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# Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis

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## Abstract

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D.K., F.R., E.J.B., and I.E.C. researched data for the article, discussed its content, and wrote, reviewed and edited the manuscript before submission. X.Y. researched data for the article. R.B.S. discussed the content of the article, and wrote, reviewed, and edited the manuscript before submission.

**Competing interests statement**

The authors declare no competing interests.

**Review criteria**

We used PubMed to search for full-text manuscripts in English language published up to September 2015. The search terms and notable inclusion/exclusion criteria for each topic are outlined in Supplementary Table S11. Additional studies were included after manually reviewing the references of relevant manuscripts. We used the following exclusion criteria for all the topics of prognosis: case-control or cross sectional design, fewer than 200 cases, inclusion of only women or men, lack of multivariable adjustments, and studies deemed to be duplicates of prior publications.

Atrial fibrillation (AF) is the most common sustained arrhythmia in women and men worldwide. During the past century, a range of risk factors have been associated with AF, severe complications from the arrhythmia have been identified, and the prevalence has been increasing steadily. Whereas evidence has accumulated regarding sex differences in coronary heart disease and stroke, the differences between women and men with AF has received less attention. We review the current literature on sex-specific differences in the epidemiology of AF, including incidence, prevalence, risk factors, and genetics, and in the pathophysiology and the clinical presentation and prognosis of patients with this arrhythmia. We highlight current knowledge gaps and areas that warrant future research, which may potentially advance understanding of variation in the risk factors and complications of AF, and ultimately aid more-tailored management of the arrhythmia.

## ToC Blurb

Differences between women and men with atrial fibrillation have received far less attention in recent years than sex differences in coronary heart disease and stroke. In this Review, Ko *et al.* discuss sex differences in the incidence, prevalence, risk factors, and pathophysiology of atrial fibrillation, and the clinical presentation and prognosis of patients with this prevalent arrhythmia.

Atrial fibrillation (AF) is the most common arrhythmia worldwide. The estimated prevalence is lower in women (373 per 100,000) than in men (596 per 100,000).[1] The true prevalence is likely to be substantially higher given that many individuals remain undiagnosed.[2] As the population ages, the prevalence and costs of AF are expected to increase.

Elevated body mass index, hypertension, diabetes mellitus, coronary heart disease, valvular heart disease, and heart failure (HF) constitute major risk factors for AF, but the prevalence of these risk factors vary between women and men.[3–5] In addition, AF has been demonstrated to be partially heritable,[6] and some studies have suggested differences in AF genetics between women and men[7–9]. Studies indicate that among individuals with AF, women are more likely than men to experience symptoms,[60,11,12] and to seek care for these symptoms.[10,11] Moreover, in women, AF is associated with worse symptoms and quality of life,[10–12] and increased risk of complications such as stroke[13] and mortality,[14] compared with men.

We review reports on sex differences in the incidence, prevalence, risk factors, genetics, and pathophysiology of AF, and in the clinical presentation and prognosis of women and men with the arrhythmia (Figure 1). We underscore the many remaining unanswered questions in sex-specific differences in AF for future studies to address. A deeper knowledge of the variation by sex of risk factors and complications for AF might aid the development of novel measures to prevent and manage the arrhythmia.

## Epidemiology

### Incidence, prevalence, and lifetime risk

In North American and European populations, the age-adjusted incidence of AF has been estimated to be 1.5 to 2 times higher in men than in women (Supplementary Tables S1 and S2). The Framingham Heart Study and the Olmstead County, Minnesota study have reported

the AF incidence (per 1000 person-years) in women to be 1.6 and 2.7, respectively, compared with 3.8 and 4.7 in men.[5,15] The lower AF incidence among women seems to be consistently observed outside North America and Europe, although fewer studies are available.[1,16] AF incidence has been shown to increase disproportionately with increasing age in both women and men, reaching as high as 30.4 per 1000 person-years in women and 32.9 per 1000 person-years in men by age 85–89 years.[17]

Similarly to incidence, age-adjusted prevalence of AF has been reported to be lower in women than in men in North America and Europe (Figure 2) (Supplementary Tables S3 and S4). A large retrospective study of older adult (≥ 65 years) U.S. Medicare recipients reported the prevalence of AF to be 7.4% in women and 10.3% in men in 2007.[18] The Framingham Heart Study showed similar results; the age-adjusted period prevalence (per 1000 person-years) during 1998–2007 was 49.4 in women compared with 96.2 in men.[5] In addition, a community-based, randomized, controlled trial in Sweden, in which individuals aged 75–76 years were enrolled for AF screening, showed a lower prevalence of this arrhythmia in women than in men (9.2% versus 15%).[19] Because women typically live longer than men, the absolute number of women exceeds the number of men with AF in Medicare data.[18]

The overall prevalence of AF varies by ancestry; prevalence studies of Asian populations have been less consistent than those of North American and European poulations. Two large cross-sectional studies of Chinese cohorts reported that age-adjusted prevalence of AF was similar in women and men (0.76% versus 0.78% and 0.63% versus 0.66%),[20,21] whereas data from Singapore indicated that prevalence was lower in women (0.6% versus 2.6%).[22] Other East Asian studies also have reported lower prevalence of AF in women compared with men; however, the results are not directly comparable owing to a lack of age-adjustment.[16,23–26]

Multiple studies have evaluated secular trends in the sex-specific incidence and prevalence of AF. In the Olmstead County, Minnesota study, a trend for increased incidence in both women and men from 1980 to 2000 was noted, but no significant sex difference was observed in the rate of increase.[15] In a community-based study in Iceland, a trend for increasing incidence for women but not for men was found during the follow-up period 1991–2008.[27] The Framingham Heart Study investigators reported that AF incidence increased during the 50-year period from 1958 to 2007 in both women and men.[5] The trend for increased AF incidence has been shown to correspond to the higher prevalence of AF over the years for both women and men in various population settings.[5,18,27,28]

In North American populations, despite higher incidence of AF in men, lifetime risk of AF in women and men were similar owing to longer life expectancy for women. In the Framingham Heart Study, the lifetime risks for AF in women and men at age 60 years were 23.4% and 25.8%, respectively.[29] In the Rotterdam Study, the lifetime risks for women and men at age 55 years were 22.2% and 23.8%, respectively.[30] A population-based study from China showed similar lifetime risk for women at age 55 years (22.2%); however, in contrast to North American populations, the lifetime risk for women in China was higher than that for men (22.2% versus 16.7%).[31]

## Risk factors

Most studies have reported a higher incidence of AF in men compared with women. However, after adjusting for height and other AF risk factors, a multivariable risk score for incident AF in a three-cohort study showed male sex was no longer significantly associated with AF.[32] The study findings indicated that part of the increased risk of AF observed in men was related to body size.

Epidemiological studies worldwide have described several major risk factors associated with AF in both women and men, including higher age, body mass index, and blood pressure, hypertension treatment, diabetes mellitus, valvular heart disease, HF, and myocardial infarction (MI).[4,5,33] Advancing age is the most important risk factor, leading to about a doubling in AF incidence with every 10-year increase in age.[4] However, in studies from North America,[5] Europe,[34,35] and Australia,[11] women with AF are, on average, older than men. In the Framingham Heart Study, 74% of women with AF were aged ≥70 years, compared with 58% of men in the time period 1998–2007.[5]

Over the past few decades, the prevalence of major risk factors have changed in both women and men with AF.[5] In particular, body mass index has increased significantly (Figure 3).[5] In the Women's Health Study[3], the population attributable risk of AF with increased BMI during the 12 years of follow-up was 18.3%. Body mass index combined with systolic blood pressure or hypertension conferred the highest AF risk in both sexes.[3,36,37] Women with AF have higher prevalence of hypertension and valvular heart disease and lower prevalence of coronary heart disease than men with AF.[5,11,34] Consistent with these findings, the population-attributable risk for coronary heart disease was higher for men compared with women in the Framingham Heart Study, and the population-attributable risk for valvular heart disease was lower.[4] Over the past few decades the prevalence of valvular heart disease in women with AF has decreased and become a less important risk factor in high-income countries.[5] However, globally, the prevalence of valvular heart disease among individuals with AF is still greater than 25%,[38,39] largely caused by the higher incidence of rheumatic heart disease in low-income and middle-income countries. The differences in risk factors for AF between women and men in low-income and middle-income countries have been inadequately defined and require further investigation.

A variety of other risk factors have been associated with AF, including alcohol intake,[40] physical activity,[41] hyperthyroidism,[42] and inflammatory pathways;[43] however, sex differences have not been consistently demonstrated for these risk factors. The relationship between physical activity and AF seems to be complicated. In men, a U-shaped association has been reported, in which sedentary lifestyle and vigorous exercise both are associated with increased AF risk,[41,44,45] whereas moderate activity is protective.[46] In women, vigorous exercise has not been shown to increase AF risk, although moderate exercise is associated with a lower risk of AF than sedentary lifestyle.[47,48] In the Women's Health Initiative[48] and the Swedish Mammography Cohort,[49] two studies with only women, leisure-time physical activity was associated with a lower risk of AF.

### Genetics

Several studies evaluating familial aggregation of AF have reported substantially increased risk of AF in individuals with affected family members.[8,9,50–55] The evidence for a differential AF risk dependent on the sex of the affected family member is more ambiguous (Supplementary Table S5). In a large register study including >300,000 Swedish individuals with AF or atrial flutter, the investigators reported increased risk of AF in mothers (OR 2.02; 95% CI 1.95–2.09) of AF or atrial flutter cases compared with fathers (odds ratio (OR) 1.85; 95% CI 1.79–1.91).[9] Likewise, mothers of female cases and women with at least two affected siblings seemed to have higher risks of AF than their male counterparts.[9] No formal tests of sex differences were performed, but the confidence intervals were not overlapping, consistent with a significant difference. In another large register study evaluating familial risks of lone AF in Denmark, men with one first-degree relative with lone AF were shown to have increased risk of lone AF compared with women (male/female ratio 1.37; 95% CI 1.02–1.82); however, whether this finding reflects the increased baseline risk of lone AF in men is unclear.[8] In a collection of 192 North American lone AF cases, Chen and colleagues reported that more women than men had confirmed familial lone AF (at least one first-degree or second-degree relative with documented lone AF; 31.7% versus 13.9%; $P = 0.03$); however, the sample size was quite small.[51] Other studies have reported sex-stratified familial risks of AF, but no statistically significant differences have been demonstrated.[52–56]

Although studies indicate that AF might be sexually dimorphic, the molecular genetic basis of variation between the sexes has received little attention. In 2005, Ravn *et al.* discovered a genetic variant in the X-linked gene *KCNE5* that was more frequent in 96 controls than in 158 patients with AF, and that was found to be protective of AF.[57] Since women have two copies of the X chromosome whereas men have one, the investigators suggested that the variant might contribute to the lower prevalence of AF in women. A similar report from Karst *et al.* in 2010 identified a deletion in the X-linked gene *EMD* in a multigenerational family with progressive sinus node dysfunction and AF.[58]

Several recent studies have investigated whether common genetic variants identify individuals at higher risk of AF. None of the genetic risk scores developed thus far have reported sex differences in AF prediction.

## Pathophysiology

AF is thought to develop through ectopic focal triggering or re-entry mechanisms.[66,121,122] Electrophysiology studies have demonstrated that electrical heterogeneity within the atria is associated with differences in $Ca^{2+}$ and $K^{+}$ handling and, therefore, resting membrane potential, refractory period, and action potential duration.[123–126] Ectopic triggering activity most commonly originates from the sleeves of myocardial tissue that extend into the pulmonary veins from the left atrium. The propensity for triggered activity in the pulmonary myocardial sleeves might be related to the shorter action potential duration, lower resting membrane potentials, and non-uniformity in myofibril arrangement.[7,122,127] Structural changes in the atria also are associated with the initiation and maintenance of AF, including fibrosis[128] and dilatation.[129–131] After initiation of AF, the arrhythmia itself is associated

with both electrical[132–135] and structural remodeling[128,136,137] that promotes its maintenance and can increase the burden of AF.

The number of studies investigating sex-related differences in the pathophysiology underlying AF (Figure 4) are limited and the mechanisms remain inadequately understood.

## Structural properties

Larger left atria and increased left ventricular wall thickness have been associated with increased risk of AF[131] and, therefore, cardiac structural differences between women and men might help explain the lower prevalence of AF among women. Women generally have reduced ventricular wall thickness and smaller left atria and ventricles compared with men.[138–141] However, in a small study of women referred for cardiac MRI, more atrial fibrosis was detected in women than in men, using delayed-enhancement magnetic resonance imaging.[142] The plasma concentrations of the inflammatory marker C-reactive protein[143] and of fibroblast growth factor-23[144] have been found to be higher in women than in men in epidemiological studies. Both factors have been associated with increased risk of AF and might contribute to increased atrial fibrosis in women.[144,145] Fibroblast growth factor-23 also has been associated with increased risk of cardioembolic stroke, but not other stroke types.[146] How the increased risk of AF associated with atrial fibrosis interacts with other risk factors that confer a lower incidence of AF among women is unclear.

## Electrical properties

A number of electrical differences have been noted between females and males. In a rabbit model, left atrial and pulmonary vein tissue from females displayed longer action potential duration, and female pulmonary vein tissue had a more negative resting membrane potential compared with males.[147] In one study of patients undergoing catheter ablation for AF, women required more-extensive ablation of non-pulmonary vein foci than men,[148] suggesting that patterns of electrical heterogeneity vary by sex.

## Hormones

Potential contributions of sex hormones to electrophysiologic properties have been explored in a few studies. Progesterone has been associated with shortened action potential[149,150] and QT interval during the luteal phase of menstrual cycle;[151] however, its role in the pathogenesis of AF in women remains unclear. Of particular interest is the role of oestrogen in modulating electrophysiological properties in women. In one study, women with a history of paroxysmal supraventricular tachycardia were found to experience significantly higher incidence and longer duration of episodes during the luteal phase compared with the follicular phase of menustrual cycle.[152] In the same study, an inverse correlation between serum oestrogen concentration and the number and duration of supraventricular tachycardia episodes was noted. In postmenopausal women, acute administration of oestradiol prolongs right intra-atrial and atrioventricular nodal conduction time, and right atrial effective refractory period.[153] The results have been replicated in a female mouse model, in which ovarectomy caused shortening of both PR interval and the conduction time from the right atrium to the atrioventricular node and His bundle, whereas oestrogen replacement had the opposite effect.[154] Nevertheless, whether oestrogen has a direct role in the reduced incidence

of AF in women compared with men remains unclear, as most women develop AF at an older age, often after menopause. Hormone replacement therapy in postmenopausal women does not seem to be associated with the risk of incident AF. In the Women's Health Initiave Study, no difference was seen in the risk of incident AF between the group of postmenopausal women randomly assigned to oestrogen replacement only and the placebo group, after adjusting for incident coronary heart disease and HF.[155] In addition, in rabbit models, oestradiol increased QT interval and decreased delayed rectifier potassium currents.[156,157] Animal models are consistent with electrocardiogram (ECG) recordings from healthy individuals demonstrating that women have a longer QTc interval than men.[158] The link between QTc interval and risk of AF in women is probably complex, as the Copenhagen ECG Study, which included ECGs from almost 290,000 individuals, showed that the association of QTc interval to risk of AF development is J-shaped, with both a shorter and longer QTc interval associated with increased risk of AF.[159] PR interval has been shown to be shorter in women compared with men,[160] but similar to the findings for QTc interval, the Copenhagen ECG Study showed that both long and short PR intervals were associated with increased risk of AF in women, whereas only longer PR intervals were associated with AF in men.[159] Oestradiol also seems to modify calcium fluxes. In a rat model, oestradiol administration to heart slices led to increased calcium influx,[161] whereas cytosolic calcium loading in response to hypoxia and reoxygenation was reduced in female guinea pig cardiomyocytes pretreated with oestradiol.[162] How the various physiological effects of oestradiol interact to modify the risk of AF in women is currently unclear.

In men, lower testosterone levels have been associated with increased risk of AF. In the Framingham Heart Study, one standard deviation decrease in testoterone level was associated with a hazard ratio (HR) of 3.53 (95% CI 1.69 – 6.37) in men ≥80 years in multivariable-adjusted models.[163] An experimental model with gonectomized male mice demonstrated that testosterone deficiency increased atrial arrhythmogenicity and that testosterone replacement attenuated the effect.[164] Whether sex hormones exert direct effects on atrial arrhythmogenesis or indirect effects by influencing the risk of cardiovascular diseases remains to be elucidated.

Higher risk of stroke in women with AF than in men with the arrhythmia has been extensively studied, and many putative mechanisms have been identified.[165] Female sex is also a risk factor for non-ST-segment elevation MI in individuals with AF; potential mechanisms include increased left ventricular wall thickness leading to subendocardial ischemia and poorly controlled heart rate leading to demand ischemia.[104] In addition, female sex is a well-known risk factor for HF with preserved ejection fraction, possibly attributable to hemodynamic changes and cardiovascular remodelling post menopause.[165,166]

The reported literature suggest that sex differences in hormones and in electrical and structural characteristics might help explain variation in incidence, prevalence, burden, and complications associated with AF in women and men. As called for by the National Institutes of Health, preclinical studies will benefit from more balance in female and male cellular and animal models.[167] More-detailed basic and clinical investigations are required to define the pathophysiological basis of sex differences in AF.

## Clinical presentation

Classical symptoms of AF are palpitations, dyspnoea, dizziness, and chest pain.[34,59] A recent systematic review of two randomized, controlled trials and four observational studies of AF reported that asymptomatic AF was less common among women than among men (relative risk (RR) 0.57; 95% CI 0.52–0.64).[60] Women seem to be more likely to seek care for symptoms, which might partly be attributable to higher mean heart rates at presentation.[10,11] In a study of patients visiting the emergency department, women were more likely to have longer duration of symptoms and to present with atypical symptoms, such as weakness and fatigue.[11,12] The presence of atypical symptoms might contribute to the worse outcomes seen in women, as they might delay diagnosis and care. All of the above factors might contribute to the worse quality of life[61] and more-frequent depression[11] experienced by women with AF than with men.

The first presentation of individuals with AF can be with stroke[12,62] or cardiomyopathy.[34,60] To our knowledge, variations in the presentation with cardiomyopathy or stroke by sex have not been reported.

## Prognosis

### Stroke and thromboembolism

Female sex is a well-recognized, independent risk factor for AF-related stroke[13] and systemic thromboemblism.[63–65] The American Heart Association/American College of Cardiology/Heart Rhythm Society[66] and the European Society of Cardiology[67] now recommend the use of the $CHA_2DS_2$-VASc score to predict stroke risk and to guide anticoagulation therapy in individuals with AF. According to the $CHA_2DS_2$-VASc schema, each of the following factors are assigned one point: HF, hypertension, age 65–74 years, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), and female sex; prior stroke/ transient ischemic attack/thromboembolism and age ≥75 years qualify for two points each.

A number of observational studies have demonstrated the association between female sex and risk of AF-related stroke and thromboembolism (Supplementary Table S6). The Framingham Heart Study (HR 1.92, 95% CI 1.2–3.07)[68], two cohort studies using Danish (HR 1.11, 95% CI 1.05–1.18)[69] and Swedish (HR 1.18, 95% CI 1.05–1.15)[70] registries, and the ATRIA study (RR 1.6, 95% CI 1.3–1.9)[71] demonstrated that female sex was associated with multivariable-adjusted increased stroke risk in patients with AF who were not on oral anticoagulation therapy. Similarly, the Copenhagen City Heart (HR 2.6, 95% CI 1.3–5.4)[72], a Japanese (HR 2.0, 95% CI 1.07–3.72)[73], and a Canadian (HR 1.14, 95% CI 1.07–1.22)[74] study, which all included a mixture of warfarin users and non-users, reported higher risk of stroke in women than in men.

The link between female sex and stroke might vary across populations and age groups.[75–84] Whether female sex confers an additional risk in women <65 years without any other risk factors is unclear. The annual stroke risk is estimated to be very low in women aged <65 years with ‘lone’ AF (i.e. $CHA_2DS_2$-VASc=1 with female sex as the only risk factor)[67,85]

and the current European guidelines do not recommend anticoagulation therapy for this group.[67] Notably, a nationwide register study of >120,000 individuals with AF in Denmark found a rate of thromboembolism as high as 1.24/100 person–years among women aged < 65 years with lone AF at 1-year follow-up.[86] In contrast, however, a Swedish nationwide study of >140,000 individuals with AF showed that the annual stroke risk for women with AF who were aged <65 years was 0.1–0.2%.[85] Some studies suggest that female sex might be a significant risk factor for AF only for those above the age of 75 years.[69,70]

## Dementia

AF has been implicated as a risk factor for dementia in several longitudinal studies.[87–94] Most recently, the investigators from the Rotterdam Study reported that prevalent AF was associated with increased risk of dementia, when adjusting for stroke (HR 1.33, 95% CI 0.99–1.78).[87] Very few studies have examined a possible interaction between sex and AF on the risk of dementia or cognitive impairment (Supplementary Table S7). All three studies identified through our search suggested that sex is not a significant modifier of dementia in individuals with AF.[88–90] In the Olmsted County, Minnesota study, no difference in the rate of dementia detection was observed between women and men with AF without a history of cognitive impairment or stroke.[88] Similarly, a Taiwanese study that used a health insurance database showed that the risk of dementia was similar in women and men.[89]

## Heart failure

AF has been shown to be an independent risk factor for HF. The temporal association between AF and HF was evaluated in the Framingham Heart Study; among 539 participants with AF, the crude incidence of new-onset HF was 33 per 1000 person-years during a mean follow-up of 5.6 years.[95] In another study using a cohort from Olmsted County, Minnesota, the investigators found that among 3,288 participants with AF and no prior history of HF, the crude incidence of new-onset HF was 44 per 1000 person-years during a mean follow-up of 6.1 years, with a cumulative incidence of nearly 20% within the first 5 years.[96]

The bulk of studies evaluating sex differences in the AF-related risk of HF have showed no significant difference; however, a few studies have suggested higher risk in women (Supplementary Table S8). In an analysis of 725 participants with AF in the Framingham Heart Study, no significant difference was noted in the 10-year HF incidence for women (4.30 per 100 person-years) and men (3.34 per 100 person-years).[97] The study suggested that women had higher incidence of HF with preserved ejection fraction than men, although the association was nonsignificant.[97] A study from Groningen, Netherlands found that AF is an independent risk factor for new-onset HF with preserved ejection fraction in women, but not in men.[98] A series of other studies have evaluated sex differences in AF-related risk of HF, reporting negative results.[34,99–103] The study from Olmsted County, Minnesota showed reduced risk of HF with male sex (multivariable adjusted HR 0.81, 95% CI 0.69–0.95).[96] Additional studies regarding sex differences in AF with reduced versus preserved systolic function are needed.

## Myocardial infarction

Studies have established an association between AF and risk of MI.[104–107] The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study showed that AF is associated with a two-fold higher risk of MI among participants without history of coronary heart disease, after adjusting for cardiovascular comorbidities (such as diabetes, hypertension, chronic kidney disease, hyperlipidemia, and history of stroke or peripheral vascular disease) and other therapies (such as anticoagulants).[105] AF also has been shown to be a risk factor for MI in men with $CHA_2DS_2$-VASc=0 and women with $CHA_2DS_2$-VASc=1.[107]

Possible sex differences in the risk of MI attributable to AF have been suggested (Supplementary Table S9). Data from the REGARDS and Atherosclerosis Risk in Communities studies indicated that the association between AF and MI was greater in women than in men.[104,105] In the Atherosclerosis Risk in Communities study, the increased association between AF and MI in women was limited to non-ST-segment elevation MI.[104] In a separate analysis of women and men with $CHA_2DS_2$-VASc scores of 0 and 1, respectively, the association between AF and MI was 1.5-fold higher in women than in men; however, the interaction was not statistically significant.[107] On the other hand, the Cardiovascular Health Study of older adults has shown a significant sex interaction ($P$ = 0.02) such that women with AF had a higher risk of coronary heart disease (HR 2.3) than their male counterparts (HR 1.6).[106]

## Mortality

In 1998, investigators from the Framingham Heart Study established that AF was associated with increased mortality, when they reported a 1.5-fold increase in risk of death in men and a corresponding 1.9-fold increase in women, adjusting for clinical risk factors.[14] In the study from Olmsted County, Minnesota, new-onset AF was shown to double the risk of death.[108] Similar findings have been reported in different population settings.[72,109–111]

Multiple longitudinal studies have evaluated whether an interaction exists between sex and AF-related risk of mortality, but the results have not been consistent (Supplementary Table S10). Substantial differences in follow-up time pose a significant challenge to direct comparison among the different studies. In the Framingham Heart Study, investigators reported that with 40 years of follow-up a significant interaction with sex existed, such that AF eliminated the survival advantage typically enjoyed by women.[14] Data from the Copenhagen City Heart Study, with mean follow-up of 4.7 years, reported a doubling of the risk of death in women with AF compared with men with AF.[72] On the contrary, results from Olmsted County, Minnesota, with mean follow-up of 5.3 years, and a *post-hoc* analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, with median follow-up of 2 years, have suggested that men with AF have greater risk of death than women.[108,112] In addition, several studies — including the Diet, Cancer, and Health cohort study in Denmark, with median follow-up of 4.9–5.1 years — have reported that female sex is associated with reduced risk of death.[80,102,113] Adding to the inconsistency, multiple studies have not demonstrated male or female sex to be a significant risk factor for mortality in AF.[34,114–119] However, a meta-analysis of 19 studies showed increased risk for

all-cause mortality in women compared with men (women-to-men RR 1.12, 95% CI 1.07–1.17).[120] Notably, the meta-analysis included disease-based samples and the results might thus not be generalizable to the general population. Nonetheless, the meta-analysis is consistent with previous reports suggesting that women with AF have a higher risk of death compared with men with AF.

## Future directions

Compared with our understanding of sex differences in coronary heart disease and stroke,[168] substantial gaps exist in our knowledge of sex differences in AF (Table 1). Well-powered longitudinal studies evaluating incidence, prevalence, risk factors, and prognosis of AF in women and men, as well as formal testing of sex as an effect modifier, are needed to establish whether the differences in the epidemiology and prognosis of AF are sex-dependent or whether they can be explained by confounding.[32] Although several studies have reported that risk factors for AF vary by sex, many of the studies had limited sample size, and did not formally test for effect modification by sex.

Another limitation of the AF epidemiological literature is the paucity of data from outside North America and Europe.[1,169] Given that substantive racial and ethnic variations exist in population age distribution, they might represent important confounders of the observed heterogeneity in the epidemiology and outcomes of AF between women and men. The AF-related sex differences in epidemiology, risk factors, and outcomes identified in populations of European ancestry might not be generalizable to other ethnic groups.

Although the pathophysiology of AF has been investigated extensively through the years,[170] our understanding of the differences between male and female cardiac anatomy and electrical mechanisms, which might contribute to difference in risks and prognosis of AF by sex, is insufficient. Moreover, the contribution of the hormonal differences in women and men on risk and prognosis of AF should be evaluated more closely.[155,163,171,172]

Study of the genetics of AF has evolved rapidly, and considerable knowledge of genes and pathways associated with AF exists.[6] However, large-scale genetic association studies performed in women and men separately, and testing for sex interactions, are needed to identify potential genetic variants that have differential effects between the sexes or that are sex-specific. If such differences exist, the studies might help us to elucidate the molecular biology underlying differences in risk, effects of treatment, and prognosis related to AF in women and men, which in turn will aid development of personalized treatment and refinement of current risk prediction models.[173,174]

Female sex has been extensively studied as a risk factor for AF-related stroke and thromboembolism, and most studies report an increased risk of stroke in women.[68–71] Nonetheless, little is known of the underlying mechanisms. Studies evaluating potential biological causes — such as differences in prothrombotic state, cerebral blood flow, genetic predisposition, and sociocultural causes such as delayed medical care — might improve stroke prevention and treatment in women and men.

To date, little attention has been paid to potential sex differences in the AF-related risks of HF, MI, and dementia. The increased risks of HF with preserved ejection fraction and non-ST-segment elevation MI in women with AF need to be validated in other populations. Additional studies with long-term follow-up will help clarify the impact of AF on the risks of dementia and mortality, and potential sex differences.

## Conclusions

Evidence for sex differences in the incidence, prevalence, population-attributable risks of major risk factors of AF, and in the clinical presentation and prognosis of patients with this arrhtyhmia is accumulating. Advancing our knowledge of the role of sex in the pathophysiology, symptoms, and complications of AF will help provide new measures of prevention and treatment of AF to alleviate the public health burden.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Chugh SS, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014; 129:837–47. [PubMed: 24345399]
2. Friberg L, et al. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). Europace. 2013; 15:135–40. [PubMed: 22791299]
3. Tedrow UB, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women’s health study). J Am Coll Cardiol. 2010; 55:2319–27. [PubMed: 20488302]
4. Benjamin EJ, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994; 271:840–4. [PubMed: 8114238]
5. Schnabel RB, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015; 386:154–162. [PubMed: 25960110]
6. Christophersen IE, Ellinor PT. Genetics of atrial fibrillation: from families to genomes. J Hum Genet. 2015
7. Chen YC, et al. Heterogeneous expression of potassium currents and pacemaker currents potentially regulates arrhythmogenesis of pulmonary vein cardiomyocytes. J Cardiovasc Electrophysiol. 2009; 20:1039–45. [PubMed: 19473300]
8. Oyen N, et al. Familial aggregation of lone atrial fibrillation in young persons. J Am Coll Cardiol. 2012; 60:917–21. [PubMed: 22726627]

9. Zoller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. J Am Heart Assoc. 2013; 2:e003384.
10. Humphries KH, et al. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation. 2001; 103:2365–70. [PubMed: 11352885]
11. Ball J, Carrington MJ, Wood KA, Stewart S, Investigators, S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). PLoS One. 2013; 8:e65795. [PubMed: 23734260]
12. Scheuermeyer FX, et al. There Are Sex Differences in the Demographics and Risk Profiles of Emergency Department (ED) Patients With Atrial Fibrillation and Flutter, but no Apparent Differences in ED Management or Outcomes. Acad Emerg Med. 2015; 22:1067–75. [PubMed: 26291513]
13. Bushnell C, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2014
14. Benjamin EJ, et al. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. Circulation. 1998; 98:946–952. [PubMed: 9737513]
15. Miyasaka Y, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006; 114:119–25. [PubMed: 16818816]
16. Chien KL, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. Int J Cardiol. 2010; 139:173–80. [PubMed: 19046608]
17. Wilke T, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace. 2013; 15:486–93. [PubMed: 23220354]
18. Piccini JP, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. Circ Cardiovasc Qual Outcomes. 2012; 5:85–93. [PubMed: 22235070]
19. Svennberg E, et al. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. Circulation. 2015; 131:2176–84. [PubMed: 25910800]
20. Li Y, et al. Prevalence of atrial fibrillation in China and its risk factors. Biomed Environ Sci. 2013; 26:709–16. [PubMed: 24099604]
21. Zhou Z, Hu D. An Epidemiological Study on the Prevalence of Atrial Fibrillation in the Chinese Population of Mainland China. J Epidemiol. 2008; 18:209–216. [PubMed: 18776706]
22. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. J Electrocardiol. 2008; 41:94–8. [PubMed: 17531253]
23. Jeong JH. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. J Korean Med Sci. 2005; 20:26–30. [PubMed: 15716597]
24. Inoue H, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol. 2009; 137:102–7. [PubMed: 18691774]
25. Iguchi Y, et al. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. Circ J. 2008; 72:909–13. [PubMed: 18503215]
26. Ohsawa M, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: an analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. J Epidemiol. 2005; 15:194–6. [PubMed: 16195640]
27. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. Europace. 2011; 13:1110–7. [PubMed: 21551478]
28. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994–1998: analysis of data from the general practice research database. Heart. 2001; 86:284–8. [PubMed: 11514479]
29. Lloyd-Jones DM, et al. Lifetime Risk for Development of Atrial Fibrillation: The Framingham Heart Study. Circulation. 2004; 110:1042–1046. [PubMed: 15313941]
30. Heeringa J, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006; 27:949–53. [PubMed: 16527828]

31. Guo Y, et al. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. Chest. 2015; 147:109–19. [PubMed: 24921459]
32. Alonso A, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013; 2:e000102. [PubMed: 23537808]
33. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004; 292:2471–2477. [PubMed: 15562125]
34. Potpara TS, et al. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: The Belgrade atrial fibrillation study. Int J Cardiol. 2012; 161:39–44. [PubMed: 21570138]
35. Dagres N, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol. 2007; 49:572–7. [PubMed: 17276181]
36. Conen D, et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. Circulation. 2009; 119:2146–52. [PubMed: 19364977]
37. Huxley RR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011; 123:1501–8. [PubMed: 21444879]
38. Chiang CE, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. Circ Arrhythm Electrophysiol. 2012; 5:632–9. [PubMed: 22787011]
39. Murin J, et al. Clinical characteristics, management, and control of permanent vs. nonpermanent atrial fibrillation: insights from the RealiseAF survey. PLoS One. 2014; 9:e86443. [PubMed: 24497948]
40. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014; 64:281–9. [PubMed: 25034065]
41. Ofman P, et al. Regular physical activity and risk of atrial fibrillation: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2013; 6:252–6. [PubMed: 23515264]
42. Selmer C, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012; 345:e7895. [PubMed: 23186910]
43. Aviles RJ, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003; 108:3006–10. [PubMed: 14623805]
44. Aizer A, et al. Relation of vigorous exercise to risk of atrial fibrillation. Am J Cardiol. 2009; 103:1572–7. [PubMed: 19463518]
45. Myrstad M, et al. Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter. Am J Cardiol. 2014; 114:1229–33. [PubMed: 25169984]
46. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2008; 118:800–7. [PubMed: 18678768]
47. Everett BM, et al. Physical activity and the risk of incident atrial fibrillation in women. Circ Cardiovasc Qual Outcomes. 2011; 4:321–7. [PubMed: 21487092]
48. Azarbal F, et al. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. J Am Heart Assoc. 2014; 3
49. Drca N, Wolk A, Jensen-Urstad M, Larsson SC. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. Heart. 2015; 101:1627–30. [PubMed: 26019224]
50. Arnar DO, et al. Familial aggregation of atrial fibrillation in Iceland. Eur Heart J. 2006; 27:708–12. [PubMed: 16428254]
51. Chen LY, Herron KJ, Tai BC, Olson TM. Lone atrial fibrillation: influence of familial disease on gender predilection. J Cardiovasc Electrophysiol. 2008; 19:802–6. [PubMed: 18363686]
52. Christophersen IE, et al. Familial aggregation of atrial fibrillation: a study in Danish twins. Circ Arrhythm Electrophysiol. 2009; 2:378–83. [PubMed: 19808493]

53. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA. Familial aggregation in lone atrial fibrillation. Hum Genet. 2005; 118:179–84. [PubMed: 16133178]
54. Fox CS, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004; 291:2851–5. [PubMed: 15199036]
55. Yang YQ, et al. Familial aggregation of lone atrial fibrillation in the Chinese population. Intern Med. 2010; 49:2385–91. [PubMed: 21088338]
56. Lubitz SA, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. JAMA. 2010; 304:2263–9. [PubMed: 21076174]
57. Ravn LS, et al. Relation of 97T polymorphism in KCNE5 to risk of atrial fibrillation. Am J Cardiol. 2005; 96:405–7. [PubMed: 16054468]
58. Karst ML, Herron KJ, Olson TM. X-linked nonsyndromic sinus node dysfunction and atrial fibrillation caused by emerin mutation. J Cardiovasc Electrophysiol. 2008; 19:510–5. [PubMed: 18266676]
59. Lip GY, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). Eur Heart J. 2014; 35:3365–76. [PubMed: 25176940]
60. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. Int J Cardiol. 2015; 191:172–7. [PubMed: 25974193]
61. Paquette M, et al. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. Am J Cardiol. 2000; 86:764–8. [PubMed: 11018197]
62. Sanna T, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014; 370:2478–86. [PubMed: 24963567]
63. Bekwelem W, et al. Extracranial Systemic Embolic Events in Patients With Nonvalvular Atrial Fibrillation: Incidence, Risk Factors, and Outcomes. Circulation. 2015; 132:796–803. [PubMed: 26224811]
64. Frost L, et al. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. Arch Intern Med. 2001; 161:272–276. [PubMed: 11176743]
65. Andersen LV, et al. Atrial fibrillation and upper limb thromboembolectomy: a national cohort study. J Thromb Haemost. 2011; 9:1738–1743. [PubMed: 21736696]
66. January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014; 130:e199–e267. [PubMed: 24682347]
67. Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillationDeveloped with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012; 33:2719–2747. [PubMed: 22922413]
68. Wang TJ, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 2003; 290:1049–56. [PubMed: 12941677]
69. Mikkelsen AP, et al. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. J Thromb Haemost. 2012; 10:1745–51. [PubMed: 22805071]
70. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ. 2012; 344:e3522. [PubMed: 22653980]
71. Fang MC, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. Circulation. 2005; 112:1687–91. [PubMed: 16157766]
72. Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). Am J Cardiol. 2004; 94:889–94. [PubMed: 15464671]

73. Inoue H, Atarashi H. Risk factors for thromboembolism in patients with paroxysmal atrial fibrillation. Am J Cardiol. 2000; 86:852–5. [PubMed: 11024400]
74. Avgil Tsadok M, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA. 2012; 307:1952–8. [PubMed: 22570463]
75. Aronow WS, Ahn C, Kronzon I, Gutstein H. Risk factors for new thromboembolic stroke in patients > or = 62 years of age with chronic atrial fibrillation. Am J Cardiol. 1998; 82:119–21. [PubMed: 9671020]
76. Stollberger C, et al. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group. Embolism in Left Atrial Thrombi. Ann Intern Med. 1998; 128:630–8. [PubMed: 9537936]
77. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011; 9:39–48. [PubMed: 21029359]
78. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest. 2012; 141:147–53. [PubMed: 21680645]
79. Poli D, Antonucci E, Testa S, Ageno W, Palareti G. Gender differences of bleeding and stroke risk in very old atrial fibrillation patients on VKA treatment: results of the EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics). Thromb Res. 2013; 131:12–6. [PubMed: 23141847]
80. Overvad TF, et al. Female sex as a risk factor for thromboembolism and death in patients with incident atrial fibrillation. The prospective Danish Diet, Cancer and Health study. Thromb Haemost. 2014; 112:789–795. [PubMed: 25055988]
81. Cha MJ, Oh GC, Hahn S, Choi EK, Oh S. Thromboembolic Risk Evaluation in Patients with Atrial Fibrillation Using a Modified CHADS2 Scoring System. J Cardiovasc Electrophysiol. 2012; 23:155–162. [PubMed: 21955174]
82. Nakagami H, et al. Mitral regurgitation reduces the risk of stroke in patients with nonrheumatic atrial fibrillation. Am Heart J. 1998; 136:528–532. [PubMed: 9736148]
83. Inoue H, et al. Impact of Gender on the Prognosis of Patients With Nonvalvular Atrial Fibrillation. Am J Cardiol. 2014; 113:957–962. [PubMed: 24461771]
84. Siu CW, Lip GYH, Lam KF, Tse HF. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. Heart Rhythm. 2014; 11:1401–1408. [PubMed: 24747420]
85. Friberg L, Skeppholm M, Terént A. Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA2DS2-VASc Score of 1. J Am Coll Cardiol. 2015; 65:225–232. [PubMed: 25614418]
86. Olesen JB, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342:d124. [PubMed: 21282258]
87. de Bruijn RF, et al. Association Between Atrial Fibrillation and Dementia in the General Population. JAMA Neurol. 2015; 72:1288–94. [PubMed: 26389654]
88. Miyasaka Y, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. Eur Heart J. 2007; 28:1962–7. [PubMed: 17459900]
89. Liao JN, et al. Risk and prediction of dementia in patients with atrial fibrillation - A nationwide population-based cohort study. Int J Cardiol. 2015; 199:25–30. [PubMed: 26173170]
90. Horstmann S, et al. Atrial fibrillation and prestroke cognitive impairment in stroke. J Neurol. 2014; 261:546–53. [PubMed: 24413641]
91. Bunch TJ, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010; 7:433–7. [PubMed: 20122875]
92. Dublin S, et al. Atrial fibrillation and risk of dementia: a prospective cohort study. J Am Geriatr Soc. 2011; 59:1369–75. [PubMed: 21806558]
93. Forti P, et al. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). Arch Gerontol Geriatr. 2007; 44(Suppl 1):155–65. [PubMed: 17317449]

94. Rusanen M, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. J Alzheimers Dis. 2014; 42:183–91. [PubMed: 24825565]
95. Wang TJ, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003; 107:2920–5. [PubMed: 12771006]
96. Miyasaka Y, et al. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J. 2006; 27:936–941. [PubMed: 16399778]
97. Schnabel RB, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. Eur J Heart Fail. 2013; 15:843–9. [PubMed: 23594831]
98. Meyer S, et al. Sex differences in new-onset heart failure. Clin Res Cardiol. 2015; 104:342–50. [PubMed: 25398254]
99. Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002; 113:359–364. [PubMed: 12401529]
100. Fukuda T, et al. Development of congestive heart failure in Japanese patients with atrial fibrillation. Circ J. 2007; 71:308–12. [PubMed: 17322626]
101. Goyal A, et al. Predictors of incident heart failure in a large insured population: a one million person-year follow-up study. Circ Heart Fail. 2010; 3:698–705. [PubMed: 20798277]
102. Andersson T, et al. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: A nationwide cohort study of 9519 patients. Int J Cardiol. 2014; 177:91–99. [PubMed: 25499348]
103. Potpara TS, et al. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation study. Chest. 2012; 141:339–47. [PubMed: 21622553]
104. Soliman EZ, et al. Atrial Fibrillation and Risk of ST-Segment–Elevation Versus Non–ST-Segment–Elevation Myocardial Infarction : The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2015; 131:1843–1850. [PubMed: 25918127]
105. Soliman EZ, et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Intern Med. 2014; 174:107–14. [PubMed: 24190540]
106. O'Neal WT, Sangal K, Zhang ZM, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. Clin Cardiol. 2014; 37:750–5. [PubMed: 25403873]
107. Chao TF, et al. Acute myocardial infarction in patients with atrial fibrillation with a CHA2DS2-VASc score of 0 or 1: a nationwide cohort study. Heart Rhythm. 2014; 11:1941–7. [PubMed: 25101483]
108. Miyasaka Y, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol. 2007; 49:986–92. [PubMed: 17336723]
109. Chen LY, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. JAMA Intern Med. 2013; 173:29–35. [PubMed: 23404043]
110. Conen D, Chae CU, Glynn RJ, et al. RIsk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011; 305:2080–2087. [PubMed: 21610240]
111. Stollberger C, Winkler-Dworak M, Finsterer J, Hartl E, Chnupa P. Factors influencing mortality in atrial fibrillation. Post hoc analysis of an observational study in outpatients. Int J Cardiol. 2005; 103:140–4. [PubMed: 16080971]
112. Marijon E, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013; 128:2192–201. [PubMed: 24016454]
113. Olsson LG, Swedberg K, Lappas G, Stewart S, Rosengren A. Trends in mortality after first hospitalization with atrial fibrillation diagnosis in Sweden 1987 to 2006. Int J Cardiol. 2013; 170:75–80. [PubMed: 24383072]
114. Stollberger C, et al. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. Clin Cardiol. 2004; 27:40–6. [PubMed: 14743856]

115. Nieuwlaat R, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. Eur Heart J. 2008; 29:1181–9. [PubMed: 18397874]
116. Gallego P, et al. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. Thromb Haemost. 2013; 110:1189–98. [PubMed: 24096615]
117. Banerjee A, et al. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. Int J Cardiol. 2013; 167:2682–7. [PubMed: 22795403]
118. Zubaid M, et al. Management and 1-year outcomes of patients with atrial fibrillation in the Middle East: Gulf survey of atrial fibrillation events. Angiology. 2015; 66:464–71. [PubMed: 24904179]
119. Badheka AO, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. Am J Med. 2010; 123:646–51. [PubMed: 20609687]
120. Emdin CA, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ. 2016; 532:h7013. [PubMed: 26786546]
121. Haissaguerre M, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339:659–66. [PubMed: 9725923]
122. Hocini M, et al. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. Circulation. 2002; 105:2442–8. [PubMed: 12021234]
123. Kamalvand K, et al. Alterations in atrial electrophysiology associated with chronic atrial fibrillation in man. Eur Heart J. 1999; 20:888–95. [PubMed: 10329094]
124. Raitt MH, Kusumoto W, Giraud G, McAnulty JH. Reversal of electrical remodeling after cardioversion of persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2004; 15:507–12. [PubMed: 15149416]
125. Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with chronic atrial fibrillation and atrial flutter. J Am Coll Cardiol. 1997; 30:1785–92. [PubMed: 9385908]
126. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995; 92:1954–68. [PubMed: 7671380]
127. Ehrlich JR, et al. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties. J Physiol. 2003; 551:801–13. [PubMed: 12847206]
128. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. J Am Coll Cardiol. 2011; 58:2225–32. [PubMed: 22078429]
129. Henry WL, et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation. 1976; 53:273–9. [PubMed: 128423]
130. Vasan RS, Larson MG, Levy D, Evans JC, Benjamin EJ. Distribution and categorization of echocardiographic measurements in relation to reference limits: the Framingham Heart Study: formulation of a height- and sex-specific classification and its prospective validation. Circulation. 1997; 96:1863–73. [PubMed: 9323074]
131. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994; 89:724–30. [PubMed: 8313561]
132. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 2008; 1:62–73. [PubMed: 19808395]
133. Anne W, et al. Self-terminating AF depends on electrical remodeling while persistent AF depends on additional structural changes in a rapid atrially paced sheep model. J Mol Cell Cardiol. 2007; 43:148–58. [PubMed: 17597147]
134. Filgueiras-Rama D, et al. Long-term frequency gradients during persistent atrial fibrillation in sheep are associated with stable sources in the left atrium. Circ Arrhythm Electrophysiol. 2012; 5:1160–7. [PubMed: 23051840]

135. Remes J, et al. Persistent atrial fibrillation in a goat model of chronic left atrial overload. J Thorac Cardiovasc Surg. 2008; 136:1005–11. [PubMed: 18954643]
136. Ravens U. Antiarrhythmic therapy in atrial fibrillation. Pharmacol Ther. 2010; 128:129–45. [PubMed: 20624425]
137. Sanfilippo AJ, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation. 1990; 82:792–7. [PubMed: 2144217]
138. Kishi S, et al. Race-ethnic and sex differences in left ventricular structure and function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. J Am Heart Assoc. 2015; 4:e001264. [PubMed: 25770024]
139. Tsang TS, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc. 2001; 76:467–75. [PubMed: 11357793]
140. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson. 2005; 7:775–82. [PubMed: 16353438]
141. McManus DD, et al. Longitudinal tracking of left atrial diameter over the adult life course: Clinical correlates in the community. Circulation. 2010; 121:667–74. [PubMed: 20100973]
142. Cochet H, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. J Cardiovasc Electrophysiol. 2015; 26:484–92. [PubMed: 25727248]
143. Khera A, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol. 2005; 46:464–9. [PubMed: 16053959]
144. Mathew JS, et al. Fibroblast growth factor-23 and incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). Circulation. 2014; 130:298–307. [PubMed: 24920722]
145. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010; 21:1064–70. [PubMed: 20455973]
146. Panwar B, et al. Fibroblast growth factor 23 and risk of incident stroke in community-living adults. Stroke. 2015; 46:322–8. [PubMed: 25563643]
147. Tsai WC, Chen YC, Lin YK, Chen SA, Chen YJ. Sex differences in the electrophysiological characteristics of pulmonary veins and left atrium and their clinical implication in atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:550–9. [PubMed: 21659634]
148. Takigawa M, et al. Differences in catheter ablation of paroxysmal atrial fibrillation between males and females. Int J Cardiol. 2013; 168:1984–91. [PubMed: 23782910]
149. Yang PC, Kurokawa J, Furukawa T, Clancy CE. Acute effects of sex steroid hormones on susceptibility to cardiac arrhythmias: a simulation study. PLoS Comput Biol. 2010; 6:e1000658. [PubMed: 20126530]
150. Nakamura H, et al. Progesterone regulates cardiac repolarization through a nongenomic pathway: an in vitro patch-clamp and computational modeling study. Circulation. 2007; 116:2913–22. [PubMed: 18056530]
151. Nakagawa M, et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol. 2006; 29:607–13. [PubMed: 16784426]
152. Rosano GM, et al. Cyclical variation in paroxysmal supraventricular tachycardia in women. Lancet. 1996; 347:786–8. [PubMed: 8622333]
153. Rosano GM, et al. Acute electrophysiologic effect of estradiol 17beta in menopausal women. Am J Cardiol. 2000; 86:1385–7. a5–6. [PubMed: 11113421]
154. Saba S, et al. Effects of estrogen on cardiac electrophysiology in female mice. J Cardiovasc Electrophysiol. 2002; 13:276–80. [PubMed: 11942597]
155. Perez MV, et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: the Women's Health Initiative randomized controlled trials. Circ Arrhythm Electrophysiol. 2012; 5:1108–16. [PubMed: 23169946]
156. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. Circulation. 1996; 94:1471–4. [PubMed: 8823008]

157. Liu XK, et al. Gender difference in the cycle length-dependent QT and potassium currents in rabbits. J Pharmacol Exp Ther. 1998; 285:672–9. [PubMed: 9580612]

158. Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. Eur Heart J. 1997; 18:1000–6. [PubMed: 9183593]

159. Nielsen JB, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart Rhythm. 2013; 10:1249–56. [PubMed: 23608590]

160. Cheng S, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009; 301:2571–7. [PubMed: 19549974]

161. Buitrago C, Massheimer V, de Boland AR. Acute modulation of Ca2+ influx on rat heart by 17beta-estradiol. Cell Signal. 2000; 12:47–52. [PubMed: 10676847]

162. Jovanovic S, Jovanovic A, Shen WK, Terzic A. Low concentrations of 17beta-estradiol protect single cardiac cells against metabolic stress-induced Ca2+ loading. J Am Coll Cardiol. 2000; 36:948–52. [PubMed: 10987624]

163. Magnani JW, et al. Association of sex hormones, aging, and atrial fibrillation in men: the Framingham Heart Study. Circ Arrhythm Electrophysiol. 2014; 7:307–12. [PubMed: 24610804]

164. Tsuneda T, et al. Deficiency of testosterone associates with the substrate of atrial fibrillation in the rat model. J Cardiovasc Electrophysiol. 2009; 20:1055–60. [PubMed: 19460074]

165. Cove CL, et al. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost. 2014; 111:385–91. [PubMed: 24305974]

166. Udelson JE. Heart Failure With Preserved Ejection Fraction. Circulation. 2011; 124:e540–e543. [PubMed: 22105201]

167. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014; 509:282–3. [PubMed: 24834516]

168. Mosca L, Barrett-Connor E, Kass Wenger N. Sex/Gender Differences in Cardiovascular Disease Prevention: What a Difference a Decade Makes. Circulation. 2011; 124:2145–2154. [PubMed: 22064958]

169. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014; 11:639–54. [PubMed: 25113750]

170. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002; 415:219–26. [PubMed: 11805846]

171. Gowd BM, Thompson PD. Effect of female sex on cardiac arrhythmias. Cardiol Rev. 2012; 20:297–303. [PubMed: 22531673]

172. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Hormone replacement therapy and adverse outcomes in women with atrial fibrillation: an analysis from the atrial fibrillation follow-up investigation of rhythm management trial. Stroke. 2014; 45:3076–9. [PubMed: 25190441]

173. Schnabel RB, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009; 373:739–45. [PubMed: 19249635]

174. Schnabel RB, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation. 2010; 121:200–7. [PubMed: 20048208]

## Key points

- Women generally have lower age-adjusted incidence and prevalence of atrial fibrillation (AF) than men; however, given the greater longevity of women, the absolute number of men and women with AF is similar
- The prevalence of major risk factors differ by sex; women have higher prevalence of hypertension and valvular heart disease, and lower prevalence of coronary heart disease, than men
- Women are more likely to present with atypical symptoms, such as weakness and fatigue, have longer duration of symptoms, and report worse quality of life and more-frequent depression than men
- Female sex has been shown to be a risk factor for AF-related stroke or thromboembolism, myocardial infarction, and mortality, but has not been associated with incident heart failure or dementia
- Future research is needed to address the knowledge gaps in sex differences in AF

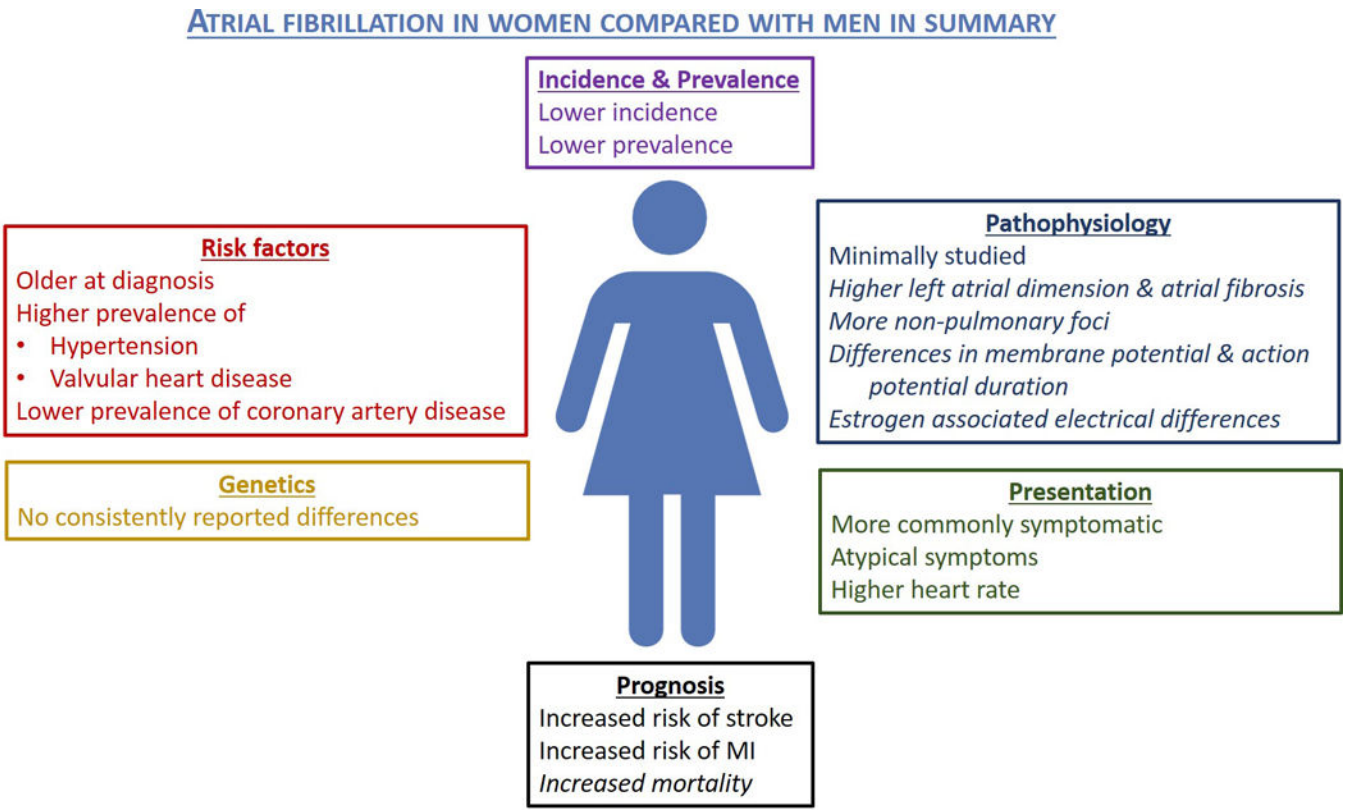


**Figure 1. Overview of atrial fibrillation in women compared with in men**

A summary of the major findings for each paramenter covered in this Review. Sex differences that are uncertain are *italicized*.

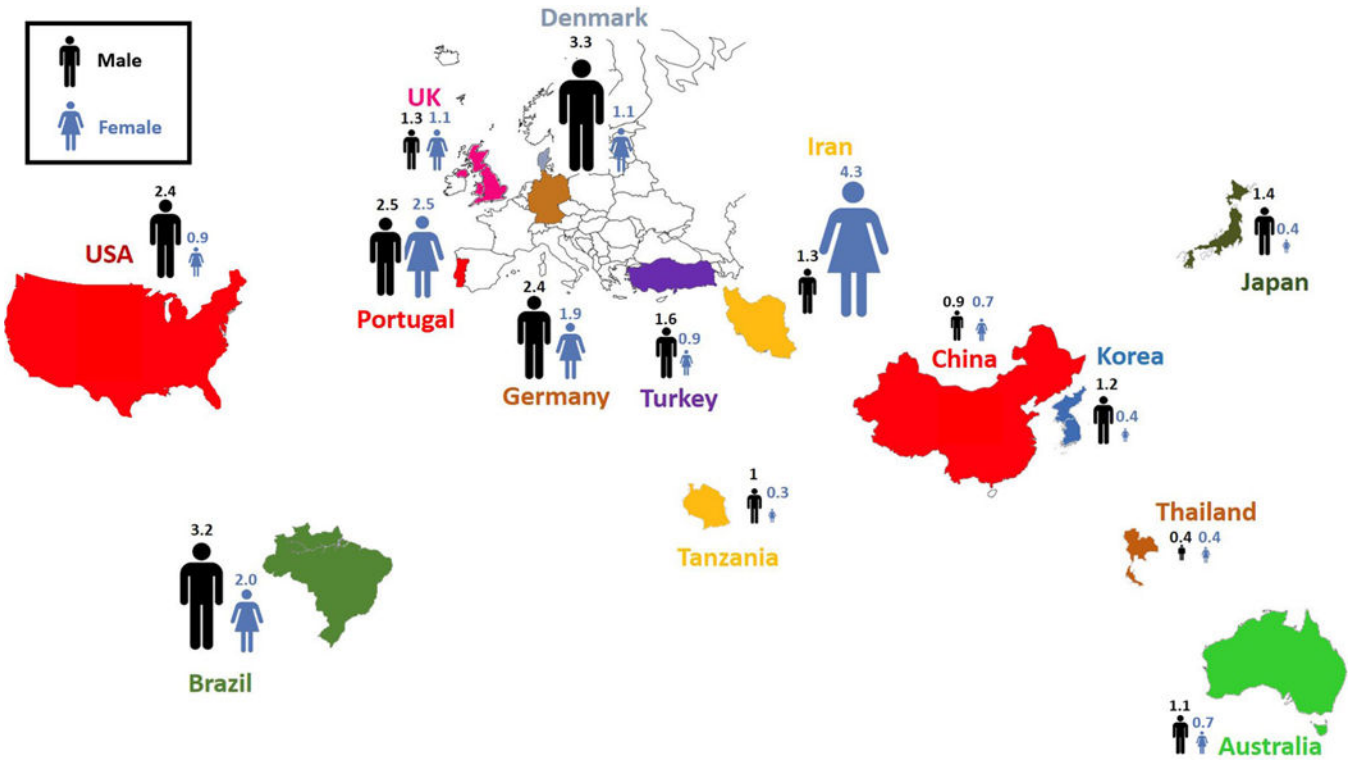


**Figure 2. Prevalence of atrial fibrillation in women and men**

Maps showing prevalence (%) in women (blue) and men (black) separately, for all countries with published data available.

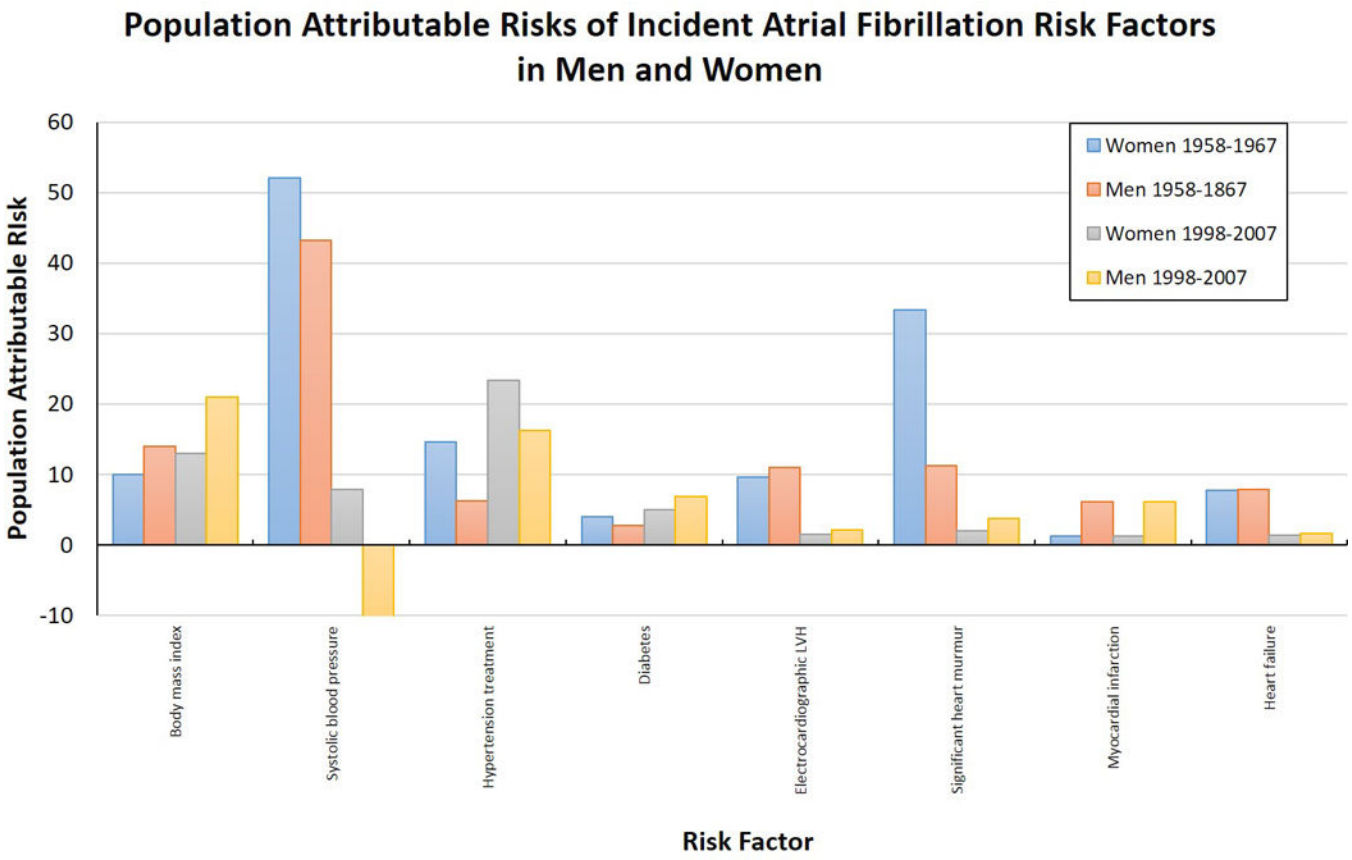


**Figure 3. Risk factors for atrial fibrillation in women and men**

Population-attributable risks of incident atrial fibrillation risk factors in women and men for different time periods in the Framingham Heart Study (unpublished data).

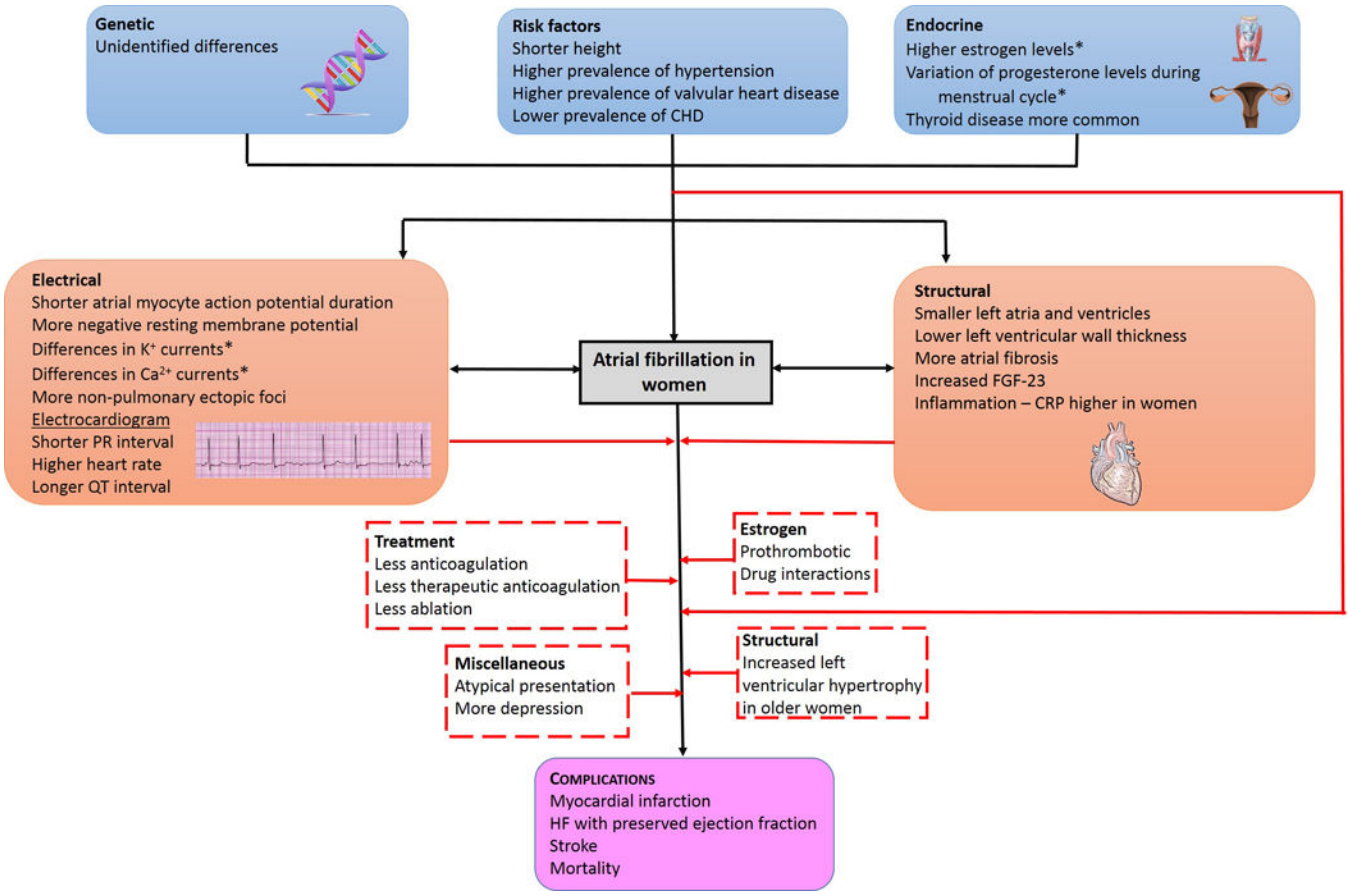


**Figure 4. Potential sex differences in pathophysiological mechanisms of atrial fibrillation (AF)**

The pathophysiological mechanisms that explain the sex differences in AF incidence and associated complications have been incompletely studied. We present potential mechanisms identified on the basis of reported sex differences in genetics, risk factors, hormones, electrical and structural properties, and other factors that might help explain why women have a lower incidence and prevalence of AF, while experiencing a higher risk of complications. AF causes electrical and structural remodelling that promotes AF, leading to the phrase 'AF begets AF'. Note that none of these interactions have been rigorously studied – please see Table 1. *See Pathophysiology section for further details. CHD, coronary heart disease; CRP, C-reactive protein; FGF-23, fibroblast growth factor 23; HF, heart failure.

## Table 1

Outline of future research and directions

| Knowledge gap | Future study |
|---|---|
| ***Incidence and prevalence*** | |
| Differences of incidence and prevalence of AF in all ancestries by sex | Perform well-powered longitudinal studies investigating the incidence and prevalence in populations of all ancestries by sex |
| Differences in incidence and prevalence of asymptomatic AF | Population screening of both women and men to detect asymptomatic AF and potential differences between sexes. Tools might include ambulatory ECG, implantable loop recorder, or mobile devices |
| ***Risk factors*** | |
| Differences in prevalence of risk factors | Perform well-powered longitudinal studies with formal testing of effect modification of sex on distribution of risk factors for AF |
| ***Genetics*** | |
| Sex-specific genetic associations | Conduct separate genetic association studies in women and men to identify genetic variants with differential effects in women and men |
| ***Clinical presentations*** | |
| Differences in presentation | Incorporate sex differences in AF-related symptoms in population screening programs<br>Investigate implications of sex differences in AF-related symptoms and outcomes |
| ***Stroke and thromboembolism*** | |
| Underlying cause of the increased risk of stroke in women with AF | Identify genetic, anatomical, physiological, sociocultural risk factors associated with increased risk of AF-related stroke in women |
| Differences in prognosis after AF-related stroke | Investigate sex differences in short-term and long-term mortality and neurological deficits after AF-related stroke |
| ***Dementia*** | |
| Differences in risk of dementia | Perform well-powered longitudinal studies investigating sex differences in association with AF and cognitive impairment and dementia, independent of stroke |
| Underlying cause of AF-related dementia | Identify sex differences in anatomy and physiology related to AF-related dementia, through studies on both women and men, and male and female animal models |
| ***HF*** | |
| Differences in risk of AF-related HF | Investigate sex differences in the incidence of AF-related HFpEF and HFrEF |
| Underlying causes of increased risk of AF-related HFpEF in women | Identify sex differences in cardiac anatomy and physiology related to AF-related HF subtypes, through studies on both women and men, and male and female animal models |
| ***MI*** | |
| Differences in risk of MI | Conduct validation studies for sex differences in the risk of AF-related MI using different population settings<br>Identify pathophysiological, genetic, clinical, social, and behavioural risk factors associated with increased risk of MI subtypes in women and men with AF, testing for effect modification by sex |
| ***Mortality*** | |
| Differences in mortality | Conduct well-powered longitudinal studies of whether sex differences in mortality associated with AF vary by ethnicity or race and country<br>Determine the mechanisms underlying sex-related differences in AF associated mortality |
| ***Pathophysiology*** | |
| Preclinical studies | Balance female and male animal models in studying mechanisms of AF |
| Sex differences in electrical mechanisms | Identify sex differences in atrial resting membrane potential, action potential duration, and refractory period<br>Evaluate if differences exist in triggered foci and re-entry mechanisms driving AF and location of origination between women and men<br>Evaluate if sex differences exist in the electrical changes that occur after the development of AF that promote AF maintenance |

| Knowledge gap | Future study |
|---|---|
| Sex differences in structural mechanisms | Evaluate if there are structural sex differences before and after development of AF |
| Hormone differences and risk of AF | Perform longitudinal studies evaluating the associations of hormonal differences related to risk of AF |

AF, atrial fibrillation; ECG, electrocardiogram; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.