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Women and atrial fibrillation

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Abstract

Atrial fibrillation (AF) remains a growing problem in the United States and worldwide, imposing a high individual and health system burden, including increased resource consumption due to repeated hospitalizations, stroke, dementia, heart failure, and death. This comprehensive review summarizes the most recent data on sex-related differences in risks associated with AF. Women

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with AF have increased risk of stroke and death compared to men, and possible reasons for this disparity are explored. Women also continue to have worse symptoms and quality of life, and poorer outcomes with stroke prevention, as well as with rate and rhythm control management strategies. Many current rhythm control treatment strategies for AF, including cardioversion and ablation, are used less frequently in women as compared to men, whereas women are more likely to be treated with rate control strategies or antiarrhythmic drugs. Sex differences should be considered in treating women with AF to improve outcomes and women and men should be offered the same interventions for AF. We need to improve the evidence base to understand if variation in utilization of rate and rhythm control management between men and women represents health inequities or appropriate clinical judgement.

Keywords

catheter ablation; left atrial appendage closure; quality of life; stroke prevention; women

1 | INTRODUCTION

Atrial fibrillation (AF) remains a growing problem in the United States and worldwide due to high healthcare burden, including increased resource consumption related to repeated hospitalizations, stroke, dementia, heart failure (HF), and death. In two community-based cohorts, even after accounting for age, duration of AF, and other comorbidities, AF conferred a pooled estimated incremental cost of US $18,601 (95% confidence interval [CI]: US $15,981–US $21,234) in 2009 dollars versus non-AF patients.[1] Experts estimate that AF cost $28.4 (95% CI, 24.6–33.8) billion in 2016.[2] Also troubling is the prediction that the incidence of AF is expected to continue to increase over the next decade.

The overall lifetime prevalence of AF is similar for both sexes. Yet, AF does not have similar consequences in women and men, an important consideration that has received limited attention. Accordingly, this review examines sex differences in AF with respect to presentation, clinical course, and outcomes.

2 | EPIDEMIOLOGY

2.1 | Sex differences in prevalence and incidence

The prevalence and incidence of AF varies by sex, age, race/ethnicity, intensity of screening, and over time. The prevalence in the United States was about 5.2 million in 2010[3] and 37.6 million in 2017 world-wide, with an estimated prevalence of 17.8 million women and 19.8 million men in 2017.[4] Importantly, AF prevalence has been increasing in both sexes over time.[5,6] Among individuals 45–94 years of age, in the Framingham Heart Study (FHS), between 1958–1967 and 1998–2007 the age-adjusted prevalence quadrupled in both women and men (from 13.7 to 49.4 and 20.4 to 96.2 cases per 1000 person-years, respectively).[5] Since on average women live longer than men, the number of women and men with AF are similar despite the higher risk of AF in men. In a 5% sample from 2007 Medicare recipients with AF, 47,719 were women and 42,475 were men; the corresponding prevalence rate per 1000 beneficiaries was 63 and 88 in women and men, respectively.[6] Regardless of sex, AF

prevalence increases markedly with advancing age, and is higher in individuals of European ancestry versus other races/ethnicities.[6]

Similar to these prevalence data, the AF incidence rate has increased over time (Table 1).[5,6] Tables 2 and 3 show incidence rates per 1000 person-years in various groups based on level of risk, and in different racial/ethnic groups.[7,8]

Most studies report a higher incidence of AF in men versus women,[5-7,9] for reasons that are unclear. However, in the CHARGE-AF model, based on three US cohort studies and replicated in two European cohorts, sex per se did not appear to be a risk factor for incident AF after accounting for participant height and other risk factors.[9]

2.2 | Sex differences in lifetime risk

The FHS (European ancestry) suggested that at age 55, the lifetime risk of AF varied by sex, as well as the presence and burden of AF risk factors (Table 2).[10] However, in the Atherosclerosis Risk in Communities (ARIC) cohort, the lifetime AF risk varied by sex in Whites, but not in Blacks (Table 4).[11]

2.3 | Sex differences in af burden: Role of screening

Detection of AF increases with the duration and intensity of screening. For instance, in a Swedish community-based screening study of individuals 74–75 years old, after 2 weeks of intermittent electrocardiogram (ECG) recordings, 3.0% were observed to have previously undiagnosed AF, and only 0.5% had AF detected on their initial ECG.[12] A meta-analysis of 13 community-based screening studies confirmed a higher rate of newly detected AF in men versus women. However, the absolute numbers of AF cases detected were similar in men and women at age 80 years, presumably because of the greater number of older women in the sample.[13]

Cardiac implantable electronic devices (CIEDs) also have contributed to increased recognition of subclinical AF—that is, AF not previously diagnosed.[14] A study of 3131 patients with CIEDs (30% women) reported that the presence of more than 6 h of AF per week was associated with increased odds of death and the association was stronger in women compared with men.[15]

2.4 | Potential mechanisms for differences

Mechanisms underlying sex differences in AF are incompletely understood.[16,17] Factors that contribute to increased incidence of AF in men are taller stature, higher body mass index (BMI), and larger atria and ventricles.[9,18-21] The greater burden of atrial fibrosis in women with AF[22,23] may predispose them to more complications with AF. In a consecutive case series, compared with men, women had more atrial fibrosis that was associated with higher prevalence of stroke or transient ischemic attack.[23] A study of patients with persistent AF undergoing cryoballoon pulmonary vein isolation showed that the extent of left atrial low voltage areas (atrial fibrosis) predicted AF-free survival, and this type of ablation appeared highly effective in patients with persistent AF without atrial fibrosis.[24]

2.5 | Mortality and AF

There is a significant AF-sex interaction with mortality, such that AF reduces the typical survival advantage enjoyed by women. In a meta-analysis of 30 studies with over 4.3 million participants, the ratio of relative risks (RRs) comparing women with men was 1.12 (95% CI, 1.07–1.17), based on a RR of mortality of 1.69 (95% CI, 1.50–1.90) in women, and 1.47 (95% CI, 1.32–1.65) in men with versus without AF.[25] In absolute terms per 1000 patient-years, compared with men, women had a 1.8 (95% CI, 1.1–2.6) excess risk of death associated with AF. These investigators concluded that women compared to men with AF had a higher RR of stroke, all-cause and cardiovascular mortality, cardiac events, and HF.[25]

3 | PRESENTATION, SYMPTOMS, AND DIAGNOSIS

Women with AF report more symptoms than men, but findings from different studies vary.[26-30] A 2019 study reported that women were more likely to report AF symptoms, and poor AF-related quality of life than men.[31] In a study of emergency department patients, women were more likely to have longer duration of symptoms and to present with atypical symptoms like weakness and/or fatigue.[16,32]

Women, compared with men, with AF also have more functional impairment, greater limitation in their daily activities, and lower quality of life scores. In some studies, such as the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), women had less persistent forms of AF compared to men.[27] However, in EORP-AF,[33] there was no difference in the subtypes of AF duration between the two sexes. In ORBIT-AF, women had 24% lower quality of life score, even after adjustment for comorbidities.[27]

Diagnostically, stress testing, and transesophageal echocardiograms for left atrial appendage (LAA) investigation are less likely to be performed in women with AF.[33,34] While some studies have not identified sex differences in the utilization of transthoracic echocardiograms or transesophageal echocardiograms, others have observed that these studies are ordered less often in women with AF.[35,36]

3.1 | Prognosis of AF with HF

Women have a higher adjusted risk of incident HF (56.0 and 50.7 per 1000 person-years, respectively).[25,37] Most likely due to less ischemic cardiomyopathy, women have less incidence of HF with reduced ejection fraction (12.4 vs. 27.2 events per 1000 person-years).[37] On the other hand, because of the higher prevalence of valvular heart disease and hypertension in women,[36,38] women have a higher incidence of HF with preserved ejection fraction (HFpEF; 35.1 vs. 21.2 events per 1000 person-years).

4 | STROKE PREVENTION IN AF-SEX DIFFERENCES IN STROKE RISK

Many studies examining associations between sex and stroke risk in AF have concluded that women are at greater risk for stroke than men; a 20–30% excess risk versus men, even after adjusting for differences in stroke risk factors and anticoagulant treatment.[25,39-44] A meta-analysis of 44 reports confirmed the higher risk of stroke in women (RR, 1.24;

95% CI, 1.14–1.36], and also confirmed that the risk increased after age 65 years.[41] These findings led to the inclusion of female sex in the CHA_2DS_2-VASc stroke risk score.[45-47]

Although the weight of evidence points toward higher risk for stroke among women compared to men, the explanation for this disparity remains unclear. Hypotheses include biological differences between women and men, higher burden of atrial fibrosis, differences in distribution, manifestation, intensity of comorbid conditions related to stroke, and differences in treatment with anticoagulants. In addition, female sex has been associated with a twofold increased risk of severe disabling or fatal ischemic stroke in consecutive AF patients with stroke, according to the "Get With the Guidelines" stroke database, even after adjustment for possible confounders.[48]

A large retrospective Swedish cohort study of (231,077 people (48.1% women)) unselected patients with AF not receiving oral anticoagulation from 2006 to 2014 found that there was 1.5-fold higher risk of ischemic stroke in women compared to men. They found that this higher risk was the result of confounding by age. They also found that in the CHA2DS2-VASc low risk end, the score underestimated the ischemic stroke risk conferred by age 65–74 years but it overestimated the risk conferred by female sex.[49]

Whether variation in stroke severity is related to underlying treatment patterns remains uncertain. Data from the PINNACLE National Cardiovascular Data Registry suggested that women with AF were significantly less likely to receive oral anticoagulants at all levels of the CHA_2DS_2-VASc score, and men received oral anticoagulants more than women.[50] Another American study of 2.3 million women and men with a new diagnosis of AF and CHA_2DS_2-VASc ≥2 from 2008 to 2015 also found women were not anticoagulated as frequently as men. The oral anticoagulation-eligible women were not as likely to receive anticoagulation; 50.0% women versus 43.9% men did not received anticoagulation. A mediation analysis revealed that not receiving oral anticoagulation partially mediated the observed increased risk of stroke but also decreased risk of intracranial bleeding in women.[51] In the global FIELD (GARFIELD)-AF anticoagulant registry, there was no significant difference in the overall rate of anticoagulant use found between the sexes (61% for both).[52]

Direct oral anticoagulants were first introduced into clinical practice in 2011 and fewer women received oral anticoagulants (53% men vs. 48% women); women were also more likely to receive aspirin only (35% women vs. 30% men). However, these sex differences were no longer observed by 2015, except for women ≥80 years and those with complicated comorbidities.[52,53]

In the Atrial Fibrillation Follow up in Rhythm Management (AFFIRM) trial, women had a higher risk of stroke than men even when they had comparable time in the therapeutic anticoagulation range on warfarin. However, women were found to spend less time in therapeutic range compared to men.[54]

Two meta-analyses of major direct oral anticoagulant versus warfarin trials found that direct oral anticoagulants resulted in better outcomes for women. These outcomes included stroke, thromboembolism, and major bleeding.[55,56] Four direct oral anticoagulants (apixaban,

dabigatran, edoxaban, and rivaroxaban) were compared in a meta-analysis that found no significant difference with regard to safety and efficacy in women compared with warfarin, suggesting that they can be used interchangeably among women.[57]

Sex-specific differences in the distribution and effect of various CV risk factors are well documented, which may contribute to higher stroke risk in women versus men with AF.[5,18,58,59] Compared with men, women with AF are, on average, older, and more likely to have thyroid dysfunction, hypertension, valvular heart disease, and HFpEF.[16] Although studies have attempted to adjust for differences in risk factors between women and men, adjustment may be insufficient or incomplete. For example, a population-based study found that the 16% higher risk of stroke observed in women with AF disappeared once women and men were matched on time-varying risk factors instead of simply adjusting for baseline factors at cohort entry.[60]

The updated AF guidelines for anticoagulation from American and European organizations are compared in Table 5. Women with CHA_2DS_2-VASc scores of ≥3 and in men with CHA_2DS_2-VASc scores of ≥2 should be anticoagulated. Women with CHA_2DS_2-VASc scores of ≥2 have variable levels of recommendation strength. All the guidelines recommend no anticoagulation for patients with CHA_2DS_2-VASc scores of 0 among men or 1 among women.[61-63] A study found that women with CHA_2DS_2-VASc of 2 or less had very low risk of stroke/systemic thromboembolism and therefore should not be anticoagulated. It was only when the CHA_2DS_2-VASc was ≥3 did women have a higher risk of stroke compared to men.[64]

4.1 | Percutaneous LAA closure devices

During AF, the LAA contractility is limited and blood flow is stagnant creating a nidus for clot formation, which increases with smaller LAA orifice and higher number of lobes.[65] The LAA is considered the primary source of cardioembolic stroke in patients with nonvalvular AF.[66] In a cohort with high AF stroke risk, women had more extensive LA remodeling and deterioration of LAA function than men, which may play a role in the higher stroke risk observed in women.[67]

The following LAA endocardial occlusion devices have been developed for stroke risk reduction in AF patients: the Watchman, the Amplatzer Cardiac Plug and Amulet, the WaveCrest, the Atri-Clip, and the Lariat. These devices are in different stages of "regulator approval" in the United States and Europe. The most extensively studied device is the Watchman and is approved by the US Food and Drug Administration.[68] There was no significant interaction with sex and a composite efficacy endpoint of stroke, systemic embolism, and CV death was found in a meta-analysis of the PROTECT-AF (Percutaneous Left Atrial Appendage Closure vs. Warfarin for Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation vs. Long-Term Warfarin Therapy) trials.[69] A small earlier study of the Watchman reported that there was a nonsignificant trend towards women having device-related thrombus (75 vs. 34%, $p = .094$) versus men.[70] More recent data indicate no significant sex differences in device-related thrombus with the Watchman.[71] In univariate and multivariate logistic regression model studies of the Amplatzer Cardiac

Plug showed that female sex (OR, 4.22; $p = .03$) and cigarette smoking (OR, 5.79; $p = .02$) were predictors of device-related thrombus in adjusted models.[72] Potential reasons for women having a higher incidence of device-related thrombus were not mentioned. Interestingly, a wider LAA mouth is associated with deeper implantation of the device, and subsequently, device-related thrombus, not smaller LAA.

Notably, mortality in candidates for LAA closure and/or undergo device implantation ranges between 5% and 10% a year, likely related to underlying comorbidities.[73-75] A recent meta-analysis suggested improvement in survival with device implantation after analyzing the results of the PROTECT AF and PREVAIL trials. In a multicenter retrospective study of 101 patients (48% women) who underwent LAA device implantation due to a contraindication to anticoagulation, 85% of whom received an Amplatzer Cardiac Plug/Amulet device, male sex, and not female sex, was independently associated with late mortality.[75]

4.2 | Surgical closure of LAA

LAA exclusion or excision may be considered in conjunction with surgical ablation for AF and at the time of cardiac operations in AF patients for thromboembolic prevention (Class IIA, level C expert opinion by the surgical guidelines, whereas the AHA/ACC/HRS guidelines consider it a Class IIB, Level of evidence B-nonrandomized data) and the European guidelines consider it a Class IIB, Level of Evidence C.[61,62,76] Despite the high prevalence of postoperative AF, there is not sufficient evidence to recommend routine left atrial exclusion during heart surgery.[77]

Surgical occlusion of the LAA (LAAO) includes excision or amputation, and exclusion (clip/stapler, suture ligation). Success rates vary according to surgical procedure with highest success with excision/amputation techniques.[78] A recent meta-analysis concluded that surgical LAAO was associated with a lower risk of thromboembolic events and stroke.[79] In a retrospective cohort of 75,782 adults with LAAO during cardiac surgery, with 29% women, the hazard ratio for stroke was higher in women [0.80 (0.51–1.25)] than men [0.59 (95% CI, 0.39–0.91)] among propensity-matched patients with AF at baseline.[80] However, there are currently no published data focused on differences in outcomes by sex in surgical closure of the LAA.

5 | RATE CONTROL–SEX DIFFERENCES

5.1 | Atrioventricular nodal blocking drugs

When treated for AF, women are more likely to receive rate control rather than rhythm control strategies compared to men,[29] but reasons for this disparity are unclear. Rate control medication alone for AF was associated with comparatively poorer functional status and quality of life.[31]

Sex hormones affect the pharmacokinetics of drugs. Differences in physiology, pharmacokinetics, and pharmacodynamics are responsible for a greater risk for adverse drug reactions in women.[81] Many factors cause sex-specific differences in pharmacotherapy in women, including a lower BMI and creatinine clearance, a higher proportion of body fat, and smaller organs.[82] Drug absorption may also be slower in women. Sex differences

are mainly modulated by the activity of drug-metabolizing enzymes, particularly the cytochrome (CYP) P450 system.[81] CYP3A4 contributes to first-pass metabolism of most CV drugs, including diltiazem and verapamil. Higher expression of CYP3A4 messenger RNA and twofold higher CYP3A4 levels are found in women on liver biopsy.[81] Whether there is a sex-specific difference for CYP2D6, which has a role in the metabolism of metoprolol and propranolol, is controversial.

Whereas it is clear that there are sex differences in β-blocker and calcium channel blocker metabolism, whether these differences affect the doses needed to achieve ventricular rate control in AF in men versus women is unknown. Differences in body size should be considered when selecting a specific drug dose, but other factors such as atrioventricular nodal conduction properties in an individual patient will also affect ventricular rate control.

Although β-blocker use has been reported to be similar in men and women (72.5% and 70.0%), women have been more likely to be prescribed digoxin (25.0% vs. 19.8%)[29] which have resulted in higher serum levels of digoxin and a higher mortality rate compared to men, despite lower doses.[83] On the other hand, a posthoc analysis of the Rivaroxaban versus Vitamin K Antagonist for Prevention of Stroke and Embolism Trial (ROCKET) AF trial, suggested a significant digoxin–sex interaction, with increased risk of all-cause mortality and vascular death among men with AF compared with women.[84] In addition to mortality, two studies found an increased risk of breast cancer when cardiac glycosides were used for AF.[85,86] The Women's Health Initiative, which enrolled 93,676 postmenopausal women from 1994 to 1998 and followed them for 15 years, reported that AF patients had a 5.7% incidence of invasive breast cancer. There was a 19% excess risk of invasive breast cancer with cardiac glycoside use. Adjusting for AF and other confounders, cardiac glycoside use was strongly associated with incident invasive breast cancer (hazard ratio [HR], 1.68; 95% CI, 1.33–2.12).[85] A meta-analysis of 29 studies found that cardiac glycoside use was associated with increased risk of breast cancer by about a third (RR, 1.33; 95% CI, 1.25–1.42).[86]

5.1.1 | Bradycardia and need for pacing—Despite higher resting sinus rates, women are more likely than men to have sinus node disease as the indication for permanent pacemaker implantation; however, in general, women are older at the time of need for pacemaker implantation.[87] There are more men than women who receive permanent pacemakers under the age of 80 years, whereas the opposite is true after that age.[87] Potential explanations for the older age at the time of development of bradycardia and the cause of bradycardia in women include the protective effect of sex hormones and later development of significant cardiovascular disease in women. Women, particularly those over 80 years old, may be more likely to receive single chamber ventricular pacing rather than dual chamber pacing system, although the reason may be because of advanced age than sex. Another potential explanation may be higher prevalence of persistent AF, especially if women are less likely to be treated with rhythm control.

Women also have higher rates of complications such as pocket hematoma and pneumothorax from permanent pacemaker implantation compared with men, adjusting for age, and type

of device implanted.[87] Smaller body habitus is one factor likely responsible for this observation.

6 | RHYTHM CONTROL–SEX DIFFERENCES

In addition to the aforementioned ECG sex differences, on average women also have higher resting heart rates, shorter P wave duration, decreased QRS width, less frequent J waves, decreased ST segment abnormalities, and increased QT duration.[88]

Female sex is independently associated with adverse left atrial remodeling.[89] Therefore, restoring and maintaining sinus rhythm was thought to present a strategy to improve quality of life and reduce mortality in women. However, in the Rate Control Efficacy (RACE) trial, women randomized to a rhythm control strategy using medications had a greater rate of cardiovascular events (i.e., cardiovascular death, HF, thromboembolic complications, bleeding, severe adverse effects of antiarrhythmic drugs (AADs), and need for pacemaker implantation), largely driven by adverse effects from AADs.[90,91] Severe AAD-related side effects were experienced at a greater rate by women than men in the RACE trial, including sick sinus syndrome, torsade de pointes, and atrioventricular conduction during atrial flutter (4.7% vs. 1.5%), as well as pacemaker implantation (3.6% vs. 1.2%).[91]

Women have higher risk of proarrhythmia and adverse effects with AADs, including Class IA[92] and class III AADs, including amiodarone, which has traditionally been thought to confer the lowest proarrhythmia risk.[93] A study of patients over 65 years old with new-onset AF found that female sex was an independent risk factor for bradyarrhythmia and need for pacemaker placement (OR, 3.86 women vs. 1.52 men).[94] With the exception of the AFFIRM trial,[95] class III AADs have been shown in multiple studies to be associated with a greater risk of torsades de pointes (TdP) in women. Lack of sex-associated differences observed in the AFFIRM trial may have been driven by very close monitoring of medications and doses. The QT prolonging drugs, including sotalol, dofetilide, and ibutilide, are associated with a greater TdP risk in women.[96-98] Interestingly, lower age (<61 years) for women, was associated with an increased adjusted probability of cardioversion with ibutilide[98] that may be related to the longer repolarization time not only of the ventricles, but also of the atria, in premenopausal women, due to higher estrogen levels. In this study, the most pronounced QTc prolongation was observed in young women whose AF converted to sinus rhythm (86 ± 41 ms).[98] Although dronedarone was shown to cause bradycardia and QT prolongation in the Effect of Dronedarone on Cardiovascular Events in AF (ATHENA) trial,[93] sex differences in clinical outcomes were not evident, and dronedarone was believed linked to few sex-related side effects.[99] However, a review of data between 2009 and 2011 from the Federal Drug Administration's adverse event reporting system, and found more adverse events, including TdP, reported with dronedarone than amiodarone (810 vs. 493). More women experienced cardiac arrhythmias due to TdP associated with dronedarone use than men (23 vs. 13 reports).[100]

Actual sex differences in AAD use for a rhythm control strategy in clinical practice are less clear. In the EORP-AF registry, rhythm control with AADs was less frequently used in women,[29] while in the ORBIT-AF, no sex differences were found with regard to AAD

use.[27] Differences in these findings may represent physician preferences, and geographical and patient population differences. On the other hand, a multivariable adjusted analysis suggested that, among Medicare beneficiaries age ≥66 years at the time of AF diagnosis, women were slightly more likely than men to receive both rate (HR, 1.16; 95% CI, 1.15–1.17) and rhythm (HR, 1.04; 95% CI, 1.03–1.05) control.[101]

With regard to electrical cardioversion as treatment for AF, women are less likely to undergo electrical cardioversion, particularly if asymptomatic.[29,36,102] In the EORP-AF registry, women were less likely to undergo electrical cardioversion (25.5% men vs. 18.9% women, $p < .0001$), and despite the potential for greater adverse effects of class III antiarrhythmic agents, women were *more* likely undergo pharmacologic cardioversion (28.2% vs. 22.4%, $p = .0002$).[29] This was further confirmed in a substudy of the Prevention of Thromboembolic Events— European Registry in AF (PREFER in AF), which collected data on 7243 patients from seven European countries, and demonstrated less use of electrical cardioversion (14.9% vs. 20.6%, $p < .0001$) or ablation in women.[26] In the United States, inpatient use of electrical cardioversion has been reported to be higher in men.[103] Rates of AF recurrence after cardioversion are higher in women.[104] Together with use of AAD therapy and renal failure, female sex predicted the risk of recurrence after successful cardioversion in a retrospective multicenter study of 1342 patients.[105]

6.1 | AF ABLATION

Sex differences in clinical characteristics, referral patterns, procedural success, and complications of AF catheter ablation have been described. Women comprise the minority of patients in catheter ablation studies. Compared with men, women referred for AF are older,[106-110] have a longer history of AF,[106,110] are more likely to have valvular heart disease,[106,108] hypertension,[106] HFpEF,[36] larger left atrial dimensions/volume index,[106] and more comorbidities.[111,112] Women, compared with men, are less likely to have “lone AF,”[113] have a lower prevalence of paroxysmal AF,[110] tend to be more symptomatic,[114,115] and treated with more antiarrhythmic agents before ablation.[109,110] Patients, especially women with HF and AF are not frequently treated with catheter ablation.[116]

Compared to men, it is established that women are less likely to undergo catheter ablation of AF.[25,91,101,117,118] Based on the prevalence of AF in the population, this raises the possibility of potential referral bias against this invasive procedure in women. In a large observational cohort study in the United States that included 10,135 patients with AF (ORBIT-AF Registry), women were less likely to undergo AF ablation (4.9% vs. 5.9%, $p = .04$).[91] Prospective observational registries in Western Europe and South Korea showed similar findings, with women significantly less likely to undergo AF ablation than men, despite having more severe symptoms.[25,118] While temporal trends in referral for a “first” AF ablation procedure in Canada have shown an almost sevenfold increase in the rate of AF ablation over the past 10 years, there has been no increase in the relatively small proportion of women undergoing AF ablation.[119] Women were three times less likely to be referred to a specialized outpatient arrhythmia clinic for management of AF.[115] However, after referral to the arrhythmia clinic, there was no difference in the proportion of women and men undergoing AF ablation.[115,120] Greater comorbidities and increased age at the time of

diagnosis of AF may contribute to lower referral rates for women, suggesting sex differences as opposed to a referral bias. In addition, the possibility that women might be more likely to decline subspecialty referral for consideration of invasive procedures cannot be excluded. Further study is needed to determine whether sex differences in treatment decisions are due to patient preferences, eligibility for invasive therapy, other comorbidities/confounders, increased risk for complications, versus true treatment disparities.[106-110,113,121,122]

Sex differences in procedural outcomes with respect to maintenance of sinus rhythm have been examined. In contrast to one study that suggested no difference in early success rates with similar freedom from arrhythmia recurrences in men and women after about 2 years of follow-up,[106] other studies have shown lower ablation success rates with higher recurrence rates in women.[107,110,113,123,124] A pooled analysis of 20 studies revealed that women have a 20% greater risk of AF recurrence compared to men, with low heterogeneity across studies, and this difference in recurrence rates was partly attributed to the percent of nonparoxysmal AF patients.[125] A more recent meta-analysis of 19 observational studies confirmed a lower rate of freedom from AF/AT recurrence in women than in men at 2.4-year follow-up (OR, 0.75; 95% CI, 0.69–0.81; $p < .0001$).[126]

Women appear to be referred later for ablation,[106,110] with a longer duration of AF than men (mean, 60 vs. 47 months; $p = .04$). With a delay in referral for ablation in women, women may have larger left atrial sizes when adjusted for body size with more adverse electrical and structural remodeling that may be responsible for lower ablation success rates. Women may also be less likely to undergo re-do ablation procedures than men,[110,112,127] and this may also help explain the potentially lower ablation success rates in women.

In addition, women are more likely to have non-pulmonary vein triggers than men,[110,128] which may increase rates of arrhythmia recurrence, if these other triggers are not targeted during the procedure. Differences in outcomes between studies may be due to differences in clinical characteristics of various patient populations, duration and type of AF, procedural techniques, sample size, healthcare provider recommendations, or likelihood of patients to undergo re-do procedures. Alternatively, sex differences may be due to differences in LA remodeling or autonomic function, with lower LA endocardial voltage and higher parasympathetic activity described in women undergoing AF ablation in one study.[123] In contrast, another study showed no systematic sex differences in underlying pulmonary vein or atrial substrate during electrophysiological testing with electroanatomic mapping in patients with or without a history of AF.[129]

Prior investigations have inconsistent findings related to sex differences in procedural complications following catheter ablation. While some studies have shown no differences in complication rates in men compared to women,[106,108] others have demonstrated higher complication rates in women,[107,110,112,113,121,122,130-132] largely driven from bleeding or vascular complications, such as hematomas and pseudoaneurysms, that have been reported to be higher in women than men,[107,110,113,121,122] Women may also have a higher rate of cardiac tamponade[112,133]; in a worldwide survey of almost 35,000 AF ablation procedures, women had a twofold increased risk (1.24% in women vs. 0.67% in men, odds ratio 1.83, $p < .001$).

7 | AF DURING PREGNANCY

Pregnancy is associated with significant hemodynamic changes, including increased blood volume, leading to four-chamber cardiac dilatation, and up to 50% increased cardiac output by 28–32 weeks' gestation.[134] Heart rate increases in the setting of increased catecholamine concentrations and adrenergic receptor sensitivity.[134] AF most often occurs during the third trimester or within 24 h postpartum. AF has been estimated to occur in 59.3 per 100,000 of all pregnancies, or in about 1.3% of pregnancies in women with pre-existing heart conditions.[135,136] AF may occur in pregnant women with pre-existing heart disease such as hypertrophic cardiomyopathy, congenital heart disease, or valvular heart disease.[137] AF may also occur in women with a structurally normal heart, either in isolation or in the setting of hyperthyroidism, pulmonary embolism, infection, drug toxicity, or pre-eclampsia.[134] Hypertension, diabetes, and hyperlipidemia were associated with higher odds of AF in pregnancy, as well as older age and higher BMI.[135]

However, studies of AF in pregnancy are limited. Thus, there is little evidence to guide the optimal management of AF occurring in pregnancy. Recommended management is in general similar to that as in nonpregnant patients, except that treatment should be expedited and potential teratogenicity of medications needs to be considered.[138] Transesophageal echocardiogram and synchronized electrical cardioversion are safe and usually successful in pregnant women, and should be performed in women with hemodynamic instability secondary to AF in women at all stages of pregnancy.[62,138]

Need for anticoagulation is currently guided by CHA_2DS_2-VASc scoring, though the added increased risk of thromboembolism due to pregnancy itself is unknown.[138] Pregnancy is a prothrombotic state, for example associated with fivefold increased risk of venous thromboembolism.[137,139] Additionally, CHA_2DS_2-VASc scoring has not been validated in pregnancy, and most pregnant women have a low CHA_2DS_2-VASc score (1 for female sex).[138] Anticoagulation during pregnancy is further complicated by teratogenicity risk for vitamin K antagonists, continuously changing pharmacokinetics of low-molecular-weight heparin, and relatively limited data with direct oral anticoagulants during pregnancy.[137,138,140] Low-molecular-weight heparin requires monitoring of peak and trough anti-Xa levels to ensure appropriate anticoagulation.[137]

Although AF is a relatively rare, potentially serious complication for both mother and fetus during pregnancy, women are now bearing children at older ages with more CV risk factors. As more women with congenital heart disease are surviving to adulthood, the incidence of AF in this population can be expected to increase.[141] Table 6 is a summary of the 2020 ESC guidelines for management of AF in pregnant women. New recommendations include: (1) guidance for patients with hypertrophic cardiomyopathy, (2) specific AADs for rate and rhythm control, and (3) anticoagulants for different pregnancy stages.[62]

7.1 | Shared decision-making in AF management

Shared decision-making is a collaborative process whereby clinicians help patients reach a decision that is both informed by evidence and congruent with their personal values and preferences. The process involves exploring and comparing the benefits, harms, and risks of

each option, relating these to what matters most to the patient, placing patients at the center of decisions about their treatment and care, with the decision reached jointly. Nowhere is this more important than for women with AF. Shared decision-making (per the Centers for Medicare and Medicaid Services) involves three components: (1) clear, accurate, and unbiased medical evidence about reasonable alternatives—including no intervention—and the risks and benefits of each, (2) clinician expertise in communicating and tailoring that evidence for an individual patient, and (3) patient values, goals, informed preferences and concerns that may include treatment burdens. Shared decision-making is a means to ensure better health decisions, that is, those that align with what matters most to the patient.[142]

It is important to discuss with patients their symptoms and, in particular, expectations of treatment—"feeling better, cure of the problem, living longer, staying out of the hospital, etc." Management options should be presented in relationship to the patient's healthcare outcome preferences. This includes the risks and benefits, as well as the burdens of diagnostic testing, medical therapies, requisite follow-up, AF recurrence, etc. What is known about AF related to sex, age, and other variables specific to the patient should be addressed. In this regard, the fact that women on average have worse symptoms and quality of life should be reviewed, as well as worse outcomes with stroke prevention, rate and rhythm control strategies.

The "talk back" approach is valuable, having the patient repeat back what has been heard regarding the therapy or therapies eventually selected. Critical questions include:

How should the clinician assess the individual patient's healthcare preferences related to the management of atrial fibrillation?

How should the management options best be presented, in terms of their relationship to the patient's healthcare outcome preferences?

8 | SUMMARY AND CONCLUSIONS

A summary of our findings appears in Figure 1. There is an epidemiologic difference in the prevalence of AF between women and men with a three to two male to female ratio; importantly, this does not consider age-related differences or the predominance of women in our elderly population. An overview of these data indicates that while women have a lower incidence and prevalence, they have a poorer prognosis with AF that includes increased risk of stroke, HF, and death. There are many knowledge gaps about pathophysiologic mechanisms accounting for these differences as summarized in Table 7 with recommendations for future research.

It appears that women have different left atrial morphology, more atrial fibrosis associated with increased cerebral infarcts, and worse outcomes with cryoballoon pulmonary vein isolation, more nonpulmonary foci, and differences in membrane action potential duration. These differences are partially driven by estrogen. Although older, women benefit from treatment of AF including cardioversion and ablation and prevention of stroke including anticoagulation. These therapies are utilized less often in women than in men, the reasons for which are unclear and require further investigation.

The role of LAA occlusion is considered a class IIb for both men and women with AF. The role of LAA occlusion, and whether there are sex differences in the benefits and complications by sex requires further study.

There are widespread sex differences in CV structure and function, risk factors, epidemiology, disease manifestations, and clinical outcomes. AF is a complex disease, with sex differences in epidemiology, risk factors, treatment, and outcomes. Women have more severe symptoms, less effective treatment options, and worse outcomes. A better understanding of these differences is critical to improve outcomes and reduce disparities of care between women and men. These improvements include increased use of appropriate stroke prevention strategies, symptom control, better monitoring of medical therapy, and optimized procedural outcomes.

Abbreviations:

AAD	antiarrhythmic drugs
AF	atrial fibrillation
BMI	body mass index
CIED	cardiac implantable electronic device
CYT	cytochrome
EHRA	European Heart Rhythm Association
FHS	Framingham Heart Study
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
LAA	left atrial appendage
RR	relative risk
TdP	torsades de pointes

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Sex Differences in Atrial Fibrillation

SUMMARY OF FINDINGS	
Epidemiology and risk	
Greater total population	Women
Higher age-adjusted prevalence of AF	Men
Prevalence and Incidence of AF increasing over time	Equal
Higher lifetime risk of AF in whites	Men
Higher lifetime risk of AF in blacks	Equal
Higher risk of stroke from AF	Women
Higher risk of death from AF	Women
Symptoms and quality of life	
Longer duration of symptoms	Women
Higher functional impairment and limitation of ADLs	Women
Worse quality of life scores	Women
Risk and Prevention of Stroke	
Higher risk for AF-related stroke	Women
Strokes from AF more severe and disabling	Women
More likely to receive anticoagulation for AF	Men
More time in TTR when on warfarin for AF	Men
Risk from rate and rhythm control	
Higher use and risk of mortality from cardiac glycoside for AF	Women
Higher risk of CV events from antiarrhythmic drugs for AF	Women
Higher risk of proarrhythmia with antiarrhythmic drugs for AF	Women
Higher risk of adverse events with catheter ablation for AF	Women

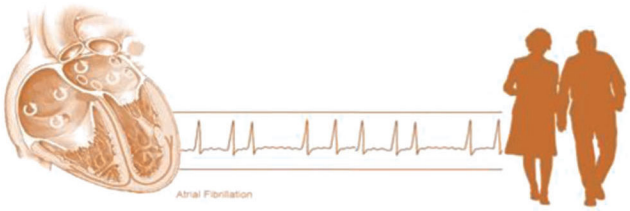

FIGURE 1.

Summary of sex differences in atrial fibrillation. ADLs, activity of daily living; AF, atrial fibrillation; CV, cardiovascular; TTR, time in therapeutic range

TABLE 1

Age-adjusted incidence rate per 1000 person-years

	1958–1967	1998–2007
Women	2.5	8.6
Men	3.7	13.4

Source: Framingham Heart Study.[5]

TABLE 2

Age-adjusted incidence rate per 1000 person-years by level of risk

Age-adjusted incidence rate by risk factor status			
	Risk factor status		
	Optimal	Borderline	Elevated
Black women	0	1.7	4.1
White women	2.0	2.7	6.0
Black men	0	2.6	6.0
White men	4.0	5.2	9.1

Source: Atherosclerosis Risk in Communities (ARIC) Study, 1987–2007.[7]

TABLE 3

Age and sex adjusted incidence rate per 1000 person-years by race

	Age- and sex-adjusted incidence rates
Chinese	3.9
Hispanic	6.1
Non-Hispanic Blacks	5.8
Non-Hispanic Whites	11.2

Source: Multiethnic Study of Atherosclerosis (MESA), 2000–2010.[8]

TABLE 4

Lifetime risk of AF according to race and sex in the ARIC at ages 45 and 55 years

Lifetime risk of developing af by risk factor status, FHS[a]			
	Optimal	**Borderline**	**Elevated**
Women	20.5%	28.0%	34.6%
Men	29.8%	39.7%	43.3%

Lifetime risk of AF according to race and sex, ARIC[b]		
	Black	**White**
Women	22%	30%
Men	21%	36%

Abbreviations: ARIC, Atherosclerosis Risk in Communities; FHS, Framingham Heart Study.

Source:

[a] FHS (European ancestry), at index age 55 years, 1968–2014[10]

[b] ARIC Study at index ages 45 and 55 years, 1987–2014.[11]

TABLE 5

Recommendations for stroke prevention for patients with nonvalvular atrial fibrillation

	2019 ACC/AHA/HRS[61]		2020 ESC/EACTS/EHRA[62]	
CHA_2DS_2-VASc	**Women**	**Men**	**Women**	**Men**
0	-	-	-	-
1	None, ASA or OAC (IIb)	None, ASA or OAC (IIb)	-	OAC (IIa)
2	None, ASA or OAC (IIb)	OAC (I)	OAC (II)	OAC (I)
≥3	OAC (I)	OAC (I)	OAC (I)	OAC (I)

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASA, aspirin; EACTS, European Association of Cardio-Thoracic Surgery; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; OSA, oral anticoagulation.

TABLE 6

Recommendations for the management of AF during pregnancy

Recommendations	Class[a]	Level[b]
Acute management		
Immediate electrical cardioversion[c] is recommended in case of haemodynamic instability or pre-excited AF	I	C
In pregnant women with HCM, cardioversion[c] should be considered for persistent AF	IIa	C
Ibutilide or flecainide IV may be considered for termination of AF in stable patients with structurally normal hearts	IIb	C
Long-term management (*oral administration of drugs*)		
Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF	I	C
β-Selective blockers are recommended for rate control in AF[d]	I	C
Flecainide,[e] propafenone,[e] or sotalol[f] should be considered to prevent AF if atrioventricular nodal-blocking drugs[f] fail	IIa	C
Digoxin[g] or verapamil[g] should be considered for rate control if β-blockers fail	IIa	C

Note: Note that the former A to X categories of drugs—the classification system for counselling of pregnant women requiring drug therapy—was replaced by the Pregnancy and Lactation Labelling Rule, which provides a descriptive risk summary and detailed information on animal and clinical data, by the US FDA in June 15.

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; IV, intravenous; LV, left ventricular; QTc, corrected QT interval; US FDA, United States Food and Drug Administration; VKA, vitamin K antagonist.

[a] Class of recommendation.

[b] Level of evidence.

[c] Cardioversion of AF should generally be preceded by anticoagulation.

[d] Atenolol has been associated with higher rates of foetal growth retardation and is not recommended.

[e] Flecainide and propafenone should be combined with atrioventricular nodal-blocking drugs, but structural heart disease, reduced LV function, and bundle branch block should be excluded.

[f] Class III drugs should not be used in prolonged QTc.

[g] Atrioventricular nodal-blocking drugs should not be used in patients with pre-excitation on resting ECG or pre-excited AF.

Source: 2020 Update of European AF guidelines[62] Copyright obtained on December 9, 2020, from Oxford University Press.

TABLE 7

Critical knowledge gaps and recommendations for future research

1	Increased prevalence and incidence over time for both sexes may be due to more people living longer. However, it may be possible to decrease incidence by decreasing the risk factors for AF such as obesity, hypertension, and heart failure. Studies are needed to ascertain if improved blood pressure control in older women decreases AF incidence
2	Unclear why there is a higher lifetime risk of AF in Whites versus individuals of other races/ethnicities. Studies to evaluate whether genetic versus environmental versus structural factors contribute to this risk
3	Studies to understand why women are not receiving anticoagulation when appropriate may decrease this disparity in treatment
4	Studies to understand the higher risk of death from AF in women are needed to decrease mortality from AF
5	Studies to better understand symptoms and what treatments are more effective in ameliorating them to improve quality of life of AF patients
6	Efforts needed to better educate healthcare professionals to avoid unnecessary or inappropriate use of cardiac glycosides may decrease risk of breast cancer and mortality from cardiac glycosides
7	Studies are needed to determine what measures can decrease risk from antiarrhythmic drugs
8	More efforts are needed to prevent vascular and bleeding risks in women may help decrease the risk of adverse events with catheter ablation

Abbreviation: AF, atrial fibrillation.