

## REVIEW ARTICLE

# Gender Differences in Atrial Fibrillation: A Review of Epidemiology, Management, and Outcomes

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## ARTICLE HISTORY

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**Abstract:** Atrial fibrillation is the most common sustained cardiac arrhythmia. The scope and impact of atrial fibrillation are wide; it can affect cardiac function, functional status, and quality of life, and it confers a stroke risk. There are sex differences in atrial fibrillation across the scope of the disease process, from epidemiology and causative mechanisms to management and outcomes. The approach to management of atrial fibrillation differs between women and men, and there are sex differences in response to medical therapy and catheter ablation. There are many gaps in our knowledge of the gender differences in atrial fibrillation, and many opportunities for future research.

**Keywords:** Atrial fibrillation, gender differences, antiarrhythmic drugs, catheter ablation, stroke, future research.

## 1. INTRODUCTION

### 1.1. Atrial Fibrillation: Scope and Epidemiology

Atrial fibrillation is a cardiac rhythm disorder characterized by rapid, disorganized excitation of the atria and irregular activation of the ventricles. It can affect cardiac function, functional status, and quality of life, and it confers a stroke risk that increases with additional risk factors. The scope and impact of atrial fibrillation are wide; it is the most common sustained cardiac arrhythmia, currently affecting at least 3 million adults in the United States [1]. The costs to the United States health care system are dramatic; the national annual incremental direct cost for patients with atrial fibrillation compared to those without is estimated to be \$6 billion. When associated with other cardiovascular costs and non-cardiovascular costs, this estimate rises to \$26 billion annually [1]. There are sex differences in atrial fibrillation across the scope of the disease process, from epidemiology and causative mechanisms to management and outcomes.

The ARIC (Atherosclerosis Risk in Communities) cohort, a group of over 15,000 participants followed for nearly 30 years showed a lifetime risk of atrial fibrillation of 36% in white men compared to 30% in white women. African American men and women both were found to have a lower lifetime risk of atrial fibrillation, at 21% and 22% respectively [2]. While women have a lower incidence of atrial fibrillation, the prevalence of atrial fibrillation in men and women >75 years of age is greater in women due to their

increased longevity, and the absolute number of men and women with atrial fibrillation is similar on a population basis [3, 4]. Medicare data show that in incident cases of atrial fibrillation in 2007, 55% were female [5].

There is conflicting data as to whether or not sex plays a role in the association of various risk factors and the development of atrial fibrillation. Women with atrial fibrillation tend to have a higher incidence of valvular heart disease, while men tend to have more coronary artery disease [6]. Men develop postoperative atrial fibrillation at higher rates than do women [4, 7]. BMI confers more of a risk of atrial fibrillation in men, though this is not a uniform finding [8]. Other risk factors including hypertension and diabetes seem to confer similar risk, and there is a trend toward an increased risk of atrial fibrillation in women with heart failure, though this is also not a universal finding [6, 9, 10]. Women are older at the time of diagnosis and have higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores [11, 12] (Table 1).

There are also female-specific factors that contribute to the development of atrial fibrillation, namely pregnancy. Data from the Women's Health Study shows a linear increase in the risk of atrial fibrillation with increasing parity, ranging from a hazard ratio of 1.15 for a single pregnancy to 1.46 for  $\geq 6$  pregnancies, as compared to no pregnancies. This may reflect repeated exposure to the physiologic, inflammatory, and hormonal stresses of pregnancy on the heart, and specifically the left atrium [13]. While gestational hypertension, gestational diabetes, and preeclampsia are independently associated with the long-term development of cardiovascular disease [14, 15], the association between these pregnancy complications and incident risk of atrial fibrillation has not been well-studied. Olmstead county data

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**Table 1. Risk factors related to the development of atrial fibrillation and odds ratio of developing atrial fibrillation in the presence of that risk factor.**

Risk Factor	Women	Men
Valvular heart disease	3.4 (OR)	1.8 (OR)
Coronary artery disease	1.0 (OR)	2.4 (OR)
Congestive heart failure	5.9 (OR)	4.5 (OR)
Hypertension	1.4 (OR)	1.5 (OR)
Diabetes	1.6 (OR)	1.4 (OR)
Body Mass Index	1.18 (HR per standard deviation increase)	1.3 (HR per standard deviation increase)

showed that hypertensive disease in pregnancy predicts the development of atrial fibrillation later in life with an odds ratio of 2.6, but this association was attenuated and not statistically significant (OR 2.12, confidence interval 0.92-5.23), when adjusted for hypertension and obesity [16].

## 2. MECHANISM: SEX DIFFERENCES IN ATRIAL REMODELING

There are known gender differences in electrophysiologic properties. Women have a prolonged QT interval compared to men, on average by 10-20 ms [4]. This difference in ventricular repolarization appears at puberty, with a shortening of the QT interval in men that persists over time [17]. The underlying mechanism for this difference is not completely understood; the change is theorized to be related to androgen hormones. Animal models suggest a sex hormone effect on the transmural dispersion of calcium channels and the density of potassium channels in the ventricular myocardium [18]. While gender differences in ventricular repolarization are well-established, gender differences in the electrophysiologic properties of the atria are not as well-studied.

Studies have shown that a longer duration of rapid atrial pacing leads to a shortening of atrial refractoriness and a tendency to maintain atrial fibrillation, changes known as electrical remodeling. Thereby, the presence of atrial fibrillation creates further susceptibility to continued atrial fibrillation. The mechanism of this electrical remodeling appears to be related to shortening of the wavelength of the atrial impulse, creating small areas of conduction block and favoring the initiation of reentry. Rapid atrial activation also leads to changes in ion channels, primarily calcium channels [19].

Published research regarding sex differences in atrial electrical remodeling between men and women is lacking. A small study looked at changes in atrial effective refractory period (ERP) during atrial pacing and found that the degree of shortening of atrial ERP was smaller in premenopausal women as compared with postmenopausal women and men. A shorter atrial ERP is a component of the electrical remodeling process that promotes atrial fibrillation. From these results, the authors conclude that female sex hormones are protective against atrial fibrillation, which may explain why the incidence of atrial fibrillation rises in post-menopausal women [20]. It could be theorized that sex hormone effects on ion channels similarly affect both ventricular and atrial

electrophysiologic function, but this topic requires further investigation.

Electrical remodeling is not the only change that influences susceptibility to atrial fibrillation; in fact, changes related to electrical remodeling are reversible after the stimulus is removed. There are structural changes that occur in the atria that predispose to the perpetuation of atrial fibrillation. One component of structural remodeling includes atrial fibrosis, which promotes non-uniform anisotropic conduction, a condition that promotes reentry and slow conduction. Structural remodeling has proven to be less reversible than electrical remodeling [19].

Atrial fibrosis has a strong association with atrial fibrillation, likely via contributing to conduction abnormalities and creating a vulnerable substrate. Histologic studies show women with long-standing atrial fibrillation have increased atrial fibrosis compared to women without atrial fibrillation, a pattern not seen in men. These gender differences were due to differential expression in genes and proteins that cause fibrotic remodeling [21]. MRI studies assessing delayed enhancement as a marker of atrial fibrosis show that female sex is a risk factor for delayed enhancement of both patients with and without atrial fibrillation [22]. This difference in fibrosis may be a cause of the finding that women have more non-pulmonary vein triggers for atrial fibrillation and tend to have lower success rates for catheter ablation of atrial fibrillation. Similar to data on gender differences in electrical remodeling, an investigation into gender differences in structural remodeling is scant.

While these findings are hypothesis-generating, there has been limited investigation in this area. Further elucidation of the sex differences in atrial electrophysiologic properties, atrial remodeling, and mechanisms for atrial fibrosis would be critical to understanding how gender plays a role in the development of atrial fibrillation.

## 3. MANAGEMENT: RATE CONTROL AND RHYTHM CONTROL

The two main treatment strategies for atrial fibrillation, apart from stroke risk reduction, are heart rate control or rhythm control, *i.e.* an attempt to maintain sinus rhythm. The AFFIRM trial, published in 2002, established that there is no mortality benefit between these two management strategies [23]. While recent data for catheter ablation of atrial fibrilla-

tion in heart failure patients has somewhat challenged this axiom [24, 25], the choice of rate vs. rhythm control is the one made between patient and doctor, based primarily on symptom management and patient preference. The literature supports that there are gender differences between these two management strategies: which treatment is recommended and response to therapy.

Multiple national and multinational registries reveal patterns of symptoms and management strategies that differ between women and men. The ORBIT-AF registry is a US nationwide observational cohort study of 10,135 patients, 42% women, enrolled between 2010 and 2011. Women were older, more likely to be symptomatic, and with lower quality of life scores. At enrollment, women were less likely to have undergone electrical cardioversion or catheter ablation. On follow up, women were more likely to have undergone AV node ablation/pacemaker implantation [26]. The Euro Heart Study on Atrial Fibrillation enrolled 5333 patients from 2003-2004. Women were older and more frequently had hypertension and valvular heart disease. Women tended to be more symptomatic overall, with more atypical symptoms such as dyspnea or chest pain, and with a lower quality of life scores. For patients with palpitations or syncope, considered to be “typical” symptoms, there was no difference in management strategy. For “atypical” symptoms including dyspnea, chest pain, dizziness, or fatigue, women were significantly less likely to be managed with a rhythm control strategy. This included class III antiarrhythmics, cardioversion, or catheter ablation [27]. Similar findings were seen in the European PREFER in AF registry of 7243 patients enrolled between 2012 and 2013. Women were older and more symptomatic. Women were less likely to undergo electrical cardioversion, catheter ablation, or surgical ablation. Women were more likely to be prescribed antiarrhythmic medications [28]. A South Korean prospective observational cohort of 6274 patients, the CODE-AF registry, showed similar results. Despite women having more atrial fibrillation-related symptoms, they were less likely to be managed with a rhythm control strategy, including less anti-arrhythmic therapy, less electrical cardioversions, and less catheter ablation [29].

When rhythm control is specifically pursued, there are significant differences between the sexes. A contemporary US cohort of 5976 patients with atrial fibrillation who were prescribed an antiarrhythmic drug was followed from 2006-2014. Women were older and with higher CHADSVASC scores, stroke and hypertension. Men had more coronary artery disease and heart failure. Women were less likely to be prescribed dofetilide and less likely to undergo electrical cardioversion or catheter ablation. They were more likely to be treated with an “ablate and pace” strategy, *i.e.* AV node ablation and pacemaker implantation [11].

### 3.1. Gender Differences in Antiarrhythmic Effects

While the AFFIRM trial showed no mortality benefit between rate and rhythm control, there was a higher rate of antiarrhythmic related adverse effects in the rhythm control group, such as bradyarrhythmias, torsades de pointes, and QT prolongation. When gender differences within a rhythm control strategy are further examined, women appear to have

more complications than men, related, in part, to adverse effects of antiarrhythmic drugs [30].

As discussed above, women have longer QT intervals at baseline, and this may affect their ability to tolerate antiarrhythmic medications, especially Vaughan Williams Class III antiarrhythmic drugs, which block potassium channels and prolong the QT interval. Women tend to have more QT prolongation with the administration of Class III antiarrhythmic agents, namely sotalol and dofetilide.

A small study on intravenous sotalol administration on a healthy population showed a greater degree of QT interval prolongation in women. Women had a longer QT interval compared to men at any concentration level of sotalol [31]. Real world data shows similar findings and a clinical impact on the continued use of sotalol. An electronic medical record cohort from a single center found 845 patients initiated on sotalol. Female sex was associated with QT prolongation, and it was a statistically significant predictor of sotalol discontinuation [32]. The difference in QT prolongation carries with it a real consequence. A meta-analysis of 22 multinational trials of patients treated with sotalol for both ventricular and atrial arrhythmias reviewed 3135 patients, 25% female. The authors found that women treated with sotalol were up to three times more likely than men to develop torsades de pointes [33].

Dofetilide is another potent class III agent. It can be an effective medication for controlling atrial fibrillation, and it has the benefit of relative safety in patients with heart failure. However, it can cause significant QT prolongation and has a 2-3% risk of torsades de pointes. The DIAMOND-CHF trial was a double-blind placebo-controlled study that examined the safety and efficacy of dofetilide for atrial fibrillation in patients with heart failure. Twenty-five percent of enrolled patients were female. Torsade de pointes occurred in 3.3% of patients. Female sex was significantly associated with the occurrence of torsade de pointes with an odds ratio of 3.2 [34].

The efficacy of dofetilide is directly related to its dosing. Steinberg *et al.* analyzed 308 patients, 24% female, admitted for dofetilide loading. There was no difference in pharmacologic conversion rates between men and women and no difference in excessive QT prolongation, though all episodes of torsades de pointes occurred in women. They found a dose-response that predicted pharmacologic conversion, where the rate of conversion based on the final dofetilide dosing was 75% for 500 mcg dosing, compared to 9% for 250 mcg dosing and 0% for 125 mcg dosing [35].

The recommended starting dose of dofetilide is 500 mcg twice daily due to the highest clinical efficacy of this dose, and dosing must be decreased for prolongation of the QT interval. Pokorney *et al.* studied a single center cohort of patients admitted between 2006 and 2012 for dofetilide initiation. 110 female and 100 male patients were matched and included in the study. Median age, creatinine clearance, and QTc interval were statistically similar between the two groups at baseline. Women were significantly more likely than men to have their dosing reduced or discontinued (55% vs 32%), primarily due to QT prolongation, but also due to bradycardia [36].

Many of the pharmacokinetic and pharmacodynamics studies performed on dofetilide enrolled only men. One pharmacokinetic study showed women have dofetilide clearance rates 12-18% lower than men, resulting in 14-22% higher plasma concentrations [36].

The fact that women may be less likely to tolerate the most effective dosing of dofetilide has clinical relevance for the efficacy of dofetilide to maintain sinus rhythm in women. Hassan Virk *et al.* evaluated the efficacy of dofetilide for cardioversion of atrial fibrillation. In a cohort of 160 patients, 26% female, female sex was associated with failure to convert to sinus rhythm and increased atrial fibrillation hospital readmissions at 1 year [37].

**3.2. Gender Differences in Catheter Ablation**

When a rhythm control management for atrial fibrillation is pursued, catheter ablation is widely used. There are differences in both the complication rates and outcomes of catheter ablation for atrial fibrillation between women and men.

The past few decades of experience have seen a substantial increase in the utilization of atrial fibrillation catheter ablation, with an eightfold rise in the number of ablation procedures from 2000 to 2013 [38]. This increase accompanies an overall increase in the use of catheter ablation for any cardiac arrhythmia. Large-scale data shows a concurrent increase in the rate of complications associated with catheter ablation for all cardiac arrhythmias, rising from 3.07% in 2000 to 7.04% in 2013. In part, this increase reflects an increase in more complex ablation procedures and comorbidities of patients. Female sex was a predictor of in-hospital complications for catheter ablation for any cardiac arrhythmia, with an odds ratio of 1.16 [38].

This trend of increased complications in women related to catheter ablation, and specifically catheter ablation of atrial fibrillation, is mirrored in multiple studies, though this finding is not uniform (Table 2).

A large retrospective study that used the National Inpatient Sample database evaluated patients who underwent catheter ablation for atrial fibrillation from 2004-2013. 85,977 patients were included, 32.4% of whom were female.

There was no mortality difference between the sexes, but women had a higher rate of major and minor complications, by an adjusted odds ratio of 1.5. This finding is echoed in other studies, most of which are retrospective. Complication specific differences show a statistically significant increase in vascular access complications, cardiac tamponade and pericardial effusions, and post-operative hemorrhage requiring transfusions in women [39-41].

In the literature, female sex is not uniformly a risk factor for increased complications from catheter ablation. Older studies more uniformly show female sex as a risk factor for increased vascular events, primarily related to pericardial effusions/cardiac tamponade and vascular injury [41-44], while more current literature does not always show this finding [45, 46]. Data from the Johns Hopkins group support this temporal trend. Their data from catheter ablation performed between 2001 and 2010 show female sex as predictive of complications [41, 42], whereas data published on ablation performed between 2003 and 2015 show that female sex alone was not a predictive factor for complications [46] (Table 2).

As vascular complications and pericardial effusions are the complications most consistently found to be higher in women, it is feasible that anatomical differences account for the increased complication rates. While there has been no sex-specific differences in left atrial volume index found, the left atrial diameter is smaller in women [47], perhaps making left atrial perforation more likely with a transeptal puncture. With the increased use of intracardiac echocardiogram, the risk of perforation overall has been reduced. This may account for more current data that does not show as much of a gender difference in complication rates. A single-center study reporting outcomes on 1192 atrial fibrillation ablations with routine use of intracardiac echocardiogram showed only a 0.25% rate of cardiac tamponade/hemopericardium, and no statistically significant difference in complication rates between men and women [48]. Similarly, the use of ultrasound guidance for vascular access has been shown to reduce vascular complications in any catheter-based EP procedure and specifically in atrial fibrillation ablation [49]. A study that compared traditional landmark based vascular access vs ultrasound guided access in women over the age of 75 under-

**Table 2. Gender differences in complication rates in catheter ablation for atrial fibrillation.**

Authors	Number of Patients	% Women	Enrollment Dates	Primary Outcome Evaluated	Odds Ratio for Women Compared to Men
Elayi	85,977	32.4	2004-2013	Major complications	1.48
Bollmann	21,141	39	2010-2017	Pericardial effusion	1.86
Hoyt	931	23	2001-2010	Major complications	2.0 (HR)
Baman	1295	26	2007-2010	Complications	2.27
Spragg	517	22	2001-2007	Major complications	3.0
Inoue	3373	24	2011-2012	Complications	1.6
Guhl	450	26	2011-2015	Major complications	NS
Yang	1475	18	2003-2015	Major complications	NS

going atrial fibrillation ablation showed a 5.1% vascular access complication rate in landmark based access vs 0.48% in ultrasound-guided access [50].

It may be that updated catheter ablation technology including the use of intracardiac echocardiogram and ultrasound guidance may reduce or eliminate the gap in complication rates between men and women, as well as reduce complications in the population as a whole.

Outcomes of atrial fibrillation ablation also differ between men and women. Similar to studies on complication rates, findings are not entirely uniform, but the majority of the literature shows an increased rate of atrial fibrillation recurrence in women after catheter ablation [51-53]. For example, the FIRE AND ICE trial, which examined cryoablation vs radiofrequency ablation for drug refractory paroxysmal atrial fibrillation, showed that women had a 36% higher rate of recurrence and a 37% higher rate of cardiovascular hospitalization after ablation [51].

The reason for this difference in outcomes is not entirely clear. Selection bias likely plays a role. Multiple studies show that women who undergo catheter ablation are older, have increased CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and higher comorbidities, have higher rates of longstanding persistent atrial fibrillation, have failed more antiarrhythmic agents, and are referred for ablation later in their clinical course [54, 55]. Both duration of atrial fibrillation and CHA<sub>2</sub>DS<sub>2</sub>-VASc score have been shown to directly correlate with a lower success rate of catheter ablation [56, 57]. During ablation, women have more non-pulmonary vein firing sites than men [55]. The presence of non-pulmonary vein triggers, especially those that are unable to be mapped and cannot be ablated, is a risk factor for atrial fibrillation recurrence [58, 59]. In the FIRE AND ICE study, recurrence rates diverged after 6 months, perhaps reflecting a less-durable ablation lesion in women [51].

The CASTLE-AF study, which showed a reduction in death or heart failure hospitalizations for patients with atrial fibrillation and heart failure who underwent catheter ablation compared with medical therapy, did not show a statistically significant difference in the primary end-point between women and men. Women only comprised 15% of the study population [24].

#### 4. MANAGEMENT: STROKE RISK REDUCTION

Atrial fibrillation is a known risk factor for stroke; it is associated with 4-5 times increased risk of ischemic stroke, accounting for approximately 15% of strokes in the US. The association of atrial fibrillation and stroke increases with age; 23.5% of strokes in people ages 80-89 is associated with

atrial fibrillation [5]. The mechanism behind this association is not completely understood. It is, in part, due to cardioembolic phenomena related to thrombus formation in the left atrial appendage. It is posited that there are additional factors related to elevated stroke risk, including atrial cardiopathy (*i.e.* abnormal atrial substrate) and systemic vascular risk factors [60]. Anticoagulants reduce the risk of stroke by at least 60% [61]. The representation of women in the major trials studying the novel oral anticoagulants, namely RE-LY, ROCKET-AF, and ARISTOTLE, was 37% when all populations were pooled. There were no significant differences in the outcome between male and female sex in a subgroup analysis in any of these three trials [62-64].

Risk stratification scores have been established to estimate an individual's stroke risk and aid clinicians in decision making for anticoagulation recommendations. Increasing evidence showed that female gender was an added risk factor for stroke. In 2010, the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scoring system, which added a female gender as a risk factor, was validated at better refining stroke risk, especially for people at intermediate risk based on older risk scoring systems.

##### 4.1. Anticoagulation

The data on gender differences in anticoagulation of patients with atrial fibrillation is not consistent. The Euro Heart Survey, a cohort of 5000 patients (42% female) showed no difference in anticoagulation rates [27]. Kassim *et al.*, in their cohort study of close to 6000 patients, showed a significant difference in the anticoagulation of women and men, 76.8% and 82.5%, respectively. This was driven by a difference in anticoagulation between women and men over the age of 75 years, perhaps due to a perception of increased bleeding in older women [11]. The South Korean CODE-AF registry showed no significant difference in the prescription of anticoagulation between women and men, though women prescribed DOACs were more likely to be insufficiently dosed [29]. The PINNACLE National Cardiovascular Data Registry from 2008-2014 showed women were less likely to receive oral anticoagulation at all CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, by a factor of up to 33% [65].

Women with atrial fibrillation treated with warfarin have a significantly increased residual risk of stroke or systemic embolism compared with men, with an odds ratio ranging from 1.2-2.9 in various studies [66, 67]. This is in contrast to treatment with DOACs, for which rates of stroke or systemic embolism are comparable between women and men. The risk of major bleeding was similar between women and men on warfarin, while women had significantly lower major bleeding rates when treated with DOACs (OR 0.84) [67]. The

**Table 3. Differences in outcomes between men and women in DOAC trials.**

Trial	% Women	Primary Outcome	P Value for Difference in Primary Endpoint Between Women and Men
ARISTOTLE (apixaban)	35	Stroke or systemic embolism	0.60
RE-LY (dabigatran)	37	Stroke or systemic embolism	0.24
ROCKET AF (rivaroxaban)	39.7	Stroke or systemic embolism	0.927

finding of increased risk of stroke and systemic embolization for women treated with warfarin may be due, in part, to a tendency for women on warfarin to have a lower time in therapeutic range compared to men [68, 69], though increased stroke rate has been documented even when quality of anticoagulation is similar [66].

The reason for increased risk of stroke for women with atrial fibrillation is not known. As discussed above, stroke risk in atrial fibrillation is likely not due to only clot formation in the left atrial appendage. If women have higher rates of atrial fibrosis in atrial fibrillation, this would contribute to the abnormal atrial substrate and atrial cardiopathy that may contribute to stroke. Female sex hormones may play a prothrombotic role *via* effects on platelet and endothelial function.

#### 4.2. Left Atrial Appendage Closure

Left atrial appendage closure has been developed as an alternative method for stroke risk reduction for people who cannot tolerate anticoagulation. There is no strong indication that women have higher complication rates with this technology. The European experience with the Watchman showed that female gender was a predictor for pericardial effusion and cardiac tamponade at 30 days, albeit with an overall low event rate of 1% [70]. Data from PROTECT-AF and PREVAIL trials did not show any gender differences in complication rates [71, 72]. A small study of 78 people that looked at device-related thrombus (DRT) found that more women than men developed DRT, but this was not statistically significant and not an associated factor in multivariate analysis [73].

### 5. OUTCOMES

#### 5.1. Quality of Life

The presence of atrial fibrillation is associated with a reduction in quality of life. This has been documented in patients with both paroxysmal and persistent atrial fibrillation. Compared with healthy controls, quality of life is reduced in patients with atrial fibrillation across a variety of studied domains, including illness intrusiveness, global life satisfaction, mental health and functional capacity. The reduction in quality of life scores is similar to that seen in heart failure and post-coronary intervention patients. These subjective measures have been found to be independent of the objective severity of atrial fibrillation, such as may be assessed by left ventricular function or duration of atrial fibrillation [74]. A substudy from the AFFIRM trial, which evaluated rate vs rhythm control for patients with atrial fibrillation, found that quality of life measures did not differ significantly between patients managed with a rate control or rhythm control strategy. Multiple studies have shown that women with atrial fibrillation have worse quality of life score across multiple domains [27, 30, 75, 76], and to be more symptomatic from their atrial fibrillation [27, 30].

The differences in quality of life measures between women and men are not fully understood. Studies have looked at somatization, depression and personality traits as predictors of lower quality of life scores, and attributed gender to influencing these factors [77, 78], but personality traits

are unlikely causative of consistently lower quality of life scores across an entire gender. Sex differences in atrial remodeling and diastolic function perhaps interplay in a way that worsens symptoms when atrioventricular dyssynchrony is lost, but this has not been studied.

Some data support that quality of life scores improve similarly after catheter ablation for atrial fibrillation for men and women [52]. However, the data on gender differences in quality of life scores after treatment for atrial fibrillation is limited and warrants more attention.

#### 5.2. Mortality

A large meta-analysis that included papers published between 1999 and 2014 showed that the preponderance of data showed no significant difference in mortality between women and men with atrial fibrillation [79].

### CONCLUSION

Atrial fibrillation is a complex and dynamic disease state. Its impact on our health system cannot be overstated, especially in the context of an aging population. While our understanding of atrial fibrillation and tools for management have advanced over the past decade, many gaps are yet to be filled. The gender differences in atrial fibrillation are vast. Mechanisms and etiology, response to treatment, stroke risk and outcomes all differ between women and men in significant ways. The literature shows many reasons for a gendered management strategy in treating atrial fibrillation. For example, antiarrhythmic drugs and catheter ablation can have more complications in women than in men. However, the data are nuanced. A better understanding of these differences and how to mitigate adverse outcomes is critical to knowing how best to treat atrial fibrillation. Basic science, translational, and clinical research into gender differences in atrial fibrillation are all lacking. Our current outcomes, specifically in regards to sex differences, are not uniform, and likely represent the rapidly changing technology and the expansion of treatment options to older patients with increased comorbidities. Women are significantly underrepresented in clinical trials and retrospective studies on atrial fibrillation, which makes interpretation of the data and understanding the true risk and benefit of different management and treatment strategies difficult.

Areas for future research include:

- Differences in atrial electrophysiologic properties and the mechanisms responsible for gender differences in atrial fibrosis and atrial remodeling
- Causes of increased stroke risk in women: association between atrial remodeling and risk of stroke, gender differences in systemic contributors to risk of stroke
- Role of diastolic dysfunction in relation to symptom burden in atrial fibrillation
- Gender differences in complication rates in catheter ablation of atrial fibrillation with use of ultrasound guidance for venous access and transseptal puncture
- Disease course timing of catheter ablation of atrial fibrillation and outcome differences in women

- Sex-specific guidelines for use of antiarrhythmic agents
- Increase in proportion of women included in clinical research on atrial fibrillation and treatment, including anticoagulation, antiarrhythmics, catheter ablation, and long-term prospective cohorts.

### CONSENT FOR PUBLICATION

Not applicable.

### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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