# Atrial Fibrillation

## Epidemiology, Pathophysiology, and Clinical Outcomes

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***Abstract:*** **The past 3 decades have been characterized by an exponential growth in knowledge and advances in the clinical treatment of atrial fibrillation (AF). It is now known that AF genesis requires a vulnerable atrial substrate and that the formation and composition of this substrate may vary depending on comorbid conditions, genetics, sex, and other factors. Population-based studies have identified numerous factors that modify the atrial substrate and increase AF susceptibility. To date, genetic studies have reported 17 independent signals for AF at 14 genomic regions. Studies have established that advanced age, male sex, and European ancestry are prominent AF risk factors. Other modifiable risk factors include sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnea, and elevated blood pressure predispose to AF, and each factor has been shown to induce structural and electric remodeling of the atria. Both heart failure and myocardial infarction increase risk of AF and vice versa creating a feed-forward loop that increases mortality. Other cardiovascular outcomes attributed to AF, including stroke and thromboembolism, are well established, and epidemiology studies have championed therapeutics that mitigate these adverse outcomes. However, the role of anticoagulation for preventing dementia attributed to AF is less established. Our review is a comprehensive examination of the epidemiological data associating unmodifiable and modifiable risk factors for AF and of the pathophysiological evidence supporting the mechanistic link between each risk factor and AF genesis. Our review also critically examines the epidemiological data on clinical outcomes attributed to AF and summarizes current evidence linking each outcome with AF. (*Circ Res*. 2017;120:1501-1517. DOI: 10.1161/CIRCRESAHA.117.309732.)**

**Key Words:** atrial fibrillation ■ epidemiology ■ prognosis ■ risk factors ■ stroke



The association of an irregular pulse and mitral stenosis was first described by Robert Adams in 1827, but it was not until the turn of the 20th century when William Einthoven invented electrocardiography that atrial fibrillation (AF) was first recorded on the ECG.[1] Its pathogenesis and clinical importance gained enhanced appreciation in the 1990s when early community-based studies, including the FHS (Framingham Heart Study),[2–4] provided critical epidemiological data on associated risk factors (RFs) and clinical outcomes. These associations empowered scientists and clinicians by focusing their attention on specific disease models. Over the past 3 decades, an explosion of research has yielded progress in the clinical treatment of AF at a time when AF is reaching epidemic proportions.

Our review provides an overview of the pathogenesis of nonvalvular AF and a comprehensive examination of the epidemiological data associating various RFs with AF (Figure 1). For each RF, we highlight key population studies supporting its association and critically review data on how the RF may lead to the development of the AF substrate and AF genesis. Last, we review clinical outcomes associated with AF and discuss possible mechanisms linking these associations. Our review focuses on the epidemiology and pathophysiology of AF rather than its clinical treatment.

## Pathophysiology and Natural History AF

AF is characterized by high-frequency excitation of the atrium that results in both dyssynchronous atrial contraction and irregularity of ventricular excitation. Whereas AF may occur in the absence of known structural or electrophysiological abnormalities, epidemiological association studies are increasingly identifying comorbid conditions, many of which have been shown to cause structural and histopathologic changes that form a unique AF substrate or atrial cardiomyopathy.[5]

### AF Initiation: Ectopic Firing

The prevailing hypothesis of AF genesis is that rapid triggering initiates propagating reentrant waves in a vulnerable atrial substrate. The relative importance of the initiating trigger may decrease because the AF substrate progresses and AF becomes more stabilized. Haïssaguerre et al[6] first identified focal ectopic firing arising from myocyte sleeves within the pulmonary veins

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**Nonstandard Abbreviations and Acronyms**

| | |
|---|---|
| **AF** | atrial fibrillation |
| **APD** | action potential duration |
| **ARIC** | Atherosclerosis Risk in Communities Study |
| **BMI** | body mass index |
| **CARAF** | Canadian Registry of Atrial Fibrillation |
| **CI** | confidence interval |
| **ERP** | effective refractory period |
| **FHS** | Framingham Heart Study |
| **HF** | heart failure |
| **HFpEF** | heart failure with preserved ejection fraction |
| **HR** | hazard ratio |
| **LAA** | left atrial appendage |
| **MESA** | Multi-Ethnic Study of Atherosclerosis |
| **MI** | myocardial infarction |
| **OR** | odds ratio |
| **OSA** | obstructive sleep apnea |
| **PV** | pulmonary vein |
| **RAAS** | renin–angiotensin–aldosterone system |
| **RF** | risk factor |
| **SEE** | systemic embolism events |
| **SNP** | single-nucleotide polymorphism |
| **VTE** | venous thromboembolism |

(PVs) in patients with paroxysmal AF; ablation of these ectopic foci reduced AF burden, demonstrating their role in AF genesis (Figure 2A). It is now known that the PVs have unique electric properties and a complex fiber architecture that promote reentry and ectopic activity to initiate AF.[7] Autopsy studies have identified pacemaker cells, transitional cells, and Purkinje cells within the PVs.[8] The molecular basis for PV triggers has been primarily attributed to abnormal calcium $Ca^{2+}$ handling. A diastolic leak of $Ca^{2+}$ from the sarcoplasmic reticulum activates an inward $Na^+$ current via $Na^+Ca^{2+}$ exchanger resulting in spontaneous myocyte depolarization (early or delayed afterdepolarization). Hyperphosphorylation of key regulatory proteins and enzymes, including protein kinase A, calmodulin kinase II, phospholamban, and the ryanodine receptor type 2, is important contributors to sarcoplasmic reticulum $Ca^{2+}$ overload and diastolic membrane instability.[9,10] A reentrant mechanism for PV triggers also has been described. Decremental conduction and repolarization heterogeneity within the PV enable localized reentry and may foster a focal driver for AF.[11]

## AF Perpetuation: Reentry

Whereas triggers are required for AF initiation, a vulnerable atrial substrate is equally important. Structural, architectural, and electrophysiological atrial abnormalities promote the perpetuation of AF by stabilizing reentry. The mechanism of reentry in AF remains controversial with 2 dominant hypotheses, including reentrant rotors[12,13] or multiple independent wavelets (Figure 2B through 2E).[14] Advances in electroanatomic mapping and ablation technologies have yielded increasing evidence supporting the former mechanism.[15,16] Recent data supporting a third hypothesis, the double layer hypothesis, suggest that electric dissociation of epicardial and endocardial layers also may facilitate reentry (Figure 2D).[17,18]

For perpetuation of functional reentry, the propagating wavefront must complete 1 circus movement in a time period long enough for atrial tissue within that circuit to recover excitability (effective refractory period [ERP]). Thus, slow conduction velocity and a short ERP promote reentry. Both reduce wavelength size increasing the likelihood of multiple simultaneous reentrant circuits and AF perpetuation.

Atrial substrates that promote reentry are characterized by abnormalities of the atrial cardiomyocyte, fibrotic changes, and alterations in the interstitial matrix with primarily noncollagen deposits.[5] These molecular and histological changes impair normal anisotropic conduction (fibrosis and reduced cell coupling) and may shorten atrial ERP. For example, in familial AF, congenital abnormalities that lead to a gain in $K^+$ channel function shorten ERP of atrial cardiomyocytes, whereas, in heart failure (HF), a combination of atrial fibrosis and alterations in cardiomyocyte function results in both a slowing of conduction velocity and shortening of ERP. Thus, the development of and characterization of the vulnerable atrial substrate is specific to the predisposing AF RF.

## Natural History

For decades, the prevailing notion was that AF began with paroxysmal episodes that increased in frequency and duration causing progression to more persistent AF subtypes. This so-called AF begets AF postulate was based on early experimental data in goats, showing that tachycardia induces electrophysiological atrial remodeling resulting in persistence of AF.[19] Regional heterogeneity and shortening of the atrial ERP[20,21] occur within 30 minutes of tachycardia onset and are a result of adaptation to intracellular $Ca^{2+}$ overload.[22] In the FHS, only 10% of participants remained free of AF 2 years after incident AF, and recurrent (26%) or sustained AF (34%) was common.[23] But other studies suggest that this abiding notion is not ubiquitous. In the CARAF (Canadian Registry of Atrial Fibrillation), progression of paroxysmal AF to more persistent (chronic) AF subtype was 8.6% at 1 year and 24.7% by 5 years.[24] The Euro Heart Survey followed 5333 patients with AF for 1 year and found that 80% of patients with paroxysmal AF remained paroxysmal, whereas 30% of patients with persistent AF progressed to permanent.[25] Studies in patients with pacemakers allow for more robust assessment of AF burden and have shown that the majority of patients (54%–76%) with paroxysmal AF remain paroxysmal.[26,27] One study showed that only 24% of patients with paroxysmal AF progressed to persistent AF in 1 year and that there was a progressive pattern of increasing arrhythmia burden in these patients except in the days before the development of persistent AF supporting the mechanism of tachy-mediated atrial remodeling.[27]

The most remarkable observation is that persistent AF may spontaneously switch to paroxysmal subtype,[26] highlighting the complex natural history of AF, the limitations of experimental data, and the existing uncertainty in the mechanisms and factors that govern the clinical course of AF. In addition, the natural history of AF may change over time because the RFs contributing to AF onset shift in prevalence and severity (eg, less smoking and lower blood pressures, higher prevalence of obesity), and primary (eg, better hypertension control) and secondary (anticoagulation) prevention treatments evolve.[28] Finally, the means

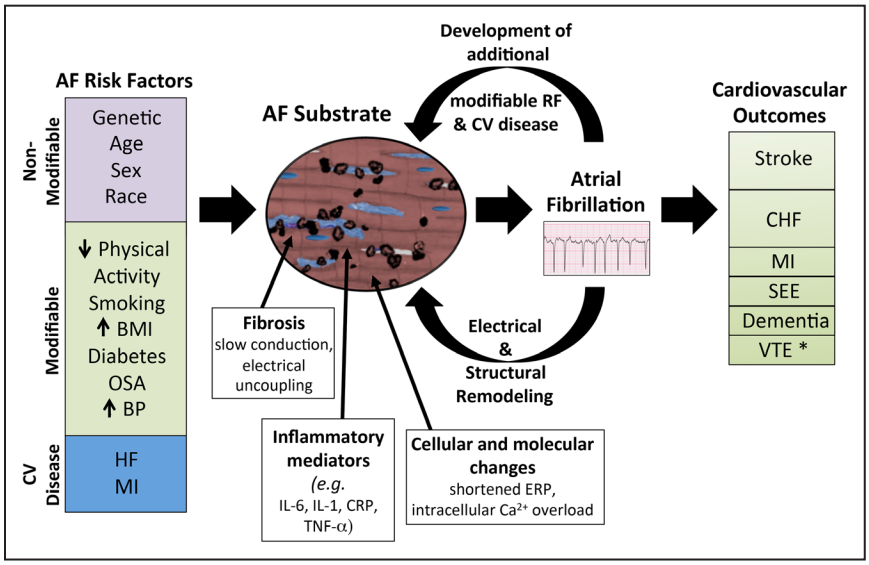


**Figure 1. Atrial fibrillation (AF) risk factors (RFs) induce structural and histopathologic changes to the atrium that are characterized by fibrosis, inflammation, and cellular and molecular changes.** Such changes increase susceptibility to AF. Persistent AF further induces electric and structural remodeling that promotes perpetuation of AF. AF also may lead to the development of additional AF risk factors that further alters the atrial substrate. Finally, AF is associated with several clinical outcomes. *There are limited data supporting the association. BMI, body mass index; ERP, effective refractory period; HF, heart failure; IL, interleukin; MI, myocardial infarction; OSA, obstructive sleep apnea; SEE, systemic embolism event; TNF, tumor necrosis factor; and VTE, venous thromboembolism.

for quantifying and assessing AF burden over time in various population studies is inconsistent leading to ascertainment bias and challenges in predicting the natural history of AF subtypes.

## RFs for Developing AF

### Unmodifiable RFs

#### *Genetics*

*Epidemiology*

Near the start of the millennium, rare familial forms of AF were identified, and loci were mapped to 10q22-24,[29] 6q14-16,[30] and 11p15-5.[31] Subsequent population-based studies showed that family history of AF is associated with a 40% increased risk of first-degree relatives developing AF.[32,33] The recognition of the heritability of AF in the general population has propelled the search for associated genetic loci.[34]

Classic Mendelian genetics and candidate gene approaches have been used to define the familial basis of AF. To date, at least 15 AF-causing mutations in $K^+$ channel genes or accessory subunit have been identified,[34] including mutations in *ABCC9* ($I_{KATP}$), *HCN4* ($I_f$), *KCNA5* ($I_{Kur}$), *KCND3* ($I_{Ks}$), *KCNE1* ($I_{Ks}$), *KCNE2* ($I_{Ks}$), *KCNE3* ($I_{Ks}$), *KCNE4* ($I_{Ks}$), *KCNE5* ($I_{Ks}$), *KCNH2* ($I_{Kr}$), *KCNJ2* ($I_{K1}$), *KCNJ5* ($I_{KAch}$), *KCNJ8* ($I_{KATP}$), *KCNN3* ($I_{AHP}$), and *KCNQ1* ($I_{Ks}$). Gain-of-function mutations

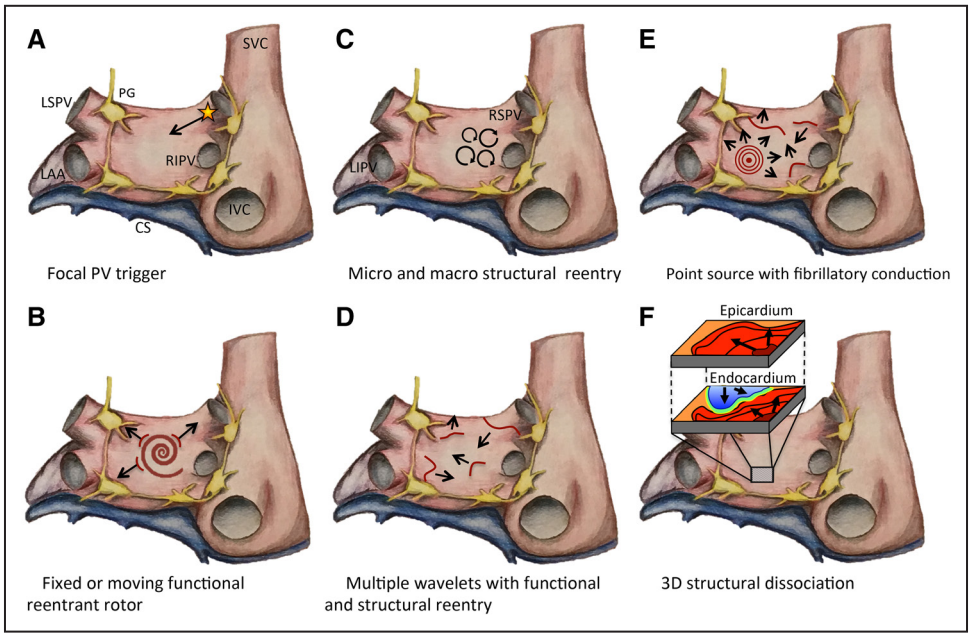


**Figure 2. Rendering of left and right atria showing various mechanisms of atrial fibrillation (AF).** **A**, Focal trigger arising from muscle sleeve of pulmonary vein (PV) propagating into left atrium and initiating AF in the vulnerable substrate. **B**, Fixed or moving spiral rotor, a result of functional reentry, acts as a driver for AF. **C**, Circus movement around anatomic structures or scar generating micro- and macro-reentrant circuits. **D**, Perpetual propagation of multiple simultaneous wavelets mediated by both functional and structural reentries. **E**, Point source with fibrillatory conduction acting as driver for persistence of AF. **F**, Electric dissociation between myocardial layers enabling reentry in 3-dimensional construct. CS indicates coronary sinus; IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior; PG, parasympathetic ganglia (yellow); RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and SVC, superior vena cava.

increase repolarizing $K^+$ current shortening the action potential duration (APD) and atrial refractoriness. Loss-of-function mutations delay repolarization and promote $Ca^{2+}$ mediated afterdepolarization that triggers AF.[35,36] Six variations in $Na^+$ channel genes have been identified, and these include *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*, *SCN5A*, and *SCN10A*.[34] Gain-of-function mutations may increase AF vulnerability by increasing cellular hyperexcitability,[37] whereas loss-of-function mutations shorten ERP and slow conduction.[38] Other important AF-causing genetic variants include mutations in the gap junctional protein-coding gene *GJA5* that diminishes cell–cell coupling and promotes reentry by slowing conduction velocity and shortening the wavelength.[39]

Instead of isolating a specific AF-causing gene, genome-wide association studies seek to scan the entire genome for disease-related genetic variants in single-nucleotide polymorphisms (SNPs). The first genome-wide association study for AF identified SNP rs2200733 located on chromosome 4q25 upstream of *PITX2* in an Icelandic population, which was strongly replicated in samples from Sweden, United States, and Hong Kong.[40] A meta-analysis of 3 AF susceptibility loci (4q25, 1q21, and 16q22) showed that the chromosome 4q25 SNP rs2200733 was associated with 30% increased risk of recurrent atrial tachycardia after AF ablation.[41] In a separate meta-analysis, this locus was associated with 38% increased risk of cardioembolic stroke.[42]

In experimental mouse models, the *Pitx2* gene encodes a transcription factor important for the embryonic organogenesis of the asymmetrical organs placed in the left side, including the heart.[43] Moreover, *Pitx2c* is involved in the formation of the PV muscle sleeves,[44] the most common site of triggered activity in AF. Loss of function of *Pitx2c* gene plays a role in the development of AF, and the differentiation, proliferation, and expansion of pulmonary myocardial cells.[45,46]

In separate genome-wide association studies, the SNP rs2106261 near gene *ZFHX3* identified on locus 16q22 was associated with increased AF risk. A knockdown of *ZFHX3* dysregulates $Ca^{2+}$, shortens the APD, and promotes arrhythmia susceptibility.[47]

AFGen consortium was formed in 2008 to increase statistical power for identifying loci associated with AF.[48] To date, 17 independent susceptibility signals for AF at 14 genomic regions have been identified. These include *KCNN3*, *PRRX1*, *CAV1*, *SYNE2*, *C9orf3*, *HCN4*, and *MYOZ1*.[49,50] The identification of genes related to AF is still in an early stage but in the future may allow for the assessment of an individuals' AF risk and the discovery of novel therapeutic targets.

### Age

#### *Epidemiology*

Advancing age is the most prominent RF for AF.[28] Understanding the influence of age on AF risk is important for assessing how changes in life expectancy will affect the prevalence of AF.

Although the prevalence of AF varies among different ethnic populations, epidemiological studies have consistently found a stepwise increase in the prevalence of AF with advancing age.[51–53] For example, a population-based multicenter cohort study reported age-specific rates in individuals aged 65 to 74 and 75 to 84 years of 3.4 (95% confidence interval [CI], 1.4–7.0) and 8.6 (95% CI, 4.6–14.9) for Chinese, 4.9 (95% CI, 3.1–7.3) and 10.6 (95% CI, 7.2–15.1) for non-Hispanic blacks, 7.3 (95% CI, 4.7–10.7) and 9.4 (95% CI, 5.9–14.4) for Hispanics, and 13.4 (95% CI, 10.6–16.7) and 19.6 (95% CI, 15.6–24.3) for non-Hispanic whites, respectively.[51]

The incidence of AF also increases with advancing age. In a Scottish study, the incidence rates per 1000 person-years was 0.5 for age 45 to 54 years, 1.1 for age 55 to 64, 3.2 for age 65 to 74, 6.2 for age 75 to 84, and 7.7 for age ≥85 years.[53]

The FHS examined temporal trends in AF RFs. During the past 5 decades, age was observed to be the greatest RF for AF when compared with other RFs, including male sex, body mass index (BMI), diabetes mellitus, smoking, alcohol consumption, systolic blood pressure, hypertension treatment, left ventricular hypertrophy, heart murmur, HF, and myocardial infarction (MI).[28] In the most recent time period studied (1998–2007), participant age of 60 to 69, 70 to 79, and 80 to 89 years was associated with 4.98-, 7.35-, and 9.33-fold risk of AF, respectively, compared with individuals aged 50 to 59 years.[28] Accordingly, a stepwise increment in age has been incorporated in AF risk prediction scores.[54,55] Among AF patients, those with age <65 years also have been found to be healthier, have a different AF RF profile, and less in-hospital deaths compared with those age ≥65 years.[56]

### Sex Differences

#### *Epidemiology*

There is now greater recognition that epidemiology of AF differs between men and women.[57] The age-adjusted incidence of AF is higher in men compared with women in North American and European populations. In the FHS, the AF incidence (per 1000 person-years) was 3.8 in men and 1.6 in women.[28] The Olmsted County Minnesota Study[58] and the Rotterdam Study[59] reported the AF incidence (per 1000 person-years) in men to be 4.7 and 11.5, respectively, compared with 2.7 and 8.9 in women. A higher incidence of AF in men also is observed in Asian populations, although less data are available.[60,61] Similarly, the age-adjusted prevalence of AF is higher in men than in women in North American and European populations. Among the Medicare beneficiaries of adults aged ≥65 years, the prevalence was 10.3% in men and 7.4% in women.[62] The higher prevalence of AF in men is also observed globally in both high-income and low- and middle-income countries.[60] However, there are less consistent data in Asian countries with some studies showing higher prevalence in men,[61,63,64] whereas others showed no sex difference.[52,65,66]

In North American and European populations, the lifetime risk for AF is similar between men and women despite higher AF incidence in men owing to their shorter life expectancy.[57] The FHS reported that the lifetime risks to develop AF at age 40 years were 26% for men and 23% for women.[67] In the Rotterdam Study, the lifetime risks at age 55 years were 23.8% for men and 22.2% for women.[59] On the contrary, among Chinese adults, the lifetime risk was consistently lower in men compared with women across all age groups.[52]

Underlying RFs of AF and taller stature in men largely explain higher AF incidence in men.[57] The CHARGE-AF consortium reported that after adjusting for AF-related RFs, male sex was no longer an independent RF for AF.[54] The population

attributable risks of the RFs for AF differ by sex.[57] The population attributable risk for AF of coronary disease is higher in men,[2] whereas the population attributable risks of elevated systolic blood pressure[57] and valvular disease[2] are higher in women.

### *Racial Differences*

*Epidemiology*

Many of the early population-based studies in AF were limited by racial diversity. However, in the last decade, there has been a determined initiative to better understand the racial and ethnic differences in AF prevalence, pathophysiology, and outcomes.

Numerous studies demonstrated that AF is less prevalent in individuals of African when compared with European ancestry.[51,68–72] These data seem counterintuitive given the higher prevalence of traditional AF RFs in blacks than whites.[68,73] The Candidate Gene Association Resource Study[68] found that among blacks, the risk of AF was independently associated with increasing percentage of European ancestry (hazard ratio [HR], 1.13; 95% CI, 1.03–1.23). Adjusted associations showed that with every 10% increase in European ancestry, there was a 16% to 20% increased risk of AF. The data are consistent with the hypothesis that either African ancestry has protective effect against AF or European ancestry enhances AF susceptibility.

Candidate SNP analysis performed in 2 cohorts showed that the rs10824026 SNP located on the 10q22 genetic locus accounted for 11.4% to 31.7% increased AF risk in white individuals when compared with blacks.[74] Furthermore, the minor allele G of the SNP confers low AF risk[49] and is more common in blacks (37.7%–37.8%) when compared with white individuals (15.5%–16.4%).[74] In a separate study that combined 3 cohorts with European and black descent, an intronic SNP rs4845625 of the *IL6R* gene was associated with AF in white individuals (relative risk, 0.9; 95% CI, 0.85–0.95) and in blacks (relative risk, 0.86; 95% CI, 0.72–1.03 with borderline significance $P$=0.09).[75] Finally, the SNP rs4611994 on chromosome 4 near *PITX2* was associated with AF risk in blacks (HR, 1.4; 95% CI, 1.16–1.69), and this chromosomal locus is associated with AF in white individuals.[40] Although traditional AF RFs are well recognized, there are increasing data that race, ethnicity, and attributed genetic ancestral variants may play a significant role in modulating AF susceptibility.

More recently, the MESA (Multi-Ethnic Study of Atherosclerosis) reported the prevalence of AF in Hispanic and Asians residing in the United States. The age- and sex-adjusted incidence rates per 1000 person-years of AF were 6.1 in Hispanics and 3.9 in Asians when compared with 11.2 in white and 5.8 in black individuals.[51] These data are comparable to The Healthcare Cost and Utilization Project that reported that Hispanics and Asians had multivariable-adjusted lower risk of AF (HR, 0.78; 95% CI, 0.77–0.79) when compared with whites.[73] Both studies showed that a larger proportion of AF in nonwhites was attributed to the greater presence of traditional RFs particularly hypertension when compared with whites.

## Modifiable RFs

### *Physical Activity and Sedentary Lifestyle*

*Epidemiology*

The relationship between level of physical activity and risk of AF has been described as nonlinear.[76–78] Sedentary lifestyle is associated with higher risk of AF,[79] but paradoxically extreme levels of physical activity also are associated with increased AF risk.[80–82]

A large retrospective cohort study of 64 561 patients showed a graded and inverse relationship between cardiorespiratory fitness as objectively assessed with treadmill testing. The incidence rate of AF in patients with lowest cardiorespiratory fitness was 18.8% when compared with 3.7% in those with highest cardiorespiratory fitness. Every 1-MET increase in cardiorespiratory fitness was associated with a dose dependent 7% reduction in AF risk.[83] A meta-analysis of pooled data from 7 studies showed that sedentary lifestyle was associated with increased risk of AF (odds ratio [OR], 2.47; 95% CI, 1.25–3.7) compared with moderate or intense physical activity.[82]

Interesting and seemingly contradictory male endurance athletes are at increased AF risk. In a prospective case–control study, individuals who had performed <2000 hours of lifetime-accumulated high-intensity exercise had an attenuated risk of lone AF (OR, 0.38; 95% CI, 0.12–0.98) when compared with sedentary individuals. But the AF risk in those with ≥2000 hours of high-intensity exercise was increased (OR, 3.88; 95% CI, 1.55–9.73).[76] The type of exercise modulates AF risk with endurance sports, such as marathon running[76] or long-distance cross-country skiing,[80] conferring the highest AF risk. A meta-analysis showed that there was over a 5-fold increased risk of AF in athletes than nonathlete referents.[84]

Sex differences in the association of physical activity with AF have been identified. In men, a U-shaped association of AF risk and physical activity was observed where moderate physical activity was found to confer lowest risk (OR, 0.81; 95% CI, 0.26–1.00) and intense activity conferred the highest risk (OR, 3.30; 95% CI, 1.97–4.63). In women, however, the association was inverse and linear. Increasing physical activity was associated with progressive and decreasing AF risk with ORs of 0.91 (95% CI, 0.77–0.97) and 0.72 (95% CI, 0.57–0.88) for moderate and intense activity, respectively.[82]

*Pathophysiology*

Sedentary lifestyle is known to increase risk of AF RFs, including hypertension,[85] obesity,[85] and diabetes mellitus.[86] Obstructive sleep apnea (OSA) is common in obese individuals and has been associated with sedentary lifestyle.[87] These conditions have been shown to independently induce structural and electric remodeling of the atrium. Physical inactivity also increases systemic inflammation,[88] which may induce atrial remodeling and has been associated with AF.[89–93] Finally, sedentary lifestyle is associated with autonomic dysfunction and elevated sympathetic tone, which enhances afterdepolarization triggering and AF susceptibility.

In endurance athletes, the pathogenesis of AF has been attributed to 2 primary mechanisms. First, increased vagal tone in these individuals[82,94] may shorten and increase the dispersion of atrial ERP promoting PV firing and localized reentry. Second, long-term endurance training causes progressive cardiac remodeling, including left atrial enlargement, which may promote AF.[95–97] Atrial fibrosis and increased AF susceptibility has been observed in a rat model of prolonged, intensive exercise.[98]

### Smoking

*Epidemiology*

Smoking is associated with incident AF.[54,99] The FHS showed that within the past 50 years, the frequency of smoking among participants with new-onset AF has decreased. Between 1998 and 2007, only 12.7% of AF-affected participants were smokers when compared with 15.6% in the previous decade.[28]

The Rotterdam Study found that both former and current smoking were equally associated with increased AF risk.[100] In the ARIC study (Atherosclerosis Risk in Communities Study), the multivariable-adjusted incidence of AF was 1.58× higher in ever smokers (former and current) and 2-fold higher (HR, 2.05) in current smokers when compared with nonsmokers.[99] A dose–response association was observed with increasing cigarette-years.[99] In the CHARGE-AF consortium, incident AF was 1.44× higher in current smokers when compared with nonsmokers.[54] Smoking is an RF for AF across various races and ethnicities.[54,99,101]

Finally, secondhand tobacco exposure also has been associated with risk of AF.[102] Exposure during gestational development or early childhood is associated with ≈40% increased risk of AF.[103]

*Pathophysiology*

Smoking is thought to increase AF susceptibility through indirect and direct mechanisms. Smoking may increase myocardial ischemia by increasing systemic catecholamine and myocardial work, reducing oxygen carrying capacity, and promoting coronary vasoconstriction.[104] In addition, smoking accelerates atherosclerosis through effects on lipids, endothelial function, oxidative stress, inflammation, and thrombosis.[105] These effects may indirectly increase AF susceptibility by predisposing to atrial ischemia, MI, and HF. Reduced lung function and chronic obstructive pulmonary disease also increase vulnerability to AF.[106]

Smoking and nicotine also have been shown to directly contribute to the AF substrate. In a case–control study of patients undergoing coronary artery bypass, the volume of atrial fibrosis in smokers was shown to be dose dependent, and in nonsmokers, nicotine was shown to induce a pattern of collagen type III expression in atrial tissue culture that was similar to that observed in smokers.[107] In a dog model, nicotine induced interstitial fibrosis and increased AF susceptibility.[108] The profibrotic effect of nicotine was attributed to downregulation of atrial microRNAs, miR-133, and miR-590, which in turn increased transforming growth factors-b1 and -b2 and connective tissue growth factor. Finally, nicotine prolongs the APD by blocking the inward rectifier potassium channel ($I_{k1}$ and $K_{irs}$)[109] and reduces the transient outward potassium current ($I_{to}$).[110] Prolongation in the APD may increase arrhythmia susceptibility, but the proarrhythmic effect of nicotine has not been confirmed.

### Obesity

*Epidemiology*

Both obesity and elevated BMI predispose to established AF RFs, including hypertension,[111] diabetes mellitus,[112] MI,[113] left ventricular hypertrophy,[114] left atrial enlargement,[115] left ventricular diastolic dysfunction,[116] HF,[117] and OSA.[2] However, when accounting for these concomitant conditions, population studies show that obesity and elevated BMI independently increase risk for AF.

Numerous population-based studies have shown an association between elevated BMI and increased risk of AF.[118–120] A meta-analyses of 5 studies found that obesity confers a 49% increased risk of developing AF.[121] A dose–response relationship was observed with each 1 U increase in BMI associated with a 3% to 4.7% increase in AF risk.[118,122,123] Other measures of obesity, including abdominal circumference and total fat mass, have been associated with 13% to 16% increase in AF risk per 1 SD over 10-year follow-up.[124] Importantly, obesity is a powerful predictor of incident AF even when regression analyses have been adjusted for OSA, which commonly coexists in such patients.[123]

*Pathophysiology*

Excess AF risk associated with obesity has been attributed to left atrial enlargement,[118] increased left ventricular mass,[114] and diastolic dysfunction.[116,125,126] In a sheep model of obesity, increasing weight correlated with increased left atrial volume and pressure, ventricular mass, and pericardial fat. Histological analysis revealed that myocardial lipidosis, fibrosis, and inflammatory infiltrates increased progressively with increasing weight. These pathological changes were associated with decreased conduction velocity and increased AF.[127] Whereas no change in atrial ERP was observed in the sheep model, a clinical study of 63 patients undergoing PV isolation reported that elevated BMI was associated with short atrial ERP and slower atrial conduction velocity,[128] properties that promote reentry.

Pericardial fat also has been implicated in the pathogenesis of the obesity–AF relation. Cross-sectional studies have shown that pericardial fat is associated with prevalence, severity, and recurrence of AF.[129,130] A recent meta-analysis of 23 studies correlated epicardial adipose tissue with AF after adjusting for traditional RFs (OR, 1.47 per SD epicardial adipose tissue increase; 95% CI, 1.17–1.84).[131] A local paracrine effect of epicardial adipose tissue mediated by inflammatory cytokines,[132] growth and remodeling factors,[133] angiogenic factors, and adipocytokines may lead to the development of the AF substrate.[133,134] Epicardial adipose tissue location on CT imaging correlates with high dominant excitation frequency during electroanatomic mapping in patients undergoing AF ablation.[135]

### Diabetes Mellitus

*Epidemiology*

The FHS showed that men and women with diabetes mellitus had a 40% and 60% increased risk of AF, respectively.[2] Level of blood glucose may be more predictive than actual diagnosis of diabetes mellitus in older adults.[136] A meta-analysis of cohort and case–control studies found that patients with diabetes mellitus or impaired glucose homeostasis had a 34% greater risk of AF than individuals without diabetes mellitus.[137] A causal association is supported by evidence that worse glycemic control and longer duration of diabetes mellitus are associated with increased AF risk.[138] The estimated risk of AF increases by 3% per additional year of diabetes mellitus. The risk of AF in patients with diabetes mellitus for >10 years was 64% but only 7% in those with diabetes mellitus ≤5 years.

*Pathophysiology*

Glucose intolerance and insulin resistance seem to mediate the development of the AF substrate.[139] The molecular mechanism by which insulin resistance alters cardiac structure is complex and involves impaired mitochondrial function and oxidative stress, which alter the transcription and translation processes essential for cardiac adaptation.[140,141] In a rat model of diabetes mellitus, prolonged intra-atrial conduction time and diffuse interstitial fibrosis were observed, predisposing to increased arrhythmogenicity.[142] In patients undergoing AF ablation, abnormal glucose metabolism was associated with prolonged atrial activation time and reduced bipolar voltages with electroanatomic mapping, a finding consistent with atrial fibrosis or scar.[143] Finally, autonomic dysfunction also has been implicated.[144]

### *Obstructive Sleep Apnea*

*Epidemiology*

OSA is highly prevalent[145] and has been associated with other AF RFs, including hypertension, diabetes mellitus, coronary heart disease, MI, and HF.[146] The Sleep Heart Health Study found a 4-fold increase in the prevalence of AF with OSA, and one third of participants had arrhythmia during sleep.[147] The Olmsted County Study similarly found that OSA and its severity strongly predicted 5-year incidence of AF (HR, 2.18; 95% CI, 1.34–3.54). In older individuals, only the magnitude of nocturnal oxygen desaturation was predictive of AF.[125] Similarly, a meta-analysis of 5 of prospective studies reported that OSA was associated with about a 2-fold increased odds of postoperative AF.[148] Patients with OSA have a higher recurrence of AF after cardioversion[149] and catheter ablation (relative risk, 1.25; 95% CI, 1.08–1.45).[150]

The impact of OSA on AF outcomes was studied in the ORBIT-AF registry.[151] Patients with OSA had more severe symptoms and were at higher risk of hospitalization (HR, 1.12; 95% CI, 1.03–1.22) than those without OSA, but had similar mortality, risk of stroke, or MI. Patients with OSA who were treated with CPAP were less likely to progress to permanent AF subtype than those who were untreated (HR, 0.66; 95% CI, 0.46–0.94).

*Pathophysiology*

Electroanatomic mapping in patients undergoing AF ablation has been used to characterize the AF substrate associated with OSA.[152] Observed structural changes included increased atrial size and expansive areas of low voltage or electric silence, which indicate fibrosis, loss of atrial myocardium, or electric uncoupling. Prolonged and regional disparities in atrial conduction also were seen. AF associated with OSA tends to be refractory to cardioversion and catheter ablation particularly in patients with untreated OSA, highlighting the expansive atrial remodeling associated with OSA.[149] In a rat model of AF, OSA was associated with atrial conduction slowing attributed to connexin-43 downregulation and increased atrial fibrosis. Such atrial remodeling promoted the persistence of AF.[153]

Several mechanisms may account for the development of AF and the AF substrate in patients with OSA. First, surges of sympathetic activity induced by hypoxia and the chemoreflex near the end of an apneic episode result in transient blood pressure rises.[154] Second, vigorous inspiratory efforts during apnea accentuate the fluctuation of intrathoracic pressure increasing left atrial volume (stretch) and pressure.[155] Third, an increase in oxidative stress signaling[156] and systemic inflammatory mediators[157] may promote atrial remodeling. Fourth, hypercapnia acutely prolongs ERP and slows conduction velocity, but with return of eucapnia delayed recovery of conduction has been associated with increased AF vulnerability.[158] Fifth, negative tracheal pressure shortens atrial ERP and atrial monophasic action potential via vagal stimulation, which enhances AF inducibility.[159]

### *High Blood Pressure*

*Epidemiology*

In the FHS, the RF-adjusted OR for AF was 1.5 and 1.4 in men and women with hypertension, respectively.[160] Later studies, including the FHS, found a limited association with mean arterial pressure but found that pulse pressure was highly predictive of AF risk.[161] The CHARGE-AF consortium observed that both systolic and diastolic blood pressure were predictive of AF risk.[54] In addition, systolic blood pressure that approaches the upper limit of normal is associated with increased AF risk in healthy, middle-aged men[162] and women.[163] The Women's Health Study also showed that when an individual's blood pressure remained elevated at follow-up visits, the risk of AF was higher when compared with those whose subsequent blood pressure recordings were lower suggesting a role for secondary prevention.[163] The recent 50-year analysis of the FHS showed that although the rate of treated hypertension increased and severe hypertension became less prevalent, the population attributed risk of AF was unaffected suggesting that antihypertensive therapy does not completely eliminate the elevated AF risk associated with hypertension.[28]

*Pathophysiology*

Increased left atrial size is a well-established, independent predictor of AF,[160,164] but other pathological features of chronic hypertension, including left ventricular hypertrophy[160,164,165] and impaired diastolic dysfunction,[166] are also associated with AF. Common to all is an elevated left ventricular end-diastolic pressure, which increases left atrial pressure and volume. Atrial remodeling is associated with slower and more heterogeneous atrial conduction and increased PV firing. In addition, increased left atrial mass supports multiple reentry circuits.

Studies of animal models of hypertension have reported that early left atrial remodeling is characterized by atrial dilation with hypertrophy, reduced atrial ejection fraction, increased refractoriness, and prominent inflammatory infiltrates.[167] Chronically, interstitial fibrosis and conduction slowing and heterogeneity are observed.[167,168] Moreover, increased atrial apoptosis has been observed.[168] Electrophysiology studies in patients with chronically treated hypertension, but without AF, have shown global conduction slowing, regionally delayed conduction in the crista terminalis, and increased AF inducibility.[169]

Animal studies have suggested that the renin–angiotensin–aldosterone system (RAAS), which stimulates myocyte hypertrophy and intracellular fibrosis, also may contribute to atrial remodeling.[170–172] Although upstream RAAS blockage was effective in animal models for reducing AF remodeling, 2 separate meta-analyses have reported that the benefit of RAAS blockade was limited to patients with HF or left ventricular hypertrophy.[173,174]

## Clinical Outcomes

### *Stroke*

*Epidemiology*

AF is associated with increased risk of stroke and transient ischemic attack[175,176]; furthermore, AF-related strokes increase the risk of long-term disability or death.[3]

In the FHS, the attributable risk of AF for stroke was 1.5% among 50 to 59 years olds, whereas among 80 to 89 years olds, it was 23.5%.[176] Often AF is asymptomatic and consequently subclinical; however, in patients with implanted cardiac devices, including pacemaker and defibrillators, the burden of AF, including subclinical AF, may be accurately assessed. Atrial tachyarrhythmia (atrial rate >190 bpm) for longer than 6 minutes has been associated with an increased risk of clinical AF (HR, 5.56; 95% CI, 3.78–8.17) and ischemic stroke (HR, 2.50; 95% CI, 1.28–4.89).[177]

The risk of stroke with AF is variable and is modulated by other RFs, including age ≥65, hypertension, diabetes mellitus, previous stroke/transient ischemic attack/thromboembolism history, vascular disease, HF, and female sex.[178–180] Stroke risk models incorporating these RFs have been validated.[181]

Strokes in AF patients are associated with increased morbidity and mortality. In the Copenhagen Stroke Study, compared with individuals without AF, patients with AF had higher rates of in-hospital death (OR, 1.7; 95% CI, 1.2–2.5), longer hospital stay (50 verses 40 days; $P<0.001$), and lower rates of discharge home (versus care facility; OR, 0.60; 95% CI, 0.44–0.85).[182] Moreover, the infarct was larger and more commonly involved the cerebral cortex in patients with AF. The same study also showed that the odds for silent infarcts were similar for patients with AF and non-AF (OR, 0.99; 95% CI, 0.65–1.5).[182] Correspondingly, the FHS showed increased 30-day mortality in AF-associated strokes than non-AF strokes (OR, 1.84; 95% CI, 1.04–3.27). Individuals with AF had worse 1-year survival after stroke and increased risk of stroke recurrences compared with those with non-AF strokes.[3]

*Pathophysiology*

Thrombogenesis in AF is not fully elucidated. A confluence of factors, including blood stasis, endothelial dysfunction, and prothrombotic state, has been implicated.

Attention has focused on the left atrial appendage (LAA). Animal models of AF demonstrate atrial contractile dysfunction from reduced myofibrillar sensitivity to $Ca^{2+}$ [183] and intracellular $Ca^{2+}$ transients.[184] Clinically, reduced LAA emptying velocity on transesophageal echocardiography is associated with the presence of spontaneous echo contrast, increased LAA thrombus, and stroke.[185] In vitro studies have attributed spontaneous echo contrast to erythrocytes and fibrinogen interaction under low flow and shear stress.[186] The role of LAA in AF-related stroke is further supported by efficacy of LAA closure devices for reducing strokes in patients with AF.[187]

Observational studies have revealed abnormalities in coagulation in patients with AF-related strokes. Increases in prothrombin fragment and thrombin–antithrombin complexes have been observed in patients with AF-related strokes[188] and in those with transesophageal spontaneous echo contrast.[189] Other hemostatic factors have been implicated in contributing to the hypercoagulable state, including fibrinogen, D-dimer, factor VIII, and von Willebrand factor.[188,190–193] However, in an adjusted model, the FHS showed that such abnormalities are ascribed to AF RFs and presence of cardiovascular disease rather than AF alone.[194] Finally, inflammation may mediate endothelial dysfunction and hypercoagulability.

### *Extracranial Systemic Thromboembolism*

*Epidemiology*

Compared with AF-related stroke, relatively less is known about epidemiology of extracranial systemic embolism events (SEEs). Data from the Danish Atrial Fibrillation Cohort showed an association between hospital diagnosis of AF and increased relative risk of SEEs in men (relative risk, 4.0; 95% CI, 3.5–4.6) and women (relative risk, 5.7; 95% CI, 5.1–6.3). Nearly, half of SEEs occurred in patients between the ages of 70 and 79 years. The highest risk period for SEE was during the first year of incident AF, which is consistent with stroke data.[195]

More contemporary data are derived from a pooled analysis of 4 AF antiplatelet and anticoagulation trials with 37 973 patients from >40 countries.[196] During the mean follow-up of 2.4 years, there were 221 SEEs accounting for 11.5% of clinically apparent embolic events. The incidence rates per 100 person-years for SEE and stroke were 0.24 and 1.92, respectively. Anatomically, SEEs were more likely to involve the lower extremities (58%) and mesenteric circulation (22%), whereas involvement of splenic and renal circulation was less common. Finally, increased morbidity and mortality was associated with SEE because 64% of patients required an interventional procedure or amputation and 24% died within 30 days.

*Pathophysiology*

The mechanisms underlying thromboembolism with SEE are similar to that of AF-related strokes.

### *Dementia*

*Epidemiology*

Whereas dementia and AF share similar RFs, including advancing age, obesity, diabetes mellitus, and hypertension, AF is associated with an adjusted increased risk of cognitive impairment,[197,198] dementia,[197,199–202] Alzheimer's dementia,[203] and vascular dementia[202] in patients with and without a history of stroke. In patients with normal baseline cognitive function and no history of stroke, meta-analysis of 8 studies found a significantly increased risk of incident dementia in those with AF (HR, 1.42; 95% CI, 1.17–1.72).[200] In patients with history of stroke, 2 meta-analyses have shown that AF is associated with ≈ 2.5-fold adjusted risk of cognitive impairment and dementia.[197,199] Twenty-year follow-up of the Rotterdam Study reported AF patients <67 years of age had greatest risk of dementia. The dementia risk increased with AF duration (exposure), whereas there was no increased risk associated with AF duration in those ≥67 years of age.[201]

*Pathophysiology*

Multiple mechanisms may explain the association of AF and dementia. Nearly, one third of patients with AF have been observed to have silent brain infarcts on brain magnetic resonance imaging,[204] and micro-thromboembolisms with covert infarction have been implicated as 1 possible mechanism. The FHS showed that over the past 3 decades, the incidence of dementia, including dementia associated with AF, has

decreased.[202] During this time period, there has been improved use of anticoagulation in individuals with AF supporting the hypothesis that anticoagulation may reduce AF-associated dementia. This supposition is supported by a retrospective study of patients receiving long-term warfarin showing that incident dementia was 2.4× higher in individuals with AF versus those without AF and that the dementia risk in those with AF and non-AF was significantly mitigated by increasing time in therapeutic range.[205]

A second possible mechanism may involve cerebral hypoperfusion associated with AF.[206,207] Interestingly, 1 study indicated that the effect of AF on cerebral perfusion was most pronounced in younger patients (<50 years) and that no difference was observed in those >65 years of age[206] consistent with epidemiological data showing age-dependent dementia risk in AF patients.[201]

### *Heart Failure*

*Epidemiology*

HF is both an RF and an adverse clinical cardiovascular outcome associated with AF. The association was first recognized in the 1940s,[208] and it is now established that HF and AF often coexist,[2] predispose to the other,[209] and share common RFs, including hypertension, diabetes mellitus, coronary disease, and valvular disease.

*HF as a RF for AF*

In major HF trials, the prevalence of AF in patients with HF ranges from 13% to 27%,[210–212] and the prevalence increases with increasing New York Heart Association Functional Class.[213] In the FHS, HF was associated with 4.5-fold risk of AF in men and 5.9-fold risk in woman.[2] Other epidemiological studies showed 2.67- to 3.37-fold risk of AF associated with HF.[214,215] Incremental reductions in systolic function are associated with increasing AF risk.[164] HF with preserved ejection fraction (HFpEF) also confers an increased risk of developing AF (HR adjusted for age and sex, 3.75; 95% CI, 2.19–6.40) with grade IV diastolic dysfunction as assessed with echocardiography conferring the highest risk.[166]

*HF as an Outcome Associated With AF*

The FHS uniquely reported the joint incidence of AF and HF and their temporal relationship. Among 931 participants with HF, 24% had previous or concurrent AF, and 17% subsequently developed AF. One fifth of participants had AF and HF detected on the same day,[209] demonstrating the closely interlinked pathophysiology. The incidence of first HF in FHS participants with AF is 33 per 1000 person-years,[209] which is comparable to that observed in the Danish nationwide cohort study.[216] In a contemporary FHS cohort, the incidence of HF was markedly higher in participants with AF than the incidence of AF in those with antecedent HF.[217] In other words, AF begets HF more than HF begets AF.

The association of AF on HF subtype has also been reported. AF precedes HFpEF more commonly than HF with reduced ejection fraction. Among patients with prevalent AF, the adjusted HRs of incident HFpEF and HF with reduced ejection fraction were 2.34 (95% CI, 1.48–3.70) and 1.32 (95% CI, 0.83–2.10), respectively.[217] The finding that AF is more predictive of HFpEF is consistent with increased incident AF in patients with HFpEF versus HF with reduced ejection fraction and suggests shared common mechanisms.[166]

In the FHS, the combination of AF and HF was associated with reduced survival.[209] Among patients with prevalent AF, incident HF was associated with increased all-cause mortality compared with those without HF (HR, 1.25; 95% CI, 1.04–1.51).[217] In one of the largest, worldwide studies, HF was found to be the leading cause of death 1 year after new onset of AF accounting for nearly a third of all deaths.[218] A meta-analysis showed a significantly higher all-cause mortality in AF patient with HF with reduced ejection fraction than those with HFpEF (relative risk, 1.23; 95% CI, 1.12–1.36) despite similar risk of stroke and HF hospitalizations.[219]

*Pathophysiology*

The strong association of HF and AF has been attributed to shared mechanisms that lead to neurohormonal and proinflammatory activation, which induces myocardial inflammation and fibrosis. The atrial substrate with HF is characterized by atrial fibrosis and abnormalities in $Ca^{2+}$ handling. It is distinct from the electrophysiological changes associated with AF-induced atrial remodeling.[220] Studies in dogs[221] and humans[222] indicate that HF induces an AF-susceptible atrial substrate without significantly altering atrial ERP (except at rapid rates) or ERP heterogeneity. These findings differ from the AF begets AF model with reduced atrial ERP. Histological studies in HF dogs revealed structural changes, including interstitial fibrosis with cellular hypertrophy, degeneration, and loss. These changes were associated with regions of delayed conduction and AF susceptibility. In human, extensive atrial fibrosis has been observed at autopsy in patients with dilated cardiomyopathy,[223] and areas of low voltage or electric silence (scar) and fractionated or delayed potentials (slow conduction) have been identified during electrophysiology studies in patients with HF (but no AF).[222] Neurohormonal activation is central to the generation of the AF substrate with HF, and the milieu of profibrotic mediators is induced through angiotensin-dependent and angiotensin-independent pathways.[224] Meta-analyses demonstrate benefit of upstream RAAS inhibition in AF patients with HF, but not in AF patients with other comorbidities, highlighting the unique pathophysiology of AF with HF.[174,176] Oxidized calmodulin-dependent protein kinase II has been shown to be a molecular signal that is increased by RAAS activation and is a common promoter of sinus node dysfunction, AF, and HF; thus, reducing this kinase with RAAS block may explain the benefit of upstream therapy in patients with both AF and HF.[225,226]

Increased trigger activity also is associated with HF and may increase risk of AF in the vulnerable substrate by generating a rapid burst of ectopic firing or maintaining a focal driver. In dogs, HF prolongs the APD and increases the phosphorylation of key regulatory kinases and phosphatases, including calmodulin-dependent protein kinase II. The net effect of these HF-mediated changes is to enhance $Ca^{2+}$ uptake into the sarcoplasmic reticulum promoting afterdepolarization initiation.[183] Similarly, HF has been shown to increase calcium sparks in cardiomyocytes isolated from the PVs of rabbits.[227]

Finally, tachycardia and shortening of diastolic filling time associated with irregular ventricular activation with AF further impair diastolic relaxation and promote clinical HF,

which further induces atrial remodeling leading to the perpetuation of AF.

### Myocardial Infarction

*Epidemiology*

As with HF, there is a bidirectional relationship between AF and MI. Coronary heart disease is associated with an increased risk of AF,[228] but AF also is associated with increased risk of MI.[229] In the REGARDS cohort, AF was associated with a 2-fold increased risk of MI,[230] that was greater in women (HR, 2.16; 95% CI, 1.41–3.31) versus men (HR, 1.39; 95% CI, 0.91–2.10) and blacks (HR, 2.53; 95% CI, 1.67–3.86) versus whites (HR, 1.26; 95% CI, 0.83–1.93). The Olmsted study reported similar unadjusted risk of coronary ischemic event, but after adjusting for age, the incidence was higher in men than woman.[231] Among those with newly diagnosed AF, the risk of death after coronary ischemic events was higher in woman than men (HR, 2.99; 95% CI, 2.53–3.53 versus HR, 2.33; 95% CI, 1.94–2.81). Interestingly, as observed with strokes and SEEs, the event rate of coronary ischemic events was highest within the first year of incident AF (4.7%, 95% CI, 3.9–5.6) and subsequently declined to 2.5% per year.

*Pathophysiology*

The mechanisms linking AF to MI are not completely understood. First, both AF and MI have overlapping RFs that may lead to the development of AF and MI in parallel. For instance, both AF and coronary heart disease are associated with proinflammatory and prothrombotic states. Second, MI in AF may be attributed to coronary artery thromboembolism. Third, myocardial ischemia may arise from supply–demand mismatch in the setting of tachycardia associated with AF. Fourth, MI may lead to left ventricular remodeling that may predispose to AF.

### Venous Thromboembolism

*Epidemiology*

Increased BMI, obesity, and smoking are associated with venous thromboembolism (VTE)[232–235] and AF. Potential direct causal relationship between AF and VTE has been proposed, but needs to be studied further.[236,237]

A few studies have reported increased risk of VTE in AF and vice versa. In a retrospective cohort study based on the national administrative database in Taiwan, the risks of VTE (adjusted HR, 1.74; 95% CI, 1.36–2.24) and pulmonary embolism (adjusted HR, 2.18; 95% CI, 1.51–3.15) were both higher in the AF group compared with non-AF referents.[238] A Norwegian administrative database study reported that AF was associated with an increased risk of pulmonary embolism (adjusted HR, 1.83; 95% CI, 1.16–2.90) but not VTE (adjusted HR, 1.04; 95% CI, 0.64–1.68).[236] In addition, the same study found that individuals with incident VTE were subsequently at a higher risk of developing incident AF (adjusted HR, 1.63; 95% CI, 1.22–2.17) compared with those without VTE.[237] It should be noted that in both the Taiwanese and Norwegian cohorts, a significant proportion of individuals had preexisting RFs for VTE, including lower extremity fracture, recent surgery, cancer, and immobility.[236,238] In comparison to individuals with AF or VTE alone, those with AF and VTE were older and had higher mean BMI. In the Norwegian study, the mean age and BMI were 64 years and 26.9 kg/m$^2$ for AF alone, 57 years and 26.7 kg/m$^2$ for VTE alone, and 68 years and 29.2 kg/m$^2$ for AF and VTE combined.[237]

*Pathophysiology*

The mechanisms underlying the AF-VTE association are inexplicable. Several studies have shown that AF is associated with a hypercoagulable state attributed to elevated hemostatic factors, including fibrinogen, D-dimer, prothrombin fragment, factor VIII, and von Willebrand factor[188,190–193]; however, many of these studies were not adjusted for coexisting cardiovascular RF. In an adjusted model, the FHS showed no significant difference in levels of fibrinogen, von Willebrand factor, or tissue-type plasminogen activator, suggesting that coexisting RFs rather than AF may explain elevated thrombotic risk.

### Mortality

*Epidemiology*

The FHS was one of the first studies to report that AF had a multivariable-adjusted association with increased risk of death.[4] In addition, the study observed a significant interaction, such that AF diminished the survival advantage generally enjoyed by women; the multivariable-adjusted OR for death in men and women was 1.5 and 1.9, respectively. At 10-year follow-up, 61.5% of men with AF between 55 and 74 years of age had died compared with 30.0% of men in the same age group without AF. A similar trend was found in women with 57.6% of those with AF dying by 10-year follow-up when compared with 20.9% in those without AF. The increased risk was consistent across all decades of age from 55 to 95 years. Even in individuals without clinical evidence of cardiovascular or valvular disease at baseline, AF was associated with a 2-fold increased risk of death.[4] A retrospective study of Medicare beneficiaries 65 years or older showed that death was the most frequent AF outcome with an incidence of 19.5% at 1 year and 48.8% at 5 years after initial diagnosis.[239] A recent systematic review and meta-analysis of 64 studies that included 1 009 501 patients with 149 746 (14.8%) having AF found a pooled relative risk of death that was 1.6 (95% CI, 1.39–1.53), although there was marked heterogeneity.[240] In 14 studies, cardiovascular mortality was assessed, and the pooled relative risk associated with AF was 2.03 (95% CI, 1.79–2.3).

It is noteworthy that there is growing evidence that AF is associated with an increased risk of sudden cardiac death. Pooled analysis of the ARIC and Cardiovascular Health Study cohorts showed that AF was associated with more than a doubling of the risk of sudden cardiac death compared with participants without AF (HR, 2.47; 95% CI, 1.95–3.13).[241] A meta-analysis of 7 studies found the relative risk of sudden cardiac death was 1.88 (95% CI, 1.36–2.6), although significant study heterogeneity was present.[241] In the RE-LY trial, 37.4% of all deaths and 60.4% of cardiac deaths were attributed to either sudden cardiac death or death because of progressive HF.[242] For comparison, only 9.8% of all deaths were attributed to stroke or hemorrhage.

A meta-analysis of antithrombotic studies has shown that oral anticoagulation reduced risk of all-cause mortality with an absolute risk reduction of 1.6% when compared with control or placebo.[243] In anticoagulated patients with AF, increased mortality is largely driven by cardiovascular

causes rather than nonhemorrhagic stroke or systemic embolism.[242,244–246] Strokes comprised a small portion of deaths from AF. In the ROCKET AF trial, cardiovascular deaths occurred over 2× more often than strokes.[244] Predictors of higher all-cause mortality included HF (HR, 1.51; 95% CI, 1.33–1.70) and age ≥75 (HR, 1.69; 95% CI, 1.51–1.90). Thus, further advances in anticoagulation strategies may have little effect on improving overall mortality in AF.

## Conclusions

Over the past 50 years, the FHS and other epidemiological studies have yielded a breadth of data associating various RFs with risk of AF and providing insight into their mechanistic link to AF genesis. However, many questions remain. Will genetic studies improve AF risk assessment, identify novel therapeutic targets, and help guide treatment strategies for both primary and secondary prevention of AF? By what degree does RF modification alter the atrial substrate, AF burden, and clinical outcomes? What are the target goals for RF modification and how will genetics alter these targets? Ongoing and future epidemiological, translational, and clinical studies may provide insight into these unanswered questions and improve clinical outcomes in patients with AF.

## Sources of Funding

This work was supported by Velux Foundation and Boston University School of Medicine and the National Heart, Lung, and Blood Institute Framingham Heart Study (contract: NIH/NHLBI N01-HC25195l; HHSN268201500001I; 2R01HL092577; 1R01HL128914; and 1P50HL120163).

## Disclosures

L. Staerk has received research funding from Boehringer Ingelheim. The other authors report no conflicts.

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