

Figure 1. Prevalence of diagnosed atrial fibrillation stratified by age and sex. Error bars represent 95% confidence intervals. Numbers represent the number of men and women with atrial fibrillation in each age category. Reproduced with permission from [1].

are significantly overrepresented, such that approximately 60% of all individuals with AF in this age group are female [4].

These differences have also been reported in regard to incident AF. The annual incidence of AF per 1000 person-years has been reported to be 1.9 cases in women compared with 3.1 cases in men in the age group between 55 and 64 years, whereas it increases to 31.4 cases in women and 38.0 cases in men in the age group between 85 and 94 years [5].

Risk factors associated with AF in women

Blood pressure has been shown to be an independent risk factor for the incidence of AF, and given the high prevalence of elevated blood pressure in the general population, it is the most common risk factor for the arrhythmia. Data from the Framingham Heart Study indicate that in both men and women, approximately 14% of the AF risk could be attributed to high blood pressure [5-7]. Furthermore, the individual components of blood pressure, including systolic and diastolic blood pressure, and pulse pressure have a differential effect on the incidence of AF [8]. The association between blood pressure and incident AF appears to be similar in women and men. In the Women's Health Study, systolic blood pressure was a more powerful predictor of AF compared with diastolic blood pressure. Women with a systolic blood pressure greater than 160 mmHg had a 2.74-fold increased risk of AF compared with those with a systolic blood pressure of less than 120 mmHg (FIGURE 2) [9]. Diastolic blood pressure was found to provide some additional information to systolic blood

pressure, again pointing at the potential importance of pulse pressure. This study also demonstrated that systolic blood pressure levels within the nonhypertensive range were independently associated with incident AF. This was true even after blood pressure changes over time were taken into account. These findings, in a large cohort of initially healthy women, suggest that the ever increasing incidence and prevalence of AF may be reduced by aiming for lower blood-pressure levels in the general population.

Obesity has been found to be strongly associated with the incidence of AF. For example, in individuals with a BMI over 30 kg/m², the risk of developing AF was increased by approximately 50% in the Framingham Heart Study [10-12]. The increased risk was similar in women and men. A longitudinal study conducted in Olmsted County (MN, USA) suggested that obesity is a risk factor for the progression of paroxysmal to persistent AF with no significant differences between women and men [13]. Obesity is related to the metabolic syndrome, which encompasses a cluster of abnormalities that increase the risk of developing cardiovascular disease and diabetes [14]. A recent Japanese study, which included a majority of women (66%), reported a significant association of the metabolic syndrome and AF. The hazard ratio of developing AF was 1.88 (95% CI: 1.40-2.52) in individuals with the metabolic syndrome (based on the National Cholesterol Education Program [NCEP]/Adult Treatment Panel [ATP] III guidelines) compared with individuals who had no metabolic syndrome [15,16]. Whether the presence or absence of the metabolic syndrome provides additional information independent of its individual components has yet to be clarified [3]. In the general population, the prevalence of obesity is higher in women compared with men [17]. Thus, while the risk of AF among obese individuals seems to be similar in women and men, the population attributable risk of obesity in women is higher, given its higher prevalence in women.

Recent evidence suggests that inflammation is another factor associated with AF. The pathophysiological concept that inflammation is involved in the occurrence of AF is supported by the fact that AF is common in patients following cardiac surgery [18,19]. However, nonpostoperative AF is also associated with inflammation as evidenced by an analysis in a population-based study in the elderly [20]. In this study, C-reactive protein, as a marker of inflammation, was independently associated with prevalent and incident AF. This association was also present in

the prespecified subgroup of 3341 women (58% of the study population). Furthermore, through its relationship with obesity, blood pressure or structural heart disease, inflammation may be an important mediator in the relationship between AF and these risk factors [21–23].

The association of alcohol consumption with AF was recognized long ago and the term ‘holiday heart’ was first used more than 30 years ago to describe alcohol-associated cardiac rhythm disorders [24,25]. Previous studies have demonstrated that men consuming 35 or more alcoholic drinks per week are at an increased risk of developing AF compared with men who do not drink alcohol [26–28]. A recent analysis from the Women’s Health Study demonstrated that the association between alcohol intake and AF is also present in women, but that the amount of alcohol intake leading to an increased risk of AF is much lower in women. In this study, there was a 60% increased risk in the incidence of AF in women with an alcohol intake of 14 or more drinks per week compared with nondrinking women. On the other hand, moderate alcohol intake (<14 drinks per week) was not associated with an increased risk of developing AF [29]. Therefore, regular alcohol consumption does not seem to be an important contributor to the AF burden in the general population.

Heart disease, especially heart failure, is another important risk factor for AF [30]. The prevalence of AF is associated with the severity of congestive heart failure, with approximately

10% of patients with New York Heart Association functional class I–II and approximately half of the patients with New York Heart Association functional class IV heart failure having AF [31]. In the Framingham Heart Study, the incidence of AF among subjects with heart failure was 54 per 1000 person-years, and in heart failure subjects, the subsequent development of AF was associated with increased mortality with a hazard ratio of 2.7 in women and 1.6 in men [32].

Finally, specific drugs may be independently associated with AF. Results from the HORIZON Pivotal Fracture Trial, a randomized controlled trial assessing the effects of once-a-year zoledronic acid on fracture risk in postmenopausal women with osteoporosis demonstrated a higher risk of AF in women treated with the bisphosphonate [33]. This was confirmed by a population-based case–control study, in which use of alendronate was associated with an increased risk (odds ratio: 1.86; 95% CI: 1.09–3.15) of incident AF after adjustment for the matching variables – osteoporosis and cardiovascular disease [34]. The reasons for this association are essentially unknown, but changes in atrial calcium concentration might be involved [35]. As the administration of bisphosphonates results in an elevation of IL-6 and TNF- α , it could be hypothesized that an inflammatory response is involved in the association between AF and these drugs [36,37]. If confirmed, this association may become an important public-health problem given the high prevalence of osteoporosis in women [38].

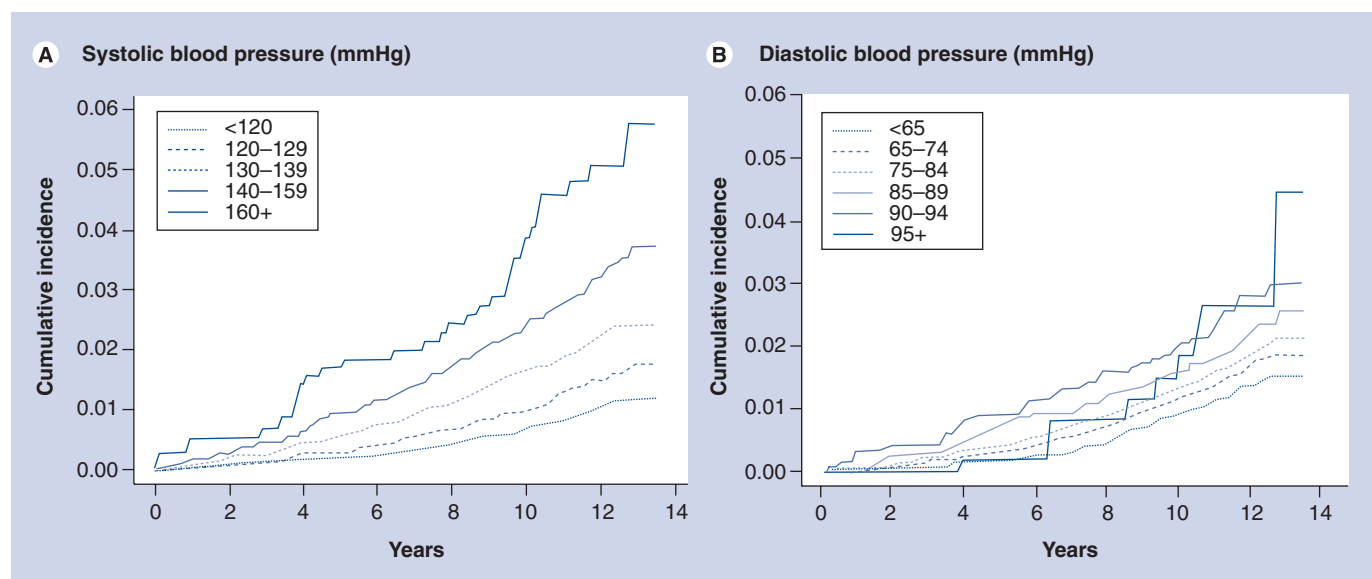


Figure 2. Cumulative incidences of atrial fibrillation estimated using a modified Kaplan–Meier approach. Systolic and diastolic blood pressure categories were updated at 12, 48, 120 and 132 months of follow-up, and the most recent blood pressure measurement before the event was used to estimate risk. Reproduced with permission from [9].

Very little data are available on other factors potentially associated with AF in women, such as fatty acid intake, lipid levels, oxidative stress and also the role of genetics. Further studies are needed to fill this gap.

Presentation of AF in women

Atrial fibrillation has an important impact on morbidity and mortality. With regard to mortality, population-based data from the Framingham Heart Study indicated that the risk of death in the setting of AF was increased in individuals with AF with a risk factor-adjusted odds ratio for death of 1.9 in women and 1.5 in men [39].

The occurrence of stroke is the most severe complication in patients with AF and may be the presenting symptom in a substantial proportion of patients. Approximately 15–20% of strokes are related to AF, and the proportion of strokes associated with AF ranges from approximately 7% in patients aged 50–59 years, up to 36% in patients aged 80–89 years [40,41]. There is prospective evidence that women with AF are more likely to develop stroke compared with men [42]. Furthermore, after a stroke, women have a higher degree of disability and a lower quality of life compared with men; however, women are less likely to die from an AF-related stroke [43].

Atrial fibrillation and heart failure are strongly associated and the clinical presentation of a patient with AF may be dominated by the symptoms and signs of heart failure. In subjects with AF who participated in the Framingham Heart Study, the incidence of heart failure was 33 per 1000 person-years. In these patients, the development of heart failure was associated with an increased mortality that was similar in women and men [32].

Atrial fibrillation has been shown to result in a considerably impaired quality of life. In a small study, women with AF reported a lower physical, but not mental, quality of life compared with men [44]. Similarly, in the Canadian Trial of Atrial Fibrillation, women reported significantly lower functional capacity and physical health but similar scores for mental health and general well-being when compared with men [45]. Furthermore, cardiac symptoms were more severe and occurred more frequently in women than in men. In female AF patients, the symptom burden appears to be higher and its effect on the quality of life more pronounced, especially in domains of physical functioning.

If paroxysms of AF occur, the likelihood of an event being symptomatic is higher, and episodes are associated with higher heart rates and tend to last longer in women compared with men [46].

The Canadian Registry of Atrial Fibrillation (CARAF) found that women had higher heart rates and were more likely to seek medical advice due to AF [47]. The clinical presentation of AF was also different in women compared with men in the Rate Control versus Electrical Cardioversion (RACE) study, in which women reported more symptoms due to AF and a lower quality of life [48]. Whether these quality of life differences are due to a different burden of comorbidities or are truly due to gender differences has to be determined in future studies.

Management of AF in women

The occurrence of stroke is a catastrophic complication of AF and this makes the prevention of thromboembolism the number one goal in patients with AF. Using an adequate anticoagulation strategy based on risk-stratification tools, such as the CHADS₂ score, is paramount to achieve this goal [49,50]. In the Anticoagulation and Risk Factors in Atrial fibrillation (ATRIA) cohort, patients receiving warfarin were less likely to be women; however, women appeared to have a greater net clinical benefit from warfarin treatment when compared with men [51]. The CARAF study demonstrated a similar overall use of warfarin in women compared with men, but women above the age of 75 years were less likely to be treated with oral anticoagulation and more likely to receive aspirin [47]. The study suggested that physicians may be reluctant to use oral anticoagulation in older women with AF despite a similar risk profile, potentially due to a higher risk of major bleeding in women [47]. However, the risk of bleeding was similar in women and men in the ATRIA study and the Stroke Prevention in Atrial Fibrillation (SPAF) studies [1,52,53]. Taken together, the available evidence suggests that oral anticoagulants are generally less used in female compared with male AF patients.

In the RACE study, women randomized to rhythm control reached more end points (heart failure, thromboembolic complications, adverse effects of antiarrhythmic drugs) compared with men with an adjusted hazard ratio of 3.1 (95% CI: 1.5–6.3). Quality of life was not better in the rhythm-control group compared with the rate-control group [48]. Furthermore, there is evidence that some antiarrhythmic drugs are associated with a higher potential for proarrhythmia in women compared with men [54,55]. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, there were no significant differences between women and men when comparing a rate-control and a rhythm-control strategy in

elderly patients with AF [56,57]. These data suggest that using a strategy aiming at adequate rate control may suffice in female patients with AF, especially if they are asymptomatic.

There are gender differences with regard to interventional treatments of AF. For example, radiofrequency catheter ablation of the atrioventricular node and implantation of a permanent pacemaker is performed later during the course of the disease in women when compared with men [58–60]. In a recent European study among AF patients referred to a tertiary care center, only 27% of patients were women. Female AF patients were older, more often had paroxysmal AF, more frequently complained of palpitations and were more likely to have side effects from amiodarone. However, there was no difference in the proportion of women (21%) and men (25%) undergoing AF ablation following the initial evaluation [61]. When looking at gender differences in patients who undergo AF ablation, women were older, more frequently had high blood pressure, had a larger diameter of the left atrium and had a longer history of AF before receiving ablation. However, freedom from AF during a follow-up of almost 2 years was similar in women and men (83%). These data suggest that women are referred for AF ablation later with a more complex clinical presentation [62].

Future perspective

Recent advances in the treatment of AF may substantially change the future management of patients with AF. A recent randomized

controlled trial demonstrated that dabigatran, an oral thrombin inhibitor, given at a dose of 110 mg twice daily was associated with similar stroke rates compared with warfarin and a lower rate of major hemorrhage [63]. When given at a dose of 150 mg twice daily, dabigatran was even associated with lower stroke rates compared with warfarin with similar rates of major hemorrhage. Although the drug was not tested specifically in a female population, the reported effect was also seen in the female subgroup of 6598 women (36% of the study population) [63]. Other anticoagulants such as rivaroxaban, a direct factor-Xa inhibitor, are currently being tested in patients with AF [64]. Another recent randomized controlled trial evaluated the use of dronedarone in 4628 patients with AF and included 2169 women (47% of the study population) [65]. The trial demonstrated that this novel antiarrhythmic drug reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF, and this effect was seen both in men and women [65]. It will be interesting to see how the results of these and future studies will impact the guidelines on the management of AF in years to come.

There is enough evidence to suggest that true gender differences exist in all the different facets of AF; however, the pathophysiological links explaining why this is the case are still missing. Differences in electrophysiological properties of the atrium, such as the atrial effective refractory period, have been described. Differences in autonomic tone and hormonal changes may

Executive summary

Epidemiology of atrial fibrillation in women

- The overall prevalence of atrial fibrillation (AF) in the general population is approximately 1%, but this current prevalence may increase substantially within the next few decades.
- The prevalence of AF is lower in women, and varies widely between different age groups in women and men.
- However, in the age group above 75 years, in which AF becomes frequent, women are significantly overrepresented. Approximately 60% of all individuals with AF in this age group are female.

Risk factors associated with AF in women

- Several risk factors have been associated with AF and some of them have been studied specifically in large female cohorts indicating that significant differences with regard to AF risk factors exist across genders.

Presentation of AF in women

- Women with AF are usually referred later and receive more conservative treatments for the arrhythmia. This is surprising since women are more symptomatic and also have a higher stroke risk with more resulting disabilities compared with men.

Management of AF in women

- Oral anticoagulants are underutilized in female AF patients, probably owing to the somewhat elevated risk of hemorrhage. However, the net clinical benefit is in favor of using anticoagulants in female AF patients at risk for stroke and appears to be even higher compared with male AF patients.

Future perspective

- New anticoagulants, such as dabigatran, and new antiarrhythmic drugs, such as dronedarone, and other novel substances that are currently tested in clinical trials will have a significant impact on the future treatment strategies in women with AF.
- The genetic background of AF is one of the avenues of further research and might provide insight as to why AF behaves differently in women and also provide pathophysiological information that might help prevent the arrhythmia.

be involved as well, but the reasons for the differences are still poorly understood and remain hypothetical [66]. Therefore, further studies are needed to fill this gap. Genetic, gene-expression and metabolomic studies may be of particular value in this regard. These studies may also provide further insights into the pathophysiology of AF and lead to potential new targets for future therapies and, ultimately, the prevention of the arrhythmia in women and men.

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▪ of interest

▪▪ of considerable interest

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