Epidemiology, risk factors, and prevention of atrial fibrillation

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. Patients are at increased risk for death, heart failure, hospitalization, and thromboembolic events [1-3].

The epidemiology of, disease associations with, and risk factors for AF will be reviewed here. An overview of the presentation and management of patients with AF is discussed elsewhere. (See "Atrial fibrillation: Overview and management of new-onset atrial fibrillation".)

EPIDEMIOLOGY

AF is a global health care problem with evidence suggesting an increasing prevalence and incidence worldwide [4-6]. A systematic review of worldwide population-based studies (n = 184) estimated that the number of individuals with AF in 2010 was 33.5 million.

Most of the studies below have evaluated individuals living in North America or Europe, but other geographies will be specified.

Prevalence — The prevalence of AF depends upon population characteristics, with differences apparent due to age, sex, race, geography, and time period. The following data are primarily

derived from studies in which an electrocardiogram was obtained during an office visit rather than ambulatory monitoring. The prevalence of paroxysmal AF, which is more likely to be detected with ambulatory monitoring, is much higher.

- **Age** – AF is uncommon in infants and children and when present, almost always occurs in association with structural heart disease. Healthy young adults are also at low risk [7]. The prevalence of AF increases with age (figure 1) [2,8-11]. This relationship to age was demonstrated in the ATRIA study, a cross-sectional study of almost 1.9 million subjects in a health maintenance organization in the United States [11]. The overall prevalence of AF was 1 percent; 70 percent were at least 65 years old and 45 percent were ≥75 years old. The prevalence of AF ranged from 0.1 percent among adults less than 55 years of age to 9 percent in those ≥80 years of age (figure 2). In the STROKESTOP study discussed below, the prevalence of AF in a 75- to 76-year-old population (2011) in Sweden was about 12 percent [12]. Similar patterns were reported in a European population-based prospective cohort study of 6808 subjects ≥55 years of age [10]. The prevalence of AF was 5.5 percent, ranging from 0.7 percent in those aged 55 to 59 years and 17.8 percent for those ≥85 years of age.

- **Sex** – The prevalence was higher in men than women (1.1 versus 0.8 percent), a difference seen in every age group (figure 2 and figure 1). In another study, the rates were 6 versus 5.1 percent, respectively [10].

- **Race/ethnicity** – In one study, AF was more frequent in Whites compared with Black Americans over the age of 50 years (2.2 versus 1.5 percent) [11]. It has not been determined whether those from a Black population are at lower risk or if those from a White population are at higher risk [13]. A study that included nearly 14,000,000 patients receiving hospital-based care in California (United States) between 2005 and 2009 evaluated the relationship between race and incident AF [14]. Adjustment was made for known AF risk factors and patient demographics. Compared with White Americans, Black (hazard ratio [HR] 0.84), Hispanic (HR 0.78), and Asian (HR 0.78) Americans each had a lower AF risk after adjustment.

- **Geography** – In one study, the age-adjusted prevalence rate (per 100,000 population) was highest in North America (700 to 775) and lowest in Japan and South Korea (250 to 325) [6]. The rate in China was also relatively low (325 to 400).

- **Time period** – The prevalence of AF in the population is increasing. In a community-based study of 1.4 million patients in England and Wales, the age-standardized prevalence of AF between 1994 and 1998 increased by 22 and 14 percent in men and women, respectively

[8]. In the ATRIA study, it was estimated that 2.3 million adults in the United States had AF in 1996 and 1997, and that this will increase to 5.6 million by the year 2050, with more than 50 percent being more than 80 years of age [11]. In a report from the United States, the prevalence of AF in 2005 was 3.03 million, and the projected prevalence for 2050 was 7.56 million [15]. In another study, the estimated age-adjusted prevalence rates (per 100,000 population) were 570 in men and 360 in women and 596 (men) and 373 (women) in 1990 and 2010, respectively [6].

Subclinical atrial fibrillation — Subclinical AF refers to asymptomatic episodes in a patient without a prior history of AF, which are detected only by monitoring techniques. The prevalence of subclinical AF is presented separately. (See "Atrial fibrillation: Overview and management of new-onset atrial fibrillation", section on 'Clinical presentation'.)

Incidence — The incidence of AF, similar to the prevalence, increases with advancing age [10,16-18]. In a longitudinal study in which 3983 male Air Force recruits were followed for 44 years, 7.5 percent developed AF [18]. The risk increased with advancing age (from 0.5 per 1000 person-years before age 50 to 9.7 per 1000 person years after age 70).

The lifetime risk for the development of AF was analyzed in a report from the Framingham Heart Study [19]. A total of 8725 patients were followed from 1968 to 1999 (176,166 person-years of follow-up); 936 developed AF. The risk of developing AF from age 40 to age 95 was 26 percent for men and 23 percent for women. Lifetime risk did not change substantially with increasing index age because AF incidence rose with age; the risk of developing AF from age 80 to age 95 was 23 percent for men and 22 percent for women.

PATHOGENESIS

Irrespective of the underlying risk factor(s), changes in the anatomy and electrophysiology of the atrial myocardium are likely important. Thus, AF is usually associated with some underlying heart disease. Atrial enlargement, an elevation in atrial pressure, or infiltration or inflammation of the atria are often seen.

Premature atrial complex (PAC; also referred to a premature atrial beat, premature supraventricular complex, or premature supraventricular beat) appears to be most important as a trigger in patients with paroxysmal AF who have normal or near-normal hearts. The relative importance of PAC or other triggers versus an abnormal substrate is much less clear in patients with significant structural heart disease. (See "The electrocardiogram in atrial fibrillation".)

The mechanisms of AF are presented in detail separately. (See "Mechanisms of atrial fibrillation".)

CHRONIC DISEASE ASSOCIATIONS

Hypertensive heart disease and coronary heart disease (CHD) are the most common underlying chronic disorders in patients with AF in developed countries. Rheumatic heart disease, although now uncommon in developed countries, is associated with a much higher incidence of AF. Paroxysmal AF (PAF) is associated with the same disorders as chronic (permanent) AF. (See "Paroxysmal atrial fibrillation".)

Hypertensive heart disease — In a longitudinal study of male air crew recruits, a history of hypertension increased the risk of developing AF 1.42-fold [18]. Although this is a relatively small increase in risk, the high frequency of hypertension in the general population results in hypertensive heart disease being the most common underlying disorder in patients with AF [16].

Coronary disease — AF is not commonly associated with CHD unless it is complicated by acute myocardial infarction (MI) or heart failure (HF). AF occurs transiently in 6 to 10 percent of patients with an acute MI, presumably due to atrial ischemia or atrial stretching secondary to HF [20-23]. These patients have a worse prognosis that is mostly due to comorbidities such as older age and HF. (See "Supraventricular arrhythmias after myocardial infarction", section on 'Atrial fibrillation'.)

The incidence of AF is much lower in patients with chronic stable CHD [24,25]. In the Coronary Artery Surgical Study (CASS), which included over 18,000 patients with angiographically documented coronary artery disease, AF was present in only 0.6 percent [24]. These patients probably had chronic AF; the prevalence of PAF may be higher. AF was associated with age greater than 60, male sex, mitral regurgitation (MR), and HF; there was no association between AF and the number of coronary arteries involved.

Valvular heart disease — Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. The following are representative frequencies:

- In a review of 89 patients with mitral valve prolapse (and grade 3 or 4 MR) and 360 with flail leaflets, the rate of development of AF was about 5 percent per year with both types of lesions [26]. The major independent risk factors were age ≥65 years and baseline left atrial dimension ≥50 mm.

- Rheumatic heart disease is now uncommon in developed countries. It is, however, associated with a high prevalence of AF [27,28]. In a study of approximately 1100 patients with rheumatic heart disease, the prevalence varied with the type of valve disease [28]:

  - Mitral stenosis (MS), MR, and tricuspid regurgitation – 70 percent
  - MS and MR – 52 percent
  - Isolated MS – 29 percent
  - Isolated MR – 16 percent

Heart failure — AF and HF often occur together, and each may predispose to the other [29]. Among patients with HF, the prevalence of AF is variable, depending in part upon the severity of HF. Issues related to AF in patients with HF and cardiomyopathy are discussed in detail separately. (See "The management of atrial fibrillation in patients with heart failure".)

Hypertrophic cardiomyopathy — AF has been reported in 10 to 28 percent of patients with hypertrophic cardiomyopathy [30-32]. The prognostic importance of AF in these patients is unclear, with some reports showing a worse prognosis [32] and others no increase in mortality [31]. (See "Hypertrophic cardiomyopathy in adults: Supraventricular tachycardias including atrial fibrillation".)

Congenital heart disease — AF has been reported in approximately 20 percent of adults with an atrial septal defect [33]. However, the incidence of AF is related to age, ranging in one series from 15 percent for those aged 40 to 60, to 61 percent for those over the age of 60 [34].

AF and/or atrial flutter also occurs in other forms of congenital heart disease that affect the atria, including Ebstein anomaly and patent ductus arteriosus, and after surgical correction of some other abnormalities, including ventricular septal defect, tetralogy of Fallot, pulmonic stenosis, and transposition of the great vessels.

Venous thromboembolic disease — Venous thromboembolic disease, which includes deep vein thrombosis and pulmonary embolism, is associated with an increased risk of AF. The mechanism is not known but has been speculated to be related to the increase in pulmonary vascular resistance and cardiac afterload, which may lead to right atrial strain [35,36]. (See "Epidemiology, pathogenesis, clinical manifestations and diagnosis of chronic thromboembolic pulmonary hypertension", section on 'Diagnostic evaluation'.)

The incidence of AF in patients with acute or chronic venous thromboembolic disease has not been well studied. It has been reported to be in the 10 to 14 percent range in patients with documented pulmonary embolism [37,38]. The impact of incident venous thromboembolism (VTE) on the future risk of AF was evaluated in a prospective population-based study of nearly

30,000 individuals of whom 1.8 percent had an incident VTE event and 5.4 percent were diagnosed with AF during 16-year follow-up [36]. The risk of AF was higher in those with VTE than in those without after multivariable adjustment (hazard ratio 1.63, 95% CI 1.22-2.17). This risk was particularly high in the first six months after the VTE event.

Obstructive sleep apnea — AF is associated with pulmonary disease and obstructive sleep apnea in particular [39-44]. In a 2020 study of 188 consecutive patients with AF and no prior diagnosis of sleep apnea who were scheduled to undergo AF ablation, home sleep apnea testing was positive in 155 (82.4 percent), and of these 82 percent had a predominant obstructive component [45]. Among the 155 patients, sleep apnea was considered severe in 23.2 percent, moderate in 32.9 percent, and mild in 43.8 percent. Continuous positive airway pressure therapy was prescribed in 85.9 percent of the patients with moderate or severe sleep apnea.

There is a possible causal relationship between obstructive sleep apnea (OSA) and AF [46-49]. In a series of 39 patients diagnosed with both PAF and OSA, patients receiving treatment with continuous positive pressure ventilation had a lower incidence of AF recurrence at 12 months (42 versus 82 percent for patients who were not treated) [46]. In another observational study, the incidence of OSA was compared between 151 patients referred for cardioversion for AF and 312 controls without AF referred for general cardiology evaluation [47]. OSA was significantly more common in the patients with AF than in the control group (49 versus 32 percent). Finally, preoperative sleep studies were performed in a series of 121 patients referred for coronary artery bypass surgery [48]. Postoperative AF was significantly more common among the 49 patients with an abnormal sleep study (39 versus 18 percent in patients with normal sleep studies). (See "Obstructive sleep apnea and cardiovascular disease in adults", section on 'Atrial fibrillation'.)

Obesity — Obese individuals (body mass index [BMI] >30 kg/m^2) are significantly more likely to develop AF than those with a normal BMI (<25 kg/m^2) [50-52]. In the Framingham Heart Study, every unit increase in BMI was associated with an approximate 5 percent increase in risk [53]. (See "Overweight and obesity in adults: Health consequences".)

A primary mechanism for the role of obesity may be an increase in the size of the left atrium. Increased left atrial pressure and volume, often associated with diastolic dysfunction, as well as a shortened effective refractory period in the left atrium and in the proximal and distal pulmonary veins have been identified as potential factors facilitating and perpetuating AF in obese patients [54]. Inflammation and pericardial fat may also play a role [50]. (See "Mechanisms of atrial fibrillation" and 'Other factors' below.)

There is some evidence to suggest that long-term weight loss is associated with a reduction of AF burden [51,55].

Diabetes — In a study of over 4700 individuals without valvular heart disease in the Framingham Heart Study, the presence of diabetes was associated with a significantly increased risk for the development of AF in multivariate analysis (odds ratio 1.1 for men and 1.5 for women) [56]. Increased left ventricular mass and increased arterial stiffness have been put forth as possible mechanisms [57].

Metabolic syndrome — As discussed above, the presence of hypertension, diabetes, or obesity is associated with an increased likelihood of the development of AF. The metabolic syndrome includes these three, as well as dyslipidemia. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)", section on 'Definition'.)

The potential relationship between the metabolic syndrome and the development of AF was evaluated in a prospective, observational cohort study of 28,449 Japanese citizens [58]. Using the 2005 criteria for the metabolic syndrome approved by the American Heart Association and the National Heart, Lung, and Blood Institute, 4544 individuals met criteria for the metabolic syndrome at baseline [59]. During a mean follow-up for 4.5 years, AF developed in 265 patients. The risk of developing AF was significantly greater in those individuals with the metabolic syndrome (hazard ratio 1.61, 95% CI 1.21-2.15), as well as in those with individual components of hypertension, obesity, low high density lipoprotein cholesterol and impaired glucose tolerance, but not elevated triglycerides.

Chronic kidney disease — Chronic kidney disease (CKD) increases the risk of the development of AF. The following two prospective, cohort studies are representative:

- In a study of 235,818 individuals, the hazard ratio for the development of AF was 1.32 for patients with estimated glomerular filtration rates (eGFRs) of 30 to 59 mL/min/1.73m^2 compared with those with normal renal function [60].

- The relationship between CKD and AF was evaluated in a report of 10,328 individuals free of AF participating in the Atherosclerosis Risk in Communities (ARIC) study who had a baseline cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$) [61]. Compared with individuals with $eGFR_{cys}$ ≥90 mL/min/m^2, the multivariable hazard ratios for the development of AF were significantly increased at 1.3, 1.6, and 3.2 in those with $eGFR_{cys}$ of 60 to 89, 30 to 59, and 15 to 29 mL/min/m^2, respectively, during a median follow-up of 10.1 years. In addition, macroalbuminuria and microalbuminuria were significantly associated with higher AF risk.

The incidence and prevalence of AF in patients with CKD are presented separately. (See "Atrial fibrillation in adults: Selection of candidates for anticoagulation", section on 'Chronic kidney disease'.)

POTENTIALLY REVERSIBLE TRIGGERS

The medical conditions listed above, which are associated with an increased risk of the development of AF, are chronic. Historically, it has been assumed that the risk of AF decreases after a non-chronic (secondary) condition has been corrected. However, there is some evidence to suggest that the risk remains. In the Framingham Heart Study, 1409 individuals with new onset AF were evaluated for their risk of subsequent occurrences based on whether they had a secondary precipitant or not [62]. A precipitant was found in 439 (31 percent) and included cardiothoracic surgery (30 percent), infection (23 percent), non-cardiothoracic surgery (20 percent), and acute myocardial infarction (18 percent). Other secondary precipitants included acute alcohol consumption, thyrotoxicosis, acute pericardial disease, acute pulmonary embolism, and other acute pulmonary pathology. While the 15-year cumulative incidence of recurrent AF was significantly lower among those with secondary causes (62 versus 71 percent), the finding that AF recurred in the majority with secondary causes was unexpected.

Surgery — AF occurs in relation to a variety of different types of surgery, with the incidence greatest in patients undergoing cardiac surgery:

- **Cardiac surgery** – AF has been reported in up to 30 to 40 percent of patients in the early postoperative period following coronary artery bypass graft surgery (CABG) [63-66], in 37 to 50 percent after valve surgery [63,66,67], and in as many as 60 percent undergoing valve replacement plus CABG [63,66]. This topic is discussed in detail separately. (See "Atrial fibrillation and flutter after cardiac surgery".)

- **Cardiac transplantation** – AF has been described in 10 to 24 percent of patients with a denervated transplanted heart, often in the absence of significant rejection [66,68]. Most episodes occur within the first two weeks, while AF developing after two weeks may be associated with an increased risk of subsequent death [68,69]. (See "Heart transplantation in adults: Arrhythmias", section on 'Supraventricular arrhythmias'.)

- **Noncardiac surgery** – AF is less common after noncardiac compared with cardiac surgery. The reported incidence of new onset AF in patients undergoing noncardiac surgery ranges from 1 and 40 percent. This broad range is likely due to variability in patient and surgical characteristics [70,71].

The largest experience comes from a review of 4181 patients over the age of 50 who were in sinus rhythm prior to major noncardiac surgery [72]. The incidence of perioperative AF was 4.1 percent; most episodes occurred within the first three days after surgery. The risk was greatest with intrathoracic surgery (odds ratio 9.2). In another series of 2588 undergoing noncardiac thoracic surgery, the incidence of AF was 12.3 percent [73].

Hyperthyroidism — Patients with hyperthyroidism have an increased risk of developing AF [74]. In one population-based study of 40,628 patients with clinical hyperthyroidism, 8.3 percent had AF or atrial flutter [75]. AF occurred in 10 to 20 percent of patients over age 60 but in less than 1 percent of patients under age 40. Men were more likely to have AF than women (12.1 versus 7.6 percent). (See "Cardiovascular effects of hyperthyroidism", section on 'Atrial fibrillation'.)

Increased beta adrenergic tone may be in part responsible for the development of AF in hyperthyroidism and may also contribute to the rapid ventricular response in this setting. In addition, excess thyroid hormone increases the likelihood of AF in experimental animals, even in the presence of beta receptor and vagal blockade [76]; it is likely that this observation applies to humans. The mechanism is unknown, but may be related to an increased automaticity and enhanced triggered activity of pulmonary vein cardiomyocytes, which can be a source of ectopic beats that initiate AF [77].

The risk of AF is also increased in patients with **subclinical hyperthyroidism** (defined as a low serum thyroid stimulating hormone concentration and normal serum thyroid hormone concentrations) [78-80]. The increase in risk is illustrated by the following observations:

- In a prospective study, 2007 subjects ≥60 years of age who did not have AF were followed for 10 years [78]. The subsequent age-adjusted incidence of AF was significantly higher among those with a low serum thyroid stimulating hormone concentration compared with those with a normal value (28 versus 10 per 1000 person-years).
- In a review of 23,638 subjects, the prevalence of AF in those with clinical and subclinical hyperthyroidism was similar (14 and 13 percent, respectively) and higher than that in euthyroid subjects (2.3 percent) [79].

A possible relationship between AF and hypothyroidism has been suggested but not proven [81,82]. Since hypothyroidism is present in 5 to 10 percent of the general population, it is not surprising that some patients with AF have hypothyroidism (7.7 percent with subclinical disease in one report [80]) that may not be causally related.

OTHER FACTORS

A number of risk factors not discussed above are associated with an increased risk for the development of AF.

Family history — The presence of AF in a first-degree relative, particularly a parent, has long been associated with an increase in risk, independent of standard risk factors such as age, sex, hypertension, diabetes, or clinically overt heart disease [83]. (See 'Epidemiology' above and 'Chronic disease associations' above.)

In an analysis of over 4400 individuals in the Framingham Heart Study, the occurrence of AF in a first degree relative was associated with a significantly increased risk of incident AF (multivariable-adjusted hazard ratio [HR] 1.40, 95% CI 1.13-1.74) [84]. The strength of this relationship was greater when only first-degree relatives with premature onset (age ≤65 years) were considered.

Genetic factors — For the vast majority of AF patients, we do not suggest genetic screening as it does not change clinical management. Exceptions are when there is concern for a rare disorder that has a high stroke risk irrespective of CHA_2DS_2-VASc score such as AF in Emery Dreifuss muscular dystrophy or Lamin disorder.

For most patients with AF, one or more of the nongenetic disease associations discussed above are present. However, evidence suggests that AF is heritable, and in younger patients, there may be increased genetic susceptibility of AF [85].

Among 1300 participants who underwent whole genome sequencing, disease-associated rare variants in cardiomyopathy and arrhythmia genes were identified in 10 percent of participants younger than 66 years and 17 percent of those younger than 30 years. Disease-associated rare variants were more prevalent in genes associated with inherited cardiomyopathy syndromes than inherited arrhythmia syndromes.

The heritability of AF is complex. For the majority of patients, genetic susceptibility, if present, is probably a polygenic phenomenon, meaning that it is due to the combined effects of a number of genes. Polygenic inheritance can explain why some diseases cluster in families, but do not demonstrate the classic Mendelian inheritance patterns of monogenic disorders. However, a small number of families demonstrate monogenic inheritance characteristics.

Polygenic inheritance — Polygenic inheritance appears to be more common and could explain the modest elevation in the relative risk of AF in first- and second-degree relatives of

affected individuals. Evidence supporting a heritable component to AF susceptibility includes:

- In a review of 914 patients with AF, 50 (5 percent) had a family history of AF (one to nine additional relatives affected) [86].
- In an analysis of 2243 offspring in the Framingham Heart Study, those with parental AF had a significantly higher incidence of developing AF than those without parental AF (4.1 versus 2.7 percent, adjusted odds ratio 1.85) [83]. This effect was more pronounced when the analysis was limited to patients with age of AF onset less than 75 years and to those without prior myocardial infarction, heart failure, or valve disease (odds ratio 3.17).
- A population study in Iceland evaluated the heritability of AF in a cohort of 5269 patients diagnosed over a 16-year period [87]. Among patients with AF, the degree of relatedness was significantly greater than among matched controls. In addition, the relative risk of developing AF was higher in the relatives of patients than those of controls.

Monogenic inheritance — Some families have been identified in which AF inheritance follows more typical Mendelian patterns, consistent with a single disease-causing gene. Both autosomal dominant and autosomal recessive forms have been identified. Genetic linkage analysis has identified loci at 10q22-q24, 11p15.5, 6q14-16, 3p22-p25, and 4q25 [88-92]. At the 4q25 locus, several single-nucleotide polymorphisms have been identified [93]. In these individuals, penetrance is variable and the polymorphisms can affect the clinical expression of familial AF [94].

An autosomal recessive pattern of AF inheritance was reported in a large family from Uruguay [95]. Clinical manifestations included AF during fetal life, neonatal sudden death, ventricular tachyarrhythmias, and waxing and waning cardiomyopathy. A genetic locus on chromosome 5p13 was linked to disease in this family.

Chromosomal loci are large areas with multiple genes, and a specific genetic defect is not yet known for most loci. Examples of a monogenic cause of AF include:

- The 11p15.5 locus is associated with a gain-of-function mutation in the KVLQT1 (KCNQ1) gene, the protein product of which is the alpha-subunit of the slowly acting component of the outward-rectifying potassium current (IKs) [89]. This mutation is thought to initiate and maintain AF by reducing the action potential duration and effective refractory period in atrial myocytes.
- A different gain-of-function mutation in this gene has been associated with the congenital short QT syndrome, while loss-of-function mutations are associated with long QT

syndrome, type 1. (See "Congenital long QT syndrome: Pathophysiology and genetics", section on 'Type 1 LQTS (LQT1)'.)

- An autosomal dominant form of AF, usually in association with a dilated cardiomyopathy, has been associated with mutations in SCN5A, the cardiac sodium channel gene. In a report of individuals with SCN5A mutations, 27 percent had early features of dilated cardiomyopathy (mean age at diagnosis 20 years), 43 percent had AF (mean age at diagnosis 28 years), and 38 percent had dilated cardiomyopathy (mean age at diagnosis 48 years) [91]. (See "Genetics of dilated cardiomyopathy".)

Mutations in SCN5A have also been identified in several other cardiac disorders, including the long QT syndrome, the Brugada syndrome, familial atrioventricular conduction block, and familial sinus node dysfunction. (See "Brugada syndrome: Epidemiology and pathogenesis" and "Congenital long QT syndrome: Pathophysiology and genetics" and "Etiology of atrioventricular block" and "Sinus node dysfunction: Epidemiology, etiology, and natural history".)

Birth weight — A possible relationship between birth weight and the development of AF was evaluated in a prospective study of nearly 28,000 women over the age of 45 years, who were free of AF at baseline [96]. The age-adjusted HRs (with <2.5 kg [5.5 pounds] being the referent group) for incident AF increased significantly (1, 1.3, 1.28, 1.7, and 1.71) from the lowest to the highest birth weight category (<2.5 [5.5], 2.5 [5.5] to 3.2 [7.1], 3.2 [7.1] to 3.9 [8.6], 3.9 [8.6] to 4.5, and >4.5 [9.9] kg [pounds]), during a median follow-up of 14.5 years.

Inflammation and infection — Inflammatory processes may play a role in the genesis of AF. Measurement of serum C-reactive protein (CRP), an acute phase reactant, has been used to assess the relationship between AF and inflammation.

Observational studies have reported elevated serum levels of CRP in patient populations with any of the following characteristics: later (after known high CRP) development of AF [97], history of atrial arrhythmias [98], failed cardioversion [99], recurrence of AF after cardioversion [100], and development of AF after cardiac surgery. (See "Atrial fibrillation and flutter after cardiac surgery".)

However, inflammation is more likely a marker for other conditions associated with AF, as opposed to being a direct cause or a perpetuating agent. The strongest evidence against a direct causal role for inflammation, as detected by an elevation in CRP, comes from a Mendelian randomization study that evaluated nearly 47,000 individuals in two cohorts from Copenhagen, Demark [101]. (See "Mendelian randomization".)

The following observations were made:

- After multifactorial adjustment, a CRP level in the upper versus lower quintile was associated with a significantly increased risk of the development of AF (hazard ratio 1.77, 95% CI 1.22-2.55).

- Genotype combinations of four CRP polymorphisms were significantly associated with up to a 63 percent increase in plasma CRP levels, but not with an increased risk of the development of AF.

Thus, inflammation, as determined by CRP, is not likely to be causative of AF. In addition to inflammation as detected by serum CRP, new onset AF and other acute cardiac events have been associated with pneumococcal pneumonia [102]. (See "Pneumococcal pneumonia in patients requiring hospitalization", section on 'Cardiac events and other noninfectious complications'.)

The risk of AF increases after infection with the influenza virus [103].

Pericardial (epicardial) fat — Pericardial fat, also referred to as epicardial fat, is the fat depot within the pericardial sac, which is in between the visceral and parietal pericardium. It has inflammatory properties: both obesity and inflammation are risk factors for AF [104,105]. In a study of 126 patients with AF and 76 controls, those with AF had a significantly higher pericardial fat volume (102 versus 76 ml) [104]. This was true for patients with either paroxysmal or persistent AF, and was independent of other traditional predictors of AF, including left atrial enlargement.

Autonomic dysfunction — The autonomic nervous system may be involved in the initiation and maintenance of AF. It may be particularly important in patients with paroxysmal AF, as both heightened vagal and sympathetic tone can promote AF. Vagal tone is predominant in normal hearts, which may explain why vagally-mediated AF is often seen in athletic young men without apparent heart disease who have slow heart rates during rest or sleep; such patients may also have an electrocardiogram (ECG) pattern of typical atrial flutter alternating with AF [106,107]. In comparison, AF induced by increased sympathetic tone may be observed in patients with underlying heart disease or during exercise or other activity [107]. (See "Paroxysmal atrial fibrillation", section on 'Pathogenesis'.)

Findings on the electrocardiogram — Abnormal QT or P-wave duration are associated with an increased risk of AF:

- **Corrected QT interval** – Individuals with either congenital long QT syndrome or short QT syndrome have an increased risk of AF [108,109]. (See "Congenital long QT syndrome: Epidemiology and clinical manifestations" and "Short QT syndrome".)

The issue of whether there is an association between the corrected QT interval (QTc) and the risk of AF in the general population was addressed in a study of 281,277 individuals without baseline AF in the greater Copenhagen region who were followed for a median period of 5.7 years after a first ECG [110]. Individuals with a QTc <372 ms (1st percentile) or ≥419 ms (60th percentile) had an increased risk (adjusted hazard ratios [HRs] 1.45 up to 1.44, respectively) compared with the reference group (411 to 419 ms). The risk increased in a dose-dependent manner above 419 ms and was strongest among individuals with lone AF.

- **P-wave duration** – The relationship between P-wave duration and the risk of AF was evaluated in a study of nearly 285,933 individuals, of whom 9550 developed AF during a median follow-up period of 6.7 years [111]. Compared with the reference group (100 to 105 milliseconds [ms]), individuals with very short (≤89 ms; HR 1.6), intermediate (112 to 119 ms; HR 1.22), long (120 to 129; HR 1.5), and very long P wave duration (≥130 ms; HR 2.06) had an increased risk.

Premature atrial complex — PAC is important as a trigger of PAF (see 'Pathogenesis' above). The issue of whether they are predictor of incident AF was evaluated in a study of 1260 adults without prevalent AF who underwent 24-hour ambulatory ECG (Holter) monitoring at baseline [112]. During a median follow-up of 13.0 years, 27 percent developed incident AF. After adjusting for other known predictors of AF, PAC count (by quartile) was significantly associated with incident AF; the adjusted HRs comparing quartile 2, 3, and 4 with quartile 1 were 2.17, 2.79, and 4.92, respectively.

Other supraventricular tachyarrhythmias — Spontaneous transition between typical atrial flutter and AF has been observed, although little is known about the mechanism of this conversion [113,114]. In addition, AF is, in some patients, associated with paroxysmal supraventricular tachycardia (PSVT) [115-117]. The most common causes of PSVT are atrioventricular nodal re-entrant tachycardia and atrioventricular reentrant tachycardia, which occurs in patients with the Wolff-Parkinson-White syndrome or concealed accessory pathways. (See "Atrioventricular nodal reentrant tachycardia" and "Atrioventricular reentrant tachycardia (AVRT) associated with an accessory pathway".)

The association between AF and PSVT was illustrated in a report that evaluated 169 patients who presented with PSVT and were followed by clinic visits and transtelephonic ECG monitoring during symptomatic episodes [115]. Nineteen percent had an episode of AF during a mean follow-up of 31 months. Neither the mechanism nor the rate of the PSVT was associated with the time to occurrence of AF.

Enhanced vagal tone, as determined by baroreflex sensitivity, or an increase in dispersion of right atrial refractory periods may contribute to the development of AF associated with PSVT [118]. Alternatively, an atrial premature beat can cause stable PSVT to degenerate into AF.

Among patients with Wolff-Parkinson-White syndrome, the mechanism of AF may be retrograde conduction via the accessory pathway of a premature beat, stimulating the atrial myocardium during its vulnerable period [119]. Ablation of the accessory pathway reduces the incidence of subsequent AF [119,120].

Low serum magnesium — In an observational study of over 3500 participants in the Framingham Offspring Study, individuals in the lower quartile of serum magnesium were approximately 50 percent more likely to develop AF compared with those in the upper quartiles after multivariable adjustment [121].

Alcohol — Alcohol is both a chronic risk factor for the development of new AF and also an acute trigger for AF episodes. AF occurs in up to 60 percent of binge drinkers with or without an underlying alcoholic cardiomyopathy [122]. Most cases occur during and following weekends or holidays when alcohol intake is increased, a phenomenon that has been termed "the holiday heart syndrome." However, even modest amounts of alcohol (one to two drinks) can trigger AF in some patients [123]. In a case-crossover study, 100 individuals free of alcohol dependence and with AF wore transdermal ethanol sensors and continuous ECG monitors for four weeks. Among the 56 persons who had an AF episode during this time period, having had one alcoholic drink doubled the odds of having AF (odds ratio [OR] 2.02 [95% CI 1.38-3.17]) and having two or more alcohol drinks tripled the odds of having an AF episode (OR 3.58 [CI 1.63-7.89]) in the next four hours. This study demonstrated a probable dose-response relationship between the amount of alcohol consumed and the likelihood of triggering an AF episode.

The evidence is mixed for long-term alcohol consumption being a risk factor for developing new AF. Moderate, long-term alcohol consumption was not shown to be a risk factor for AF in relatively small studies [56,124,125]. However, a positive association was found in a 2014 study of 79,019 men and women free from AF at baseline [126]. Compared with current drinkers of <1 drink per week, the multivariable risk ratios of AF were 1.01 (95% CI 0.94-1.09) for one to six drinks per week, 1.07 (95% CI 0.98-1.17) for 7 to 14 drinks per week, 1.14 (95% CI 1.01-1.28) for 15 to 21 drinks per week, and 1.39 (95% CI 1.22-1.58) for >21 drinks per week.

Heavy alcohol consumption is associated with a greater increase in incidence of AF. Two large cohort studies found an increased incidence among men with heavy alcohol consumption (HR 1.45 in both) [127,128]. Neither study found a correlation between heavy alcohol use and AF in women, but the ability to detect such a correlation was limited by the small numbers of women

with alcohol consumption in this range. Another study of 1055 cases of AF occurring during long-term follow-up found an increased risk (relative risk 1.34, 95% CI 1.01-1.78) with consumption of more than 36 grams per day (approximately >3 drinks/day) [125].

Caffeine — There is a widespread belief that caffeine, particularly at high doses, is associated with palpitations and a number of arrhythmias, including AF and supraventricular and ventricular ectopy. However, despite the theoretical relationship between caffeine and arrhythmogenesis, there is no evidence in humans that ingestion of caffeine in doses typically consumed can provoke AF or any other spontaneous arrhythmia [129]. (See "Cardiovascular effects of caffeine and caffeinated beverages", section on 'Other arrhythmias'.)

Fish and fish oil supplements — Observational data has suggested that dietary fish intake or fish oil supplements, particularly those rich in long-chain n-3 fatty acids, may reduce the incidence of arrhythmias, although evidence is mixed with regard to both atrial and ventricular arrhythmias. (See "Overview of sudden cardiac arrest and sudden cardiac death", section on 'Fish intake and fish oil'.)

With regard to dietary fish intake and incident AF, three cohort studies (approximately 45,000, 48,000, and 5000 individuals) found no relationship [130-132], while one (approximately 5000 individuals) suggested a reduction in AF burden [133].

Medications — Certain medications can cause or contribute to the development of AF [134]. These include theophylline [135], adenosine [136], and, since increased vagal tone can induce AF [107], drugs that enhance vagal tone, such as digitalis. (See 'Autonomic dysfunction' above.)

Bisphosphonates (eg, alendronate, risedronate, etidronate) are widely used in the treatment of osteoporosis, and concern has been raised that these drugs can cause AF. The weight of evidence suggests that the risk of AF from oral bisphosphonates is small, if it exists at all. (See "Risks of bisphosphonate therapy in patients with osteoporosis", section on 'Atrial fibrillation'.)

Case-control studies have suggested a modest increased risk for the development of AF in patients taking nonsteroidal anti-inflammatory drugs [137-140]. However, the absence of an accepted biologic mechanism and the susceptibility of case-control studies to unmeasured confounders makes us cautious about the strength of this association [141].

Certain antiarrhythmic drugs may increase the risk of AF. A 2020 scientific statement from the American Heart Association details drugs associated with AF [142]. While exhaustive, this statement includes many medications for which the association with AF is likely relatively weak.

Ivabradine, a selective blocker of the I_f channel that slows the sinus rate, has been associated with a higher incidence of AF [143]. A meta-analysis of 11 studies suggests a 15 percent excess of AF in patients treated with ivabradine [144].

Regular physical activity — The relationship between physical activity and the development of AF is uncertain. Some [145-147], but not all [148-150], studies have suggested that regular physical activity is associated with a risk of AF in the general population. In a 2013 meta-analysis of four prospective cohorts (n = 43,672), and after dividing subjects into four or five groups on the basis of cumulative physical activity per week, there was no difference in the risk of AF comparing patients in the maximum and minimal groups (odds ratio 1.08, 95% CI 0.97-1.21) [151].

Air pollution — Air pollution, and specifically fine particulate matter, is associated with increased cardiovascular disease mortality. (See "Overview of possible risk factors for cardiovascular disease", section on 'Air pollution'.)

Whether air pollution is associated with episodes of AF was evaluated in a study of 176 patients with dual chamber implantable cardioverter-defibrillators that were capable of detecting episodes of AF. After follow-up of nearly two years, there were 328 episodes of AF lasting 30 seconds or more found in 49 patients [152]. The potential impact of multiple parameters of air pollution, (measured hourly) on the development of AF was examined. The odds of AF increased significantly as the concentration of particulate matter increased in the two hours prior to the event.

Night shift work — Data from The United Kingdom Biobank study showed that both current and lifetime night shift exposures were associated with increased AF risk, regardless of genetic AF risk [153]. This cohort had 283,657 participants with 5777 incident AF events over an approximately 10-year follow-up. Usual or permanent night shift workers (4 percent), compared with day workers (83 percent), had higher risks of AF (HR 1.16, 95% CI 1.02-1.32). Workers with a >10-year duration of night shifts (2.4 percent) had a higher AF risk compared with day workers (HR 1.18, 95% CI 0.99-1.40). Workers with three to eight night shifts per month but not <3 per month or >8 per month had an increased risk of developing AF (HR 1.22, 95% CI 1.02-1.45; HR 0.88, 95% CI 0.64–1.21; HR 1.05, 95% CI 0.86-12.8, respectively). A potential limitation of this study is the inability to fully account for underlying socioeconomic factors. A limitation of this sub-analysis was relatively low AF event rates in the group with <3 and >8 shifts per month. Whether decreasing or stopping shift work protects against later AF is uncertain.

RISK PREDICTION MODELS

Models that attempt to predict the risk of development of AF have been developed but are not widely employed.

Using the Framingham Heart Study population, age, sex, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, body mass index, and heart failure were incorporated into a risk prediction model that predicts an individual's absolute risk over 10 years [154]. This model has been validated in two geographically and racially diverse cohorts in the age range of 45 to 95 years and predicted the five-year incidence of AF with moderate accuracy (C statistic 0.66 to 0.68) [155]. Other models have been studied, including one in a racially diverse population [156].

However, the benefit of using risk prediction models in this setting has not been established. There are no studies linking this with improved outcomes.

PREVENTION

For many risk factors of AF, preventive strategies that significantly reduce risk of incident AF have not been identified. The following are possible preventive strategies:

- **Healthy fats** – There is weak evidence that dietary modifications such as extra virgin olive oil or n-3 polyunsaturated fatty acids in fish oil lower the risk of the development of AF [157,158].

- **Mediterranean diet** – The PREDIMED primary prevention trial found that a Mediterranean diet enriched with either extra virgin olive oil or mixed nuts reduces the incidence of stroke, MI, and cardiovascular mortality [159]

(See "Prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Diet'.)

  In a post-hoc analysis of PREDIMED, the group that received the Mediterranean diet supplemented with extra virgin olive oil had a lower risk of development of AF compared with the control group (hazard ratio [HR] 0.62; 95% CI 0.45-0.85) [160].

- **Blood pressure lowering** – Among patients with hypertension, a study suggests that lowering blood pressure reduced the risk of the development of AF. In the SPRINT trial, intensive compared with standard blood pressure lowering was associated with a lower risk of developing new AF (HR 0.74, 95% CI 0.56-0.98) [161]. (See "Goal blood pressure in adults with hypertension".)

- **Mineralocorticoid receptor antagonists (MRAs)** – MRAs may reduce the risk of development of AF, with consistent effects for new-onset and recurrent AF [162]. A meta-analysis of 10 randomized trials with a total of 11,356 adults showed that MRAs reduced the risk of AF occurrence by 23 percent compared with the control therapy (risk ratio [RR] 0.77, 95% CI 0.65-0.91). Subgroup analysis demonstrated that MRAs reduced the risk of new-onset AF (RR 0.84, 95% CI 0.61-1.16) and recurrent AF (RR 0.73, 95% CI 0.59-0.90) similarly.

- **Cardiac pacing** – The role of pacing for the prevention of AF is discussed separately. (See "The role of pacemakers in the prevention of atrial fibrillation".)

Although cardiac resynchronization therapy (CRT) improves some potential risk factors for AF. such as atrial size and left ventricular systolic function, CRT has **not** been shown to decrease the incidence of new or recurrent AF. This is discussed in detail separately. (See "Cardiac resynchronization therapy in atrial fibrillation".)

SUMMARY

- **Epidemiology** – The incidence and prevalence of atrial fibrillation (AF) depends upon the population studied and the intensity of monitoring. Both increase significantly with increasing age. (See 'Epidemiology' above.)

- **Chronic disease associations** – Hypertensive heart disease and coronary heart disease are the most common chronic disease associations in patients with AF in developed countries. Other frequent causes include alcohol excess, heart failure, valvular heart disease including both regurgitant and stenotic lesions, and hyperthyroidism. (See 'Chronic disease associations' above.)

  AF occurs in relation to a variety of different types of surgery; the incidence is greatest in patients undergoing coronary artery bypass graft or cardiac valve surgery. (See 'Chronic disease associations' above.)

  Chronic, heavy alcohol use does increase the risk of AF in men, while the impact of heavy alcohol use in women is less clear. Chronic moderate alcohol use does not appear to increase the incidence of AF in men or women. (See 'Chronic disease associations' above.)

- **Genetic factors** – The heritability of AF is complex. For the majority of patients, genetic susceptibility, if present, is probably a polygenic phenomenon, meaning that it is due to the combined effects of a number of genes. (See 'Genetic factors' above.)

- **Risk Prediction** – Models to predict the risk of subsequent AF have been developed. However, a benefit from using such models has not been established. (See 'Risk prediction models' above.)

- **Prevention** – There is some evidence that dietary intake of healthy fats, a Mediterranean diet, and blood pressure lowering can prevent the onset of AF. (See 'Prevention' above.)

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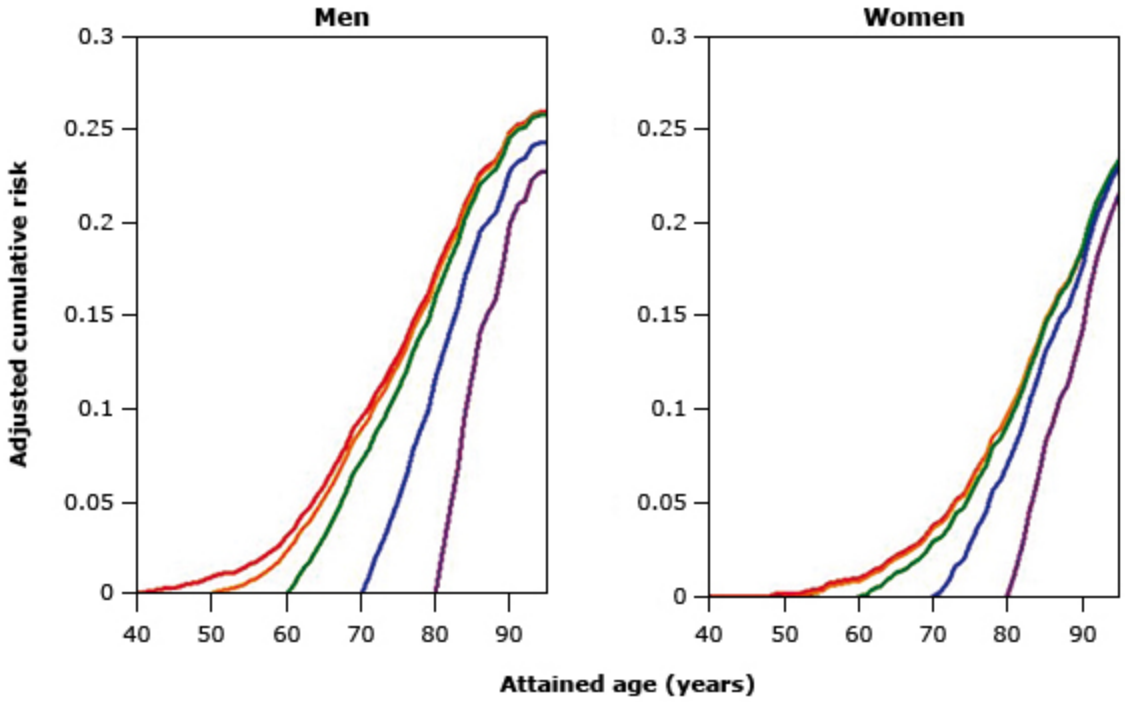
Topic 1004 Version 61.0

GRAPHICS

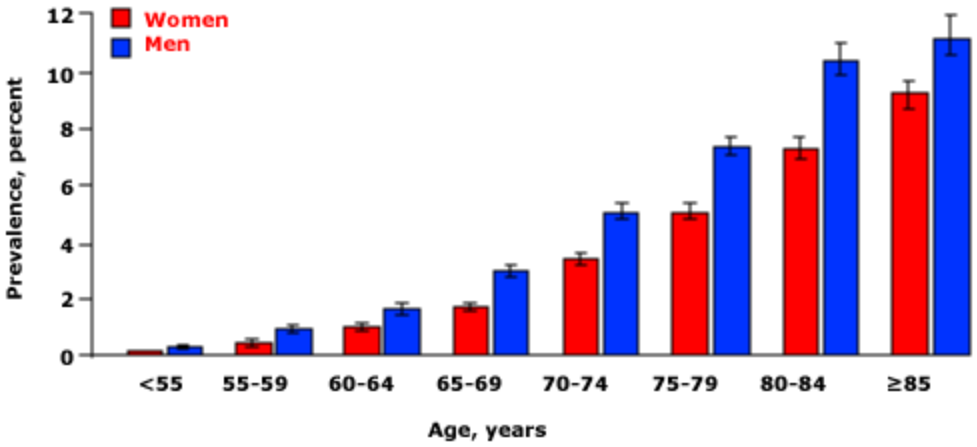
Prevalence of atrial fibrillation by sex and age



Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study. Men and women without AF at 40 years of age were determined to have a 26 and 23 percent likelihood of developing incident AF by 80 years of age.

Graphic 82929 Version 4.0

Prevalence of atrial fibrillation with age



In a cross-sectional study of almost 1.9 million men and women, the prevalence of atrial fibrillation increases with age, ranging from 0.1 for those <55 years of age to over 9 percent in those ≥85 years of age. At all ages, the prevalence is higher in men than women.

Data from Go AS, Hylek EM, Phillips K, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370.

Graphic 77268 Version 5.0