

Sex Differences In Outcomes Of Ablation Of Atrial Fibrillation

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Abstract

Sex-related differences in the presentation, treatment, and outcomes of cardiovascular disease have been reported in many areas of cardiovascular medicine, including the clinical course and treatment of atrial fibrillation (AF). Women appear to be more symptomatic, have a lower quality of life, and are less tolerant of antiarrhythmic drugs than men. However, the rate of referral of women for catheter ablation of AF is significantly lower than men, and women are referred much later after failing more antiarrhythmic drugs. There is a trend toward a lower success rate and a higher failure rate for catheter-based AF ablation in women. This finding may be related to the later referral of women for the procedure, resulting in high risk features such as more severe hypertension, greater left atrial size, and more persistent AF at the time of the procedure, all of which are associated with future recurrences. The complication rate from AF ablation is significantly higher in women, particularly with respect to bleeding and vascular complications such as hematomas and pseudoaneurysms. Individualized care including earlier referrals, pre-procedural case planning, and close monitoring intra- and post procedure may improve the outcomes for women with catheter ablation of AF.

Introduction

Sex-related differences in the presentation, treatment, and outcomes of cardiovascular disease have received increasing attention in recent years. There is widespread underuse of cardiovascular procedures in women, including coronary angiography, revascularization, and implantable cardioverter-defibrillators.¹⁻⁴ Such sex-related differences have also been reported in the presentation and management of atrial fibrillation (AF), including catheter ablation.⁵⁻⁸ Women appear to be more symptomatic from the arrhythmia,⁹⁻¹⁰ have higher heart rates at the time of presentation,⁹ and present with a lower quality of life.¹¹ Although these characteristics would seem to encourage a rhythm control approach, the use of antiarrhythmic drugs is not always possible, as both bradyarrhythmias and torsade de pointes have been observed more frequently in women.¹²⁻¹⁴ In this setting, catheter ablation of AF is certainly an attractive option to both patients and physicians.

The use of catheter ablation is rapidly growing. In Cappato's worldwide survey between 1995 and 2002, the median number of

procedures per center was 37.5 (range, 1-600), whereas in his updated survey between 2003-2006, it rose to 245 (range, 2-2715).¹⁵⁻¹⁶ The 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Document on Catheter Ablation of AF determined that catheter ablation of AF should have a Class I Level of Evidence A recommendation in patients with paroxysmal AF who have failed treatment with at least one antiarrhythmic medication, and a Class IIa Level of Evidence B recommendation for patients with paroxysmal AF who have not failed antiarrhythmic drug therapy.¹⁷ Although commonly used in younger patients with paroxysmal AF, catheter ablation is increasingly employed as well in patients with persistent or long-standing persistent AF.¹⁸ With increasingly widespread use of the procedure, it is prudent to understand the various factors that affect outcomes in AF ablation. The purpose of this article is to review the presentation and treatment outcomes of AF in women, with particular attention to the success rates and complication rates of AF ablation, in order to highlight differences compared to men and opportunities for improved outcomes.

Search engines including PubMed were used for all publication types in the English language, using the search terms describing the concepts of AF and sex. These terms included atrial fibrillation ablation, sex, gender, women, outcome, success, efficacy, recurrence, complications, prevalence, incidence, epidemiology, presentation, and treatment. Full-length manuscripts were reviewed. The reference sections from the identified publications were also used for further search. Several studies specifically addressed sex differences in outcomes and complication rates, as discussed below. Most of the

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other available major reports on outcomes of AF ablation did not specifically report on outcomes in men versus women, although sex was often included in multivariable analyses of predictors of success rates. In addition, several of them reported on sex differences in complication rates, which we have included in our review.

Presentation And Treatment Of AF In Women

AF is the most common arrhythmia in clinical practice, with an estimated prevalence in the United States of 2.7 to 6.1 million that is expected to increase to 5.6 to 12.2 million by 2050.¹⁹⁻²¹ The prevalence of AF is higher at all ages in men than in women.²² However, since there are almost twice as many women as men older than 75 years in the general population, the absolute number of women with AF is equal to or greater than men.^{22,23}

Multiple studies have found that women are more symptomatic from AF and have a lower quality of life.⁹⁻¹¹ One of the explanations for this finding may be due to their higher presenting heart rates. A prospective study by Hnatkova et al. showed the mean heart rate of women at the onset of AF was 123±35 beats/minute vs. 115±20 beats/minute in men.²⁵ Similar heart rate differences in AF between sexes were observed in an analysis of the Canadian Registry of AF, which found higher mean heart rates during AF in women (126.2±1.9 vs. 119.1±1.4 beats/minute in men). It has also been reported that women are more likely to experience longer (>24 hours) symptomatic episodes and frequent recurrences of AF.⁹ Women have a lower quality of life related to AF, which may be attributed to depression as well as a more heightened sense of symptoms. Ong et al. performed a cross-sectional study of 93 patients with AF to evaluate the role of depression on quality of life. It revealed that women reported higher depression scores relative to men, and depression was related to lower physical and mental quality of life.²⁶

Women have more episodes of bradyarrhythmias when treated with antiarrhythmic drugs. In a sub-analysis from the Rate Control Versus Electrical Cardioversion (RACE) Study, severe adverse effects of antiarrhythmic drugs and pacemaker implantations occurred more often in women. Such adverse events included manifestations of sick sinus syndrome on flecainide, sotalol, or amiodarone, and torsades de pointes on sotalol.^{12,14} More frequent episodes of torsades de pointes in women have previously been reported on multiple antiarrhythmic drugs, including ibutilide and sotalol.²⁷⁻²⁹ Sex differences in susceptibility to torsades de pointes may be related to fluctuating QT intervals on antiarrhythmic drugs due to hormonal changes^{30,31} and longer baseline QT intervals in women.

As women are more symptomatic from AF and less tolerant of antiarrhythmic drugs, catheter ablation appears to be a suitable option. However, multiple studies indicate that women are referred less often for catheter ablation.^{15,16,32-42} The percentage of women among patients referred for ablation in these studies ranged from 15.8 to 33.2%. Later referral of women is suggested by the significantly older age of women compared to men at the time of ablation, although this later referral may reflect at least in part the higher prevalence of AF in men in younger age groups.^{32,33,35} Roten et al. also reported a trend of fewer and later referrals of women to electrophysiology consultation in an outpatient-based study.⁴³

Overall Success and Complication Rates of AF Ablation

Multiple studies have described overall outcomes and complication rates of AF ablation. A majority of these publications, including randomized clinical trials and meta-analyses, have high percentages of male patients with paroxysmal AF and few co-morbidities. With

this caveat in mind, the efficacy of AF ablation in randomized trials has been reported to be in the range of 66 to 89% with up to 12 months of follow-up.^{17,18,36-42} Despite the heterogeneity of these studies due to variables such as definition of recurrence, ablation methods, choices of antiarrhythmic drugs, the number of repeat procedures and the above-mentioned patient characteristics, several meta-analyses report consistent overall success rates of 75.6-77.8% in the ablation arms as compared with 18.8-29% in the control groups of clinical studies.⁴⁴⁻⁴⁷ A more recent meta-analysis evaluated long-term outcomes of AF ablation and reported the overall long-term success rate after ≥3 years of follow-up to be 79.8%, with an average of 1.51 procedures per patient.⁴⁸ In addition to these randomized clinical trials and meta-analyses, two worldwide surveys have been published, representing the outcomes from over 180 centers. An initial worldwide survey (1995 -2002) reported the success rate, defined as freedom from symptomatic AF in the absence of antiarrhythmic therapy, to be 52%. In the updated worldwide survey (2003-2006), a 70% efficacy rate free of antiarrhythmic drugs and an additional 10% efficacy rate in the presence of previously ineffective antiarrhythmic drugs were reported.^{15,16}

Complication rates from some of the meta-analyses, which included evaluations of 10 randomized controlled trials and 18 non-randomized controlled trials, are in the range of 2.9 to 7.9%.^{44,46,47} Two worldwide surveys reported major complication rates of 6% (1995-2002 and 4.5% (2003-2006).^{15,16} Recently, in-hospital complications associated with catheter ablation of AF in the U.S. were analyzed for 93,801 procedures performed between 2000-2010, utilizing data from the Nationwide Inpatient Sample, a nationally representative survey of hospitalizations conducted by the Healthcare Cost and Utilization Project, including a 20% sample of U.S. community hospitals. This study reported the overall complication rate to be 6.29%, comparable to other findings.⁴⁹

Success Rates Of AF Ablation In Women

There has not been any consistent evidence to support female sex as a predictor for recurrence after AF ablation based on multiple univariate and multivariate analyses.^{48,50,51} Balk et al. performed a systemic review of predictors of AF recurrence after catheter ablation and reported that none of 23 studies with Cox hazard predictor analyses found female sex to be a predictor of recurrence. A recent meta-analysis by Ganesan et al. reported conflicting data among various studies, including two that showed male sex as a predictor of recurrence and two other studies that found female sex to be a predictor of recurrence of AF. Heist et al. reported male sex as a multivariate predictor of overall clinical success in their analysis of 143 patients with persistent and longstanding persistent AF patients who failed antiarrhythmic therapy.⁵¹

In an attempt to evaluate sex-related differences in depth, at least four major studies have examined outcomes in women as primary end points in the past decade (Tables 1,2). A study by Forleo et al. evaluated 221 consecutive patients from two centers who underwent catheter ablation for drug-refractory AF.³² This study provided early objective evidence of sex-related differences in AF ablation. Women had a longer history of AF (median 60 vs. 47 months; P = 0.042), yet they represented only 32.1% of the patients referred for catheter ablation. Left atrial dimensions were significantly larger in women (Table 1). The success rate was evaluated in terms of freedom from arrhythmia recurrence on or off antiarrhythmic drugs after the last ablation following a one month blanking period. Despite these

Table 1: Characteristics of Patients Undergoing AF Ablation by Sex

Study	Left atrial diameter (mm)		LVEF (%)		Comorbidities (%)		
	Women	Men	Women	Men	Type	Women	Men
Forleo, 2007	44.0±6.5	40.6±6.3*	57.4±3.4	57.0±7.5	HTN	52.1	30.7*
					Valvular disease	15.5	5.3*
					Stroke	8.5	8.7
					Structural heart disease	32.4	23.3
Patel, 2009	43±0.5	46±0.3*	56±8	49±5*	HTN	55.2	40*
					Diabetes type II	15	11*
					Stroke	3.8	1.6*
					CAD	11.3	7*
Zhang, 2013	45.9±0.5	45.5±5.7	59.6 ± 4.2	58.3± 6.2	HTN	42.5	40.1
					Rheumatic heart disease	19.2	1.4*
					Stroke	11.0	8.8
Takigawa, 2013	37.2±5.0	38.0±5.1	68.6 ± 6.2	65.6± 7.0*	HTN	46.5	43.1
					Valvular disease	7.0	4.4
					Stroke	7.7	7.5
					Structural heart disease	17.8	16.4

AF: atrial fibrillation; CAD: coronary artery disease; HTN: hypertension; LVEF: left ventricular ejection fraction. *P < 0.05

high risk profiles in women, after 22.5±11.8 months of follow-up with holter monitoring at periodic intervals, overall freedom from arrhythmia recurrence was similar (Table 2). Improvement in quality of life measured at six months also did not show significant sex differences, as assessed by the Medical Outcome Study 36-Item Short-Form General Health Survey (SF-36), although there was a trend toward better improvement in quality of life in women. Thus, in this study, there was no statistically significant difference in the success rate or improvement in quality of life after pulmonary vein isolation despite sex disparities in risk factors.

Subsequently, a large retrospective multicenter study was performed by Patel et al. on 3265 consecutive patients with highly symptomatic and drug-refractory AF who underwent pulmonary vein antral isolation between January 2005 and May 2008 to evaluate outcomes in women.³³ Again, women constituted a much lower percentage of the patients referred for ablation, and they were older at the time of the procedure (Table 2). Women failed more antiarrhythmic drugs and were referred later for catheter ablation compared to men. Significantly more women had hypertension. Success rates were reported after initial ablation at each participating center off antiarrhythmic drugs. After 24±16 months of follow-up, women had significantly lower success rates than men (68.5 vs. 77.5% <0.001). Cox regression analysis demonstrated that in female patients, higher body mass index (BMI), non-paroxysmal AF, and non-pulmonary vein triggers predicted procedural failure. Women with non-paroxysmal AF or non-pulmonary vein triggers were twice as likely to fail catheter ablation. Although retrospective, this larger multicenter study suggested significantly lower success rates and higher failure rates in women who underwent pulmonary vein isolation.

Zhang et al. performed a prospective, single center, observational cohort study, evaluating 220 consecutive patients with long-standing, persistent, symptomatic and drug-refractory AF who underwent pulmonary vein isolation with or without complex fractionated atrial electrogram ablation (CFAEs) and linear ablation between January 2010 and May 2011.³⁴ This was the first study to focus on sex differences in ablation of persistent AF. This study also revealed a lower referral rate in women for ablation. After an average follow-up of 19±5.0 months, women had a lower success rate than men after

a single catheter ablation procedure (35.6% in women vs. 57.1% in men; P = 0.003). However, once repeat ablation was taken into consideration, there was no significant sex difference in success rates (54.8% in women and 66.0% in males; P = 0.417) (Table 2). Given the lower initial success rate, it is not surprising that more women underwent re-ablation procedures compared to men. A Cox regression analysis demonstrated that total duration of AF and sex were independent predictors of recurrence after the first catheter ablation

Most recently, a large scale prospective analysis of sex-related differences in catheter ablation of AF that enrolled 1124 paroxysmal AF patients was reported from Japan.³⁵ After a mean follow-up of 31.7±24.4 months following the index ablation, there was no significant difference in success rates between women and men. When redo procedures were included, the success rate was significantly lower in women compared to men after the last ablation, with a mean follow-up period of 39.0±21.8 months (Table 2). No significant predictors of recurrence in women were found either by univariate or multivariate Cox proportional analysis. This study also found no significant difference in the rates of complications between women and men.

The differences in these four studies with respect to outcomes of ablation of AF may be due to differences in patient population, sample size, and physician's decision making. The most recent study (Takagawa et al.) evaluated paroxysmal AF only, whereas Zhang's study targeted persistent AF patients. As persistence and duration of AF correlate with a high recurrence rate, such differences would be expected to affect the findings. The studies by Patel and Zhang appear to agree that women have lower success rates after the first ablation for AF, and they also have more high risk features for recurrence.^{34,35}

Sex-related recurrence rates have been reported as non-primary end points in at least 17 other studies. Most of these trials did not reveal significant sex-related differences in success rates.⁵²⁻⁶⁷ All of these trials reported low referral rates for ablation in women, in the range of 14-35%, and some reported late referral of women for ablation,^{32,33,35,52-67} as observed in other procedures in cardiovascular medicine.¹⁻⁴ Under referral and late referral of women for ablation of AF may increase the likelihood that women will have more advanced disease and higher risk features by the time of ablation and may lower

Table 2: Outcomes of AF Ablation in Women

Study	Design (enrollment, N)	% Women	Age, years		% Paroxysmal AF		Success Rate, % (includes redo)		Complication Rate, %		Major Complication Type, %		
			Women	Men	Women	Men	Women	Men	Women	Men	Type	Women	Men
Forleo, 2007	Prospective, two center, cohort (221)	32.1	61.6 ± 8.3	56.9 ± 10.8*	56.3	61.3	83.1	82.7	5.6	4.7	Pericardial tamponade	2.8	1.3
											Thromboembolic	0	1.3
											Pericardial effusion	1.4	1.3
											PV stenosis	1.4	0.7
Patel, 2009	Retro-spective, multi-center (3265)	15.8	59 ± 13	56 ± 19*	46	55*	68.5	77.5*	5	2.4*	Hematomas	2.1	0.4
											PV stenosis	1.2	0.6
											Stroke	0.8	0.29
											Pericardial effusion	0.4	0.1*
											Pseudoaneurysms	0.6	0.9*
Zhang, 2013	Prospective, single center (220)	33.2	62.7 ± 10.6	61.1 ± 10.4	All persistent AF		35.6 (54.8)	57.1* (66.0)	8.2	3.4	Pericardial effusion	1.4	1.4
											Pericardial tamponade	0	0.7
											PV stenosis	0	0
											Hematomas	6.8	0.7*
											Pseudoaneurysms	8.2	3.4
Tagigawa, 2013	Prospective, single center (1124)	24	63.2 ± 9.1	60.0 ± 10.5*	All paroxysmal AF		56.4 (76.5)	59.3 (81.3*)	3.7	4.1	Tamponade/effusion	1.8	1.3
											PV stenosis	0.3	0.1
											Vascular injury	0.59	0.1

n: number of patients enrolled. AF: atrial fibrillation; PV: pulmonary vein. *P < 0.05

the success rate. Anatomical differences in left atrial size have also been suggested as a possible culprit in the sex-related difference in success/failure rate; however, a recent study did not find a significant sex difference in left atrial antrum size despite significant differences in outcome.³⁴

Complication Rates Of AF Ablation In Women

Female sex has been reported as a predictor of complications after AF ablation, and higher complication rates from AF ablation in women have been found repeatedly.^{15,33,34,48,68-73} The multicenter U.S. retrospective study by Patel et al. reported total complications of 3265 (518 in women vs. 2747 in men), with a 5% complication rate in women vs. 2.4% in men (P < 0.001). This study also found more hematomas and pseudoaneurysms in women (Table 2).³³ In Zhang's study, the complication rate was higher in women, with a marked increase in hematomas.³⁴ A prospective analysis of 641 procedures (22.3% women) who underwent catheter ablation of AF from a single center reported more major adverse clinical events, defined as those that required intervention, resulted in long-term disability, or prolonged hospitalization, in women (P = 0.014; odds ratio 3.0, 95% confidence interval 1.3-7.2).⁶⁸ The same group reported female sex as a predictor of complications in both univariate and multivariate analyses.⁷²

Another prospective single-center analysis of procedural complications in the Vanderbilt AF Registry evaluated 445 patients who underwent AF ablation. This study reported a significant increase in complications in obese women. Morbidly obese patients experienced a higher rate of complications (14.3% vs. 6.2% in non-morbidly obese patients; P = 0.046). Using a discrete BMI cutoff, the odds of complications increased 3.1-fold in those with morbid obesity and 2.1-fold in women. With BMI as a continuous variable, the odds ratio for complications increased by 5% per 1 unit increase in BMI, and the risk in women was increased 2.2-fold.⁶⁹ A recent in-hospital analysis also revealed overall higher complication rates in women (7.51% vs. 5.49%; P < 0.001).⁴⁹ A large multicenter registry data from Italy enrolling 2323 patients also reported a significantly higher complication rate in women (7% vs. 4.4%), and female sex was reported to be an independent predictor of a higher risk of complications by univariate analysis (odds ratio 2.643, 95% confidence

interval 1.686-4.143, P < 0.0001).⁷⁰ Shah et al. also reported female sex to be a predictor of a higher risk of complications from AF ablation in their retrospective data analysis of 4156 patients.⁷³

Why do women, particularly those who are morbidly obese, pose a higher risk for complications? As hematomas and pseudoaneurysms are reported to occur more often in women, vascular access appears to play a significant role in the higher rate of complications. Variations in the anatomy of the femoral vasculature have been well reported.^{74,75} Schnyder et al. performed a prospective analysis of 200 consecutive common femoral artery angiograms. Their multivariate analysis revealed female sex as a predictor of small vessel size (P = 0.0005).⁷⁵ Although no specific studies have been performed, femoral venous anatomy, size, and proximity to the femoral artery could well be affected by sex, potentially increasing the risk of access-related complications in women, particularly in morbidly obese individuals. As systemic heparinization is routinely used during AF ablation, a differential effect of heparin in men and women may also play a role in sex differences in complication rates. Campbell et al. prospectively studied 199 consecutive patients presenting with proximal deep vein thrombosis not related to catheter ablation procedures. They assessed activated partial thromboplastin time (aPTT) values and heparin levels every 4 to 6 hours after a standard heparin bolus and infusion. The results revealed significantly higher heparin levels and higher aPTT values in women (P = 0.0002). After achieving therapeutic aPTT levels, women received lower heparin doses than the men, yet had higher heparin levels.⁷⁶ A sex difference in the pharmacokinetics of heparin was also suggested by Winkle et al., who found significantly higher activated clotting times (ACT) in women in an analysis of 1122 AF ablations. Women received less heparin but were over-represented in the higher ACT ranges (P < 0.0001).⁷⁷ This variation in the pharmacokinetics of heparin in women may contribute to a higher bleeding risk, predisposing women to a greater risk for hematomas. With these anatomical and pharmacological variations in women, extra modalities, such as vascular ultrasound or closer monitoring of activated clotting time, may be necessary to help reduce the number of complications in women.

Conclusions:

Success rates for AF ablation are clearly higher in earlier stages of

the disease process, when the arrhythmia is paroxysmal, left atrial size is relatively normal, and left ventricular function is preserved. Thus, it becomes clear that in order to have a comparable success rate of AF ablation in women, symptomatic women need appropriately early referrals for ablation before they develop a high risk profile.

When ablation is chosen as the treatment option for AF, it should be performed with extra attention to complications in women, particularly with respect to vascular access, as women appear to be at increased risk for these complications

Individualized care involving early referrals, pre-procedural case planning, and close monitoring intra- and post procedure may improve the odds for women to have better outcomes with catheter ablation of AF.

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