8%)	0.14
HTN	802 (59.6%)	538 (60.0%)	264 (58.7%)	0.63
CHF	201 (14.9%)	134 (15.0%)	67 (14.9%)	0.97
Stroke or TIA	109 (8.1%)	64 (7.1%)	45 (10.0%)	0.070
OSA	269 (20.0%)	205 (22.9%)	64 (14.2%)	**<0.001**
CKD	54 (4.0%)	33 (3.7%)	21 (4.7%)	0.38
Hyperlipidemia	483 (35.9%)	324 (36.2%)	159 (35.3%)	0.77
Asthma or COPD	96 (7.1%)	51 (5.7%)	45 (10.0%)	**0.004**
Smoking History	335(24.8%)	174(19.4%)	97(21.5%)	0.074
Anticoagulant	1209(89.8%0	794(88.6%0	415(92.2%)	**0.012**
ACEi	246(18.2%)	194(21.6%)	52(11.5%)	**0.001**
ARB	259(19.2%)	163(18.1%)	96(21.3%)	0.74
LA diameter (cm)	4.41	4.47	4.31	**0.024**
LVEF by TEE (%)	56.7	55.9	58.4	**<0.001**

Table 2. Procedural characteristics in male and female groups.

Characteristic	Total(N=1346)	Male(N=896)	Female(N=450)	p-v
Mean Duration of AF (months)	44.4	44.6	44.1	0.91
total no. of AAD used	1 (1-1)	1 (1-1)	1 (1-2)	**0.0**
No. of Electrophysiologist appointment	5.08 (7.76)	4.95 (7.47)	5.35 (8.30)	0.37
AF Type at Diagnosis				**<0**

Characteristic	**Total(N=1346)**	**Male(N=896)**	**Female(N=450)**	**p-v**
Paroxysmal	916(68.1%)	580(64.7%)	336 (74.7%)	
Persistent	430 (31.9%)	316 (35.3%)	114 (25.3%)	
AF Type at Ablation				**<0**
Paroxysmal	817 (60.7%)	510 (56.9%)	307 (68.2%)	
Persistent	529 (39.3%)	386 (43.1%)	143 (31.8%)	
Ablation Type				0.74
Cryo	440 (32.7%)	297 (33.1%)	143 (31.8%)	
RF	816 (60.6%)	542 (60.5%)	274 (60.9%)	
Cryo and RF	90 (6.7%)	57 (6.4%)	33 (7.3%)	
Recurrence in 1 year	383 (28.5%)	248 (27.7%)	135 (30.0%)	0.38
DCV during ablation	430 (31.9%)	306 (34.2%)	124 (27.6%)	**0.0**
Redo ablation	147 (10.9%)	105 (11.7%)	42 (9.3%)	0.19
Duration from first ablation to redo ablation (in months)	9.20 (5.22-16.36)	8.51 (5.13-16.36)	9.76 (6.90-14.49)	0.69

Table 3. Procedural complications in male and female groups.

Complications	**Total (n = 1346)**	**Men (n = 896)**	**Women (n = 450)**	**P-value**
Overall, n (%)	29 (2.1%)	17(1.9%)	14(3.1%)	0.56
Vascular Complication, n (%)	12	7	5	0.55
Phrenic Nerve Injury, n (%)	2	1	1	0.62
Pericardial Effusion, n (%)	13	6	7	0.12
Esophageal Injury, n (%)	0	0	0	NA
Stroke/TIA, n (%)	4	3	1	0.71