Atrial Fibrillation in the 21st Century: A Current Understanding of Risk Factors and Primary Prevention Strategies

Arthur R. Menezes, MD; Carl J. Lavie, MD; James J. DiNicolantonio, PharmD; James O’Keefe, MD; Daniel P. Morin, MD, MPH; Sammy Khatib, MD; and Richard V. Milani, MD

Abstract

Atrial fibrillation (AF) is the most common arrhythmia worldwide, and it has a significant effect on morbidity and mortality. It is a significant risk factor for stroke and peripheral embolization, and it has an effect on cardiac function. Despite widespread interest and extensive research on this topic, our understanding of the etiology and pathogenesis of this disease process is still incomplete. As a result, there are no set primary preventive strategies in place apart from general cardiology risk factor prevention goals. It seems intuitive that a better understanding of the risk factors for AF would better prepare medical professionals to initially prevent or subsequently treat these patients. In this article, we discuss widely established risk factors for AF and explore newer risk factors currently being investigated that may have implications in the primary prevention of AF. For this review, we conducted a search of PubMed and used the following search terms (or a combination of terms): atrial fibrillation, metabolic syndrome, obesity, dyslipidemia, hypertension, type 2 diabetes mellitus, omega-3 fatty acids, vitamin D, exercise toxicity, alcohol abuse, and treatment. We also used additional articles that were identified from the bibliographies of the retrieved articles to examine the published evidence for the risk factors of AF.

Our understanding of atrial fibrillation (AF) has developed over the centuries, from Maimonides, Wenkebach, and MacKenzie to Einthoven and Sir Thomas Lewis. Today, insights into the pathogenesis of and treatment options for AF are rapidly evolving, and a PubMed search yields thousands of results on this topic.

Atrial fibrillation is the most common sustained arrhythmia worldwide, and it has a significant effect on morbidity and mortality rates. Moreover, from age 40 years and older, the lifetime risk of AF is 26%. Currently, it is estimated that approximately 2.3 million adults in the United States have AF, and it is projected that this number will increase to 5.6 million to 15.9 million individuals by 2050.3,3 It has been shown that there is a steep age-related increase in the risk of stroke in patients with AF, ranging from 1.5% at age 50 to 59 years to 23.5% at age 80 to 89 years.7

Despite established associations between AF and other cardiovascular (CV) disease processes, such as coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), hypertension (HTN), heart failure (HF), and valvular heart disease, in some patients, the underlying etiology is unknown.8 In these instances, the condition is termed lone AF (LAF) and is present in approximately 3% to 11% of all patients with AF.9

Our current understanding of the pathogenesis of AF is incomplete, and, as a result, we lack specific primary preventive strategies. Thus far, our most viable options for preventing stroke associated with AF have included modification of general CV risk factors and use of systemic anticoagulation drug therapy.10 Although connections have been made between AF and risk factors such as age, HTN, T2DM, HF, and
a few others (Figure), many patients with AF do not fall into any of these categories. As a result, the scientific community is continuously trying to unearth new risk factors for this disease process. A better understanding of the pathogenesis of AF improves the prospect of finding and developing better prevention measures.

The goals of this article are to provide an overview of established risk factors for AF and to discuss newer proposed risk factors. Based on this, we also explore potential primary preventive strategies that may potentially decrease the risk of AF (Table 1). However, note that it is beyond the scope of this article to discuss invasive approaches to the management and treatment of AF.

For this review, we conducted a search of PubMed using the following search terms (or a combination of terms): atrial fibrillation, metabolic syndrome, obesity, dyslipidemia, hypertension, type 2 diabetes mellitus, omega-3 fatty acids, vitamin D, exercise toxicity, alcohol abuse, and treatment. We also used additional articles that were identified from the bibliographies of the retrieved articles to examine the published evidence for the risk factors of AF.

**GENETIC IMPLICATIONS**

There is evidence to suggest that parental AF increases the risk of AF in the offspring. In 2004, data from the Framingham Heart Study showed that AF in at least one parent increased the risk of AF in the offspring (odds ratio [OR], 1.85; \( P = .02 \)). This heightened risk of AF among the progeny was independent of established AF risk factors, such as HTN and T2DM.\(^{11}\) Similarly, an Icelandic study demonstrated strong evidence of heritability of AF between individuals with AF and first- to fifth-degree relatives. According to the study, first-degree relatives of individuals younger than 60 years with AF were nearly 5 times more likely to have AF compared with the general population.\(^{12}\)

It has been determined that up to 30% of patients with AF have no underlying cause and are said to have LAF,\(^{13}\) which seems to have an even greater heritability component than AF associated with a known risk factor.\(^{14}\) A 2005 study demonstrated that relatives of probands with LAF have a markedly increased risk of AF.\(^{15}\) Another study showed that 15% of probands had a first- or second-degree relative with a family history of AF.\(^{16}\)

Furthermore, monozygotic twins have been shown to have an increased risk of AF compared with dizygotic twins (concordance rates, 22% vs 12%; \( P < .001 \)), suggesting a strong genetic component.\(^{17}\)

**AGE AND SEX**

The risk of AF increases with increasing age and is uncommon in individuals younger than 50 years.\(^{3}\) After the sixth decade of life, the prevalence of AF doubles approximately every 10 years, from 0.5% at age 50 to 59 years to almost 9% at age 80 to 89 years.\(^{18}\) In fact, approximately 70% of individuals with AF are aged 65 to 85 years.\(^{19}\) Furthermore, the age-adjusted prevalence of AF is higher in men than in women.\(^{20,21}\)

**METABOLIC SYNDROME**

Metabolic syndrome consists of a group of risk factors that have been shown to be associated with a higher risk of atherosclerotic CV disease.
These CV and metabolic disturbances include central obesity, HTN, insulin resistance, a decreased high-density lipoprotein cholesterol (HDL-C) level, and hypertriglyceridemia. Metabolic syndrome (MetS) is a growing epidemic in the United States and currently has a prevalence of approximately 20%. Recently, multiple studies have shown an association between MetS and AF. In addition, MetS and most of its components have been shown to increase the risk of AF in white and African American patients. Finally, in addition to the role of MetS as a risk factor for AF, patients with MetS and nonparoxysmal AF tend to have no response to single catheter ablation more frequently than do patients without MetS. We review each of the components of MetS and subsequently their effect on AF.

Obesity
Multiple studies have shown an association between obesity and AF. Although the pathogenesis for this is unclear, a correlation between the two has been demonstrated. Left atrial (LA) enlargement is a known precursor of AF and subsequent CV prognosis and overall mortality, and obesity has been strongly linked to LA size. Obesity has also been shown to be an independent predictor of ventricular diastolic dysfunction, which is also a risk factor for AF.

A prospective, community-based, observational cohort study evaluated 5282 participants (mean ± SD age = 57 ± 13 years; 2898 women [55%]) without baseline AF. At mean follow-up of 13.7 years, 526 participants (234 women) had AF. The study observed a 4% increase in AF risk per 1-U increase in body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) in men and women.

This effect of obesity on AF was also shown in a meta-analysis of 16 studies that included 123,249 individuals. The study demonstrated that obese individuals have a 49% increased risk of AF compared with nonobese individuals. Similar results were observed in another study that evaluated a large cohort of women for the relationship between changes in BMI and incident AF. In that study, women in whom obesity developed during 60-month follow-up demonstrated a 41% increase in AF risk compared with women who maintained a BMI of less than 30.

In part because of the association between AF and BMI, a study published in 2008 attempted to determine whether obesity was a risk factor for the progression of paroxysmal AF to permanent AF. The study evaluated 3248 patients (mean ± SD age = 71 ± 15 years; 54% men) diagnosed as having paroxysmal AF. During median follow-up of 5.1 years, 557 patients (17%) progressed to permanent AF (unadjusted incidence, 36 per 1000 person-years). After adjusting for age and sex, BMI independently predicted progression to permanent AF (hazard ratio [HR], 1.04; P < .0001). Compared with normal BMI (18.5-24.9), obesity (30.0-34.9) and severe obesity (≥35.0) were associated with an increased risk of progression to permanent AF (HR, 1.54 [P = .0004] and 1.87 [P < .0001], respectively).

A recently published study aimed to investigate the relationship between AF recurrence, AF burden, and BMI. Data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial were used. The study observed that in the 2518 patients who had their
BMIs recorded, higher BMI was associated with more electrical cardioversions (ECVs) (OR, 1.017, 1.088, and 1.183 for a BMI increase of 1, 5, and 10, respectively). Furthermore, the authors observed that an increased BMI was also associated with a higher likelihood of having AF on follow-up. However, in contrast to the previously mentioned studies, multivariable analysis of the data in this study showed that LA size, not BMI, was an independent predictor of AF recurrence and AF burden. Because LA size has been shown to be correlated with BMI, the effects of BMI on AF can most likely be explained by greater LA size in patients with higher BMIs.

A few small studies have recently suggested that atrial electromechanical delay, frequently present in more obese patients, may be an early predictor of AF development. A small study of 40 obese and 40 normal-weight individuals with normal coronary angiogram results evaluated whether atrial electromechanical delay measured by tissue Doppler imaging was an early predictor of AF in obese patients. It was observed that mean ± SD interatrial and intra-atrial electromechanical delays were significantly longer in obese individuals compared with controls (44.08±10.06 vs 19.35±5.94 ms and 23.63±6.41 vs 5.13±2.67 ms, respectively; P<.0001 for both). They also observed that mean ± SD P-wave dispersion, an electrocardiographic marker that has been independently associated with AF, was higher in obese individuals (53.40±5.49 vs 35.95±5.93 ms; P<.0001). Last, interatrial electromechanical delay was correlated with P-wave dispersion (P=.009).

Among the various components of MetS, obesity appears to be the most strongly related to the development of AF. Furthermore, obesity may increase the risk of AF recurrence after ECV and increase the risk of progression of paroxysmal AF to permanent AF.

### Type 2 Diabetes Mellitus

The relationship between AF and T2DM has been controversial, and various studies have demonstrated conflicting results. The Valsartan Antihypertensive Long-term Use Evaluation trial evaluated the influence of new-onset T2DM on the development of new-onset AF. Of the 15,245 participants in the trial, 5250 had T2DM at baseline. During 4.2-year follow-up, 1298 of the initially nondiabetic patients were diagnosed as having T2DM, and 551 of these patients had new-onset AF, demonstrating that patients with new-onset T2DM had significantly higher rates of new-onset AF compared with patients without T2DM. Patients with new-onset T2DM also had more persistent AF.

Although most studies have demonstrated a direct correlation between T2DM and AF, no specific mention has been made of the duration of persistent T2DM necessary to pose a risk for the development of AF. A recent population-based case-control study of approximately 3600 participants suggested that persistent uncontrolled T2DM (based on hemoglobin A1c level) might pose a cumulative risk of AF initiation. Of the 1410 patients with AF, 252 (17.9%) had T2DM compared with 311 of the 2203 controls (14.1%). The adjusted OR for AF was 1.40 for those with T2DM compared with those without T2DM. It was also observed that the risk of AF was 3% higher for each additional year of persistent T2DM. Furthermore, the study demonstrated that compared with patients without T2DM, the OR for AF in patients with T2DM increased with increasing hemoglobin A1c levels. This finding suggests that strict long-term glucose control may play a significant role in decreasing the incidence of new-onset AF.

In addition to an increased risk of AF, a recent study suggested that patients with T2DM and concomitant AF have an increased risk of CV events and death. The largest study of its kind, Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation evaluated 11,140 patients with T2DM, 7.6% of whom had AF at baseline. During follow-up of 4.3 years, the study group evaluated and compared total mortality and CV disease outcomes between patients with and without AF at baseline. After multiple adjustments, AF was associated with a 61% greater risk of all-cause mortality and increased risks of CV death, stroke, and HF in patients with T2DM.

Despite the evidence presented, the correlation between T2DM and AF is disputable because of the presence of various studies that have not demonstrated any significant association between the two. In 1994, data from the Framingham Heart Study demonstrated that T2DM was associated with an increased risk of AF (ORs, 1.4 for men and 1.6 for women). However, a later analysis of
Framingham Heart Study data, published in 2009, did not show any statistically significant association between the two.\textsuperscript{51} This disparity may be due to the fact that the primary goal of the latter study was to develop a risk stratification score to predict an individual’s absolute risk of AF, not to evaluate the association between AF and T2DM.

Another example involves a population-based cohort study that used the General Practice Research Database in the United Kingdom and attempted to (1) estimate the incidence rate of AF, (2) identify predisposing factors for this condition, and (3) describe treatment patterns.\textsuperscript{52} Although they demonstrated that age, high BMI, valvular heart disease, HF, and excessive alcohol consumption were major risk factors for AF, the study did not show any significant association with T2DM. One of the most significant limitations of the study that may account for these findings is the small population size of individuals with T2DM (n=73) compared with the overall study group comprising 1035 participants in the AF arm and 5000 in the control group. Furthermore, the study evaluated only patients with chronic AF, thus rendering the study ineffective in evaluating the role of new-onset T2DM in AF.

Similarly, a study consisting of 1739 patients (798 men and 941 women) evaluated the prevalence of AF in patients with T2DM and HTN.\textsuperscript{53} Patients were categorized as those with only HTN (n=597), those with both HTN and T2DM (n=171), and those with only T2DM (n=147). The study showed that the adjusted ORs were 0.7 in patients with HTN only, 3.3 in those with HTN and T2DM, and 2.0 (95% CI, 0.9-4.7) in patients with T2DM only, suggesting no statistically significant association between T2DM and AF. Although this was a well-conducted study, the non–statistically significant finding was most likely secondary to the small population size of the overall study group and the T2DM cohort, especially compared with the much larger studies mentioned earlier that did demonstrate a correlation between T2DM and AF.

There is a large amount of data to suggest that T2DM is strongly associated with an increased risk of AF. Furthermore, the duration of T2DM prevalence may also increase the risk of AF. However, although there is convincing evidence to suggest a correlation between T2DM and AF, there also exists evidence to suggest that there may be no significant association between the two. Although it is impossible to completely explain this discordance, possible reasons include methodologic differences such as failure to adjust for covariants (such as obesity) and insufficient sample size. Furthermore, many of these studies were not designed to specifically study the effects of T2DM.

**Dyslipidemia**

Dyslipidemia, a major CV disease risk factor, has been shown to have a role in the development of AF. However, although most of these studies have demonstrated a correlation between decreasing HDL-C levels and AF,\textsuperscript{16} the impact of triglyceride levels on AF has been less apparent.

A Japanese study evaluated 28,449 individuals without AF at baseline from the general population using annual health examinations to assess the association between lipid profiles and the risk of new-onset AF.\textsuperscript{54} They found that low levels of HDL-C were associated with the development of AF in women but not in men. The study concluded that women had a 28% higher risk of AF with each 10% decrease in HDL-C level. However, they did not demonstrate a significant correlation between triglyceride levels and AF.

Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial also demonstrated that AF was significantly more prevalent in individuals with HDL-C levels less than 35 mg/dL (to convert to mmol/L, multiply by 0.0259) (P<.01).\textsuperscript{35} Another study analyzed 13,969 participants without AF at baseline from the Atherosclerosis Risk in Communities study. Fasting HDL-C, low-density lipoprotein cholesterol (LDL-C), triglyceride, and total cholesterol levels were measured at baseline and at 3 subsequent follow-up visits.\textsuperscript{56} Multivariable HRs (95% CIs) of AF associated with a 1-SD increase in lipid levels were as follows: 0.97 (0.91-1.04) for HDL-C, 0.90 (0.85-0.96) for LDL-C, 0.89 (0.84-0.95) for total cholesterol, and 1.00 (0.96-1.04) for triglycerides. This suggests that elevated levels of LDL-C and total cholesterol were associated with a lower incidence of AF, whereas HDL-C and triglyceride levels were not independently associated with AF.
Despite the previously mentioned association between elevated LDL-C and total cholesterol levels and AF, the relationship between statin therapy and AF is controversial.57 A meta-analysis of 20 studies with 23,577 patients demonstrated that statin therapy was associated with a significantly decreased risk of AF compared with the control group.58 Furthermore, this beneficial effect was observed in the atorvastatin and simvastatin subgroups but was not seen in the pravastatin and rosuvastatin subgroups. However, several longer-term studies of more intensive statin therapy vs standard statin regimens (28,964 randomized patients and 1419 events) showed no evidence of a reduced risk of AF.59 Finally, note that statin therapy may lower the risk of recurrent AF after ECV.60 However, this is controversial61 and further studies are necessary.

In conclusion, although a few studies demonstrate an association between lower levels of HDL-C and risk of AF, the impact of dyslipidemia on AF is uncertain owing to discordance among the various studies.

Hypertension
Uncontrolled HTN is one of the most commonly known risk factors for AF.62 Although the mechanism behind this is not fully understood, the development of AF in these patients is most likely secondary to atrial remodeling secondary to activity of the renin-angiotensin-aldosterone system.63 Currently, there is no clear evidence to suggest an optimal blood pressure (BP) to decrease the risk of AF.

A recent study demonstrated that the pulse pressure was an important determinant of the incidence of AF.64 The study included 5331 Framingham Heart Study participants 35 years and older and initially free of AF. Incidence rates of AF were 5.6% for pulse pressure of 40 mm Hg or less (25th percentile) and 23.3% for pulse pressure greater than 61 mm Hg (75th percentile). After adjusting for various risk factors, pulse pressure was associated with an increased risk of AF (HR, 1.26 per 20-mm Hg increment). Furthermore, it was observed that mean arterial pressure was unrelated to incident AF (HR, 0.96 per 10-mm Hg increment). However, systolic BP was related to AF (HR, 1.14 per 20-mm Hg increment).

There have been other studies that have shown a correlation between systolic BP and incident AF.65,66 A recently published article evaluated 34,221 women from the Women’s Health Study for incident AF based on risk factors such as systolic and diastolic BP.67 They observed 644 incidents of new-onset AF during 12.4-year follow-up. The authors concluded that systolic and diastolic BP significantly increased the long-term risk of AF. The multivariable-adjusted HRs for the systolic BP categories (<120, 120-129, 130-139, 140-159, and ≥160 mm Hg) were 1.0, 1.00, 1.28, 1.56, and 2.74, respectively. The adjusted HRs for the diastolic BP categories (<65, 65-74, 75-84, 85-94, and ≥95 mm Hg) were 1.0, 1.17, 1.18, 1.53, 1.35, and 2.15, respectively. This suggests that among women, elevated systolic BP is a long-term risk factor for AF and a better predictor of incident AF than is diastolic BP. The study hypothesized that this association with low systolic BP may have been secondary to unmeasured confounders in participants with low systolic BP, such as atherosclerosis, CHD, and a history of myocardial infarction.

Because HTN is an established risk factor for AF, an important question arises: Would varying degrees of BP control affect the risk of incident AF? A case-control study was conducted to explore the relationship between BP control and risk of AF, with follow-up of approximately 2 years in patients with no initial history of AF.68 All the patients were pharmacologically treated for HTN for at least 30 days before the index date (the date on which AF was first diagnosed). For average achieved systolic BP of less than 120, 130 to 139, 140 to 149, 150 to 159, 160 to 169, and 170 mm Hg or more, the ORs for incident AF were 1.99, 1.19, 1.40, 2.02, 2.27, and 1.84, respectively. It was estimated that in patients with treated HTN, 17.2% of incident AF was attributable to an average achieved systolic BP of 140 mm Hg or greater. In addition, evaluation of the data also suggests that in addition to elevated systolic BP, a systolic BP less than 120 mm Hg also increased the risk of incident AF.

Obstructive Sleep Apnea
Obstructive sleep apnea (OSA) is a common health concern and plays a role in many disease processes, including AF.69,70 This association between OSA and AF seems to be independent of HTN, BMI, and cardiac function.71
Approximately half of all patients presenting with AF have OSA (although many are unaware of their sleep-disordered breathing). The mechanisms behind this very strong association between OSA and AF remain speculative but likely relate to disturbed autonomic tone, hypoxia, and atrial stretch. A recent study suggested that atrial remodeling associated with OSA may be responsible for the development of AF secondary to reduction in atrial myocardial voltage, site-specific and widespread conduction abnormalities, and longer sinus node recovery. Apnea-induced stretch in the atrium and pulmonary veins may also result in drastic changes in transmural pressure that may further result in atrial dilation and, subsequently, AF. It has also been suggested that negative tracheal pressure during obstructive events is a strong trigger for AF secondary to enhanced vagal activation. Other theories on the relationship between OSA and AF include higher levels of serum amyloid and elevated levels of inflammatory markers, such as C-reactive protein and interleukin 6.

In addition to the increased risk of AF in patients with OSA, a recent study has shown that patients with severe OSA and AF are less likely to respond to antiarrhythmic drug (AAD) therapy compared with patients with milder forms of OSA. The study evaluated the impact of OSA severity on the treatment of patients with AF using AADs. This investigation included 61 patients with symptomatic AF who were treated for AF with AADs and underwent overnight polysomnography. They found that nonresponders to AAD therapy were more likely to have severe OSA compared with patients with milder forms of the disease (52% vs 23%; P < .05). Furthermore, nonresponders had higher mean ± SD apnea-hypopnea indexes than responders (34±25 vs 22±18 events per hour; P = .05). There was no difference between these groups with respect to minimum oxygen saturation or percentage of time spent in rapid eye movement sleep.

Similarly, findings from a recent meta-analysis suggest that patients with OSA have a greater risk of recurrence of AF after pulmonary vein isolation. The meta-analysis included 6 studies and 3995 patients and determined that patients with OSA have a 25% greater risk of AF recurrence after catheter ablation than those without OSA. Furthermore, OSA diagnosed using polysomnography was a much stronger predictor of AF recurrence compared with OSA diagnosed using the Berlin questionnaire. The study investigators determined that the presence of severe OSA was an independent risk factor for AF ablation failure.

Fortunately, evidence suggests that patients with OSA treated with continuous positive airway pressure have a lower recurrence rate of AF after ECV compared with untreated patients, with the risk returning to approximately that of control patients.

Obstructive sleep apnea is a well-established risk factor for AF. As mentioned earlier in this section, there are many possible and probable mechanisms for this. It is important to consider that patients with severe OSA and AF may have a decreased response to AAD therapy compared with patients with milder forms. Furthermore, the presence of untreated OSA may be a predictor of AF ablation failure.

**ALCOHOL CONSUMPTION**

For several decades, alcohol consumption has been considered a potential cause of AF. One of the earliest descriptions of alcohol-induced arrhythmias was in 1978 by Ettinger et al and was called **holiday heart syndrome**. This syndrome was first described in typically healthy individuals with heavy alcohol consumption who typically presented with AF after holidays or on weekends. However, this type of AF has been shown to likely convert to normal sinus rhythm in approximately 24 hours. Regardless, since then there have been multiple studies that have demonstrated the arrhythmogenic properties of alcohol consumption.

A recent meta-analysis showed that compared with nondrinkers, women consuming 24, 60, and 120 g of ethanol (a standard alcoholic drink contains approximately 12 to 15 g of ethanol) daily had AF-related relative risks (RRs) of 1.07, 1.42, and 2.02, respectively. Similarly, among men, the corresponding RRs were 1.08, 1.44, and 2.09.

The Framingham Study did not demonstrate a statistically significant association between long-term moderate alcohol consumption and risk of AF. However, in individuals consuming more than 36 g/d (approximately >3 drinks daily), there was a significantly increased risk of AF. Another large study evaluated the risk of
alcohol-induced AF specifically in women. They found that consumption of fewer than 2 alcoholic drinks per day was not associated with an increased risk of AF. However, consumption of 2 or more drinks per day was associated with a small, but statistically significant, increased risk of AF (HR, 1.60).

The Copenhagen City Heart Study concluded that consumption of 35 or more alcoholic drinks per week among men was associated with an HR of 1.45. According to the study, approximately 5% of all cases of AF are related to alcohol consumption.

Finally, the meta-analysis by Kodama et al shows a direct relationship between alcohol dose and future AF, with an 8% increase in AF risk for every 10-g (approximately two-thirds to three-quarters of an alcoholic drink) increase in alcohol daily dose. Considering this and other information suggesting beneficial effects of small doses of alcohol for CV disease prevention, not related to AF, it seems prudent to recommend consuming only low doses of alcohol (eg, 1-2 drinks per day for larger people and probably only 1 drink per day for smaller people.) In patients with a high risk of AF, consideration should be given to keeping alcohol doses very low (eg, <1 drink per day). Note that the impact of light alcohol consumption on the development of AF is still unclear. Further studies are needed to assess this association.

In conclusion, there seems to be a large amount of data that supports the correlation between alcohol consumption and AF. This relationship is dose dependent, with higher amounts of alcohol associated with an increased risk of AF, although there may be some increase in AF even at low doses of alcohol.

PHYSICAL EXERTION

Many studies have demonstrated the beneficial effects of exercise on CV health. Multiple small studies have also demonstrated a relationship between vigorous physical activity, related to either long-term endurance sport participation or occupational activities, and increased risk of AF. We recently reported the potential cardiotoxicity of extreme levels of endurance exercise. Among athletes, AF is the most common pathologic arrhythmia. The association between endurance sports and AF was described in a longitudinal prospective study published in 1998. The study evaluated a series of orienteers (athletes who participate in vigorous cross-country skiing) over a 10-year period. They observed an RR for AF of 5.5 (95% CI, 1.3-24.4) in the orienteers. Furthermore, the rate of AF in the orienteers was 5.3% (95% CI, 2.8%-9.0%) compared with 0.9% (95% CI, 0.1%-3.4%) in the control group. They concluded that long-term vigorous exercise in men was associated with an increased risk of AF.

These findings have been confirmed in many subsequent studies. A study of 160 participants (51 patients with LAF and 109 controls from the general population) demonstrated that participation in more than 1500 lifetime hours of sports was associated with an increased risk of LAF (OR, 2.87; 95% CI, 1.20-6.91) compared with controls. Another study of 134 Swiss former professional cyclists demonstrated that these athletes, with a very high number of previous bicycling years, had a higher incidence of AF compared with the control group (P=.028).

CAFFEINE AND AF

Individuals with cardiac dysrhythmias are often advised to avoid drinking tea and coffee. However, there is a large body of scientific evidence to suggest that drinking moderate amounts of coffee and tea does not cause AF and may even decrease its occurrence. Still, many patients anecdotally report that caffeine, especially from excess coffee consumption, seems to precipitate AF spells.

A prospective study evaluated 33,638 initially healthy women who participated in the Women’s Health Study to assess the relationship between caffeine intake and incident AF. Participants were 45 years and older and free of CHD and AF at baseline. During median follow-up of 14.4 years, 945 AF events occurred. Median caffeine intakes across increasing quintiles of caffeine intake were 22, 135, 285, 402, and 656 mg/d, respectively. Using Cox proportional hazards models, the corresponding multivariable-adjusted HRs were 1.0, 0.88, 0.78, 0.96, and 0.89, respectively, suggesting no association between caffeine intake and AF in this cohort of women.

Finally, in a long-term observational study beginning in 1976, Klatsky followed up
130,000 patients in the Kaiser Permanente health system. He reported that consumption of 4 or more cups of coffee per day was associated with an 18% reduction in the risk of being hospitalized for rhythm disturbances, especially AF.\(^{111}\)

In conclusion, there seems to be no associated risk between caffeine intake and AF development. In fact, caffeine consumption may actually decrease the risk of AF.

**VITAMIN D LEVELS**

During the past few years, there has been growing interest regarding the role of vitamin D with respect to CV health.\(^{112,113}\) Deficiency in vitamin D has been linked to HTN,\(^{114,115}\) stroke,\(^{116,117}\) myocardial infarction,\(^{118}\) and other CV-related disease processes, such as T2DM.\(^{119}\)

Although inadequate levels of vitamin D are associated with CV disease, a recent study did not demonstrate an association between vitamin D deficiency and AF.\(^{120}\) In 2930 Framingham Heart Study participants without prevalent AF, vitamin D status was assessed by measuring 25-hydroxyvitamin D levels. The investigators observed that 25-hydroxyvitamin D levels were not associated with the development of AF. A multivariable-adjusted HR of 0.99 per 1-SD increment in 25-hydroxyvitamin D levels was observed. Finally, vitamin D levels have also been related to mental stress\(^{121,122}\) and to abnormal left ventricular geometry,\(^{123}\) both of which may be related to increased risk of AF. The Inter-Mountain Study, a long-term observational study, recently reported an increased risk of AF in individuals with very high vitamin D levels (>100 ng/mL [to convert to nmol/L, multiply by 2.496]).\(^{124}\)

**OMEGA-3 FATTY ACIDS AND AF**

Recent clinical and experimental studies have shown that omega-3 polyunsaturated fatty acids (N3-PUFAs) may be effective in preventing AF.\(^{125-127}\) However, this topic is still controversial and debated among experts.\(^{128}\)

A prospective, population-based cohort of 4815 individuals 65 years or older demonstrated that increased consumption of tuna and other broiled or baked fish 1 to 4 times a week was associated with a 28% lower risk of AF and a 31% lower risk when such fish were consumed at least 5 times per week (HR, 0.69; \(P \leq 0.008\)).\(^{129}\) However, note that this statistically significant reduction in AF was not observed with fried fish or fish burgers.

Similarly, 2174 men from the Kuopio Ischemic Heart Disease Risk Factor Study were evaluated over 17.7 years to determine the efficacy of N3-PUFAs in reducing the risk of AF in men.\(^{130}\) The study consisted of men aged 42 to 60 years and free of AF at baseline. Results demonstrated that higher serum concentrations of N3-PUFAs may be associated with a lower risk of AF in men.

However, another study of 5184 individuals did not find any association between high intake of fish and very long-chain PUFAs and incident risk of AF.\(^{131}\) In fact, no demonstrable decrease in AF risk was observed with intake of more than 20 g/d of fish compared with no fish intake. Note that in this study, fish intake was assessed using a self-administered food frequency questionnaire that was issued only 3 times during the mean ± SD 6.4±1.6-year study. This method calls into question the accuracy of the exact amount of fish consumed by the participants.

Similarly, a meta-analysis of 10 randomized controlled trials consisting of 1955 patients demonstrated no significant evidence of the beneficial effects of N3-PUFAs on the prevention of AF.\(^{132}\) Furthermore, subgroup analyses showed no significant beneficial effect of fish oils in any subset of the population. However, there was significant heterogeneity among the studies owing to differences in patient population, follow-up duration, and dosage, duration, and type of N3-PUFAs.

A recently published randomized, prospective, placebo-controlled trial involving 586 participants with symptomatic paroxysmal AF evaluated the role of N3-PUFAs in preventing the recurrence of AF.\(^{133}\) Participants were allocated to receive 1 g/d of N3-PUFA or placebo. After 12 months of follow-up, the data did not demonstrate a statistically significant difference between the 2 groups with respect to reduction in AF recurrence.

Furthermore, the evidence supporting the use of N3-PUFAs to prevent postoperative AF is also controversial. A recent meta-analysis of 4 randomized studies that included 538 patients did not demonstrate a significant reduction in postoperative AF associated with N3-PUFA use.\(^{134}\) The major limitation of the data is the clinical and statistical heterogeneity of the
included studies. To overcome this degree of heterogeneity, it would be necessary to conduct a large randomized study that was adequately powered. However, another study of 530 individuals demonstrated that preoperative use of N3-PUFAs was independently associated with a 46% reduction in the risk of early AF.135

The efficacy of N3-PUFAs in preventing the occurrence of AF after coronary artery bypass graft surgery has been evaluated in multiple studies.136,137 A prospective, randomized study of 160 patients randomized to a control group or to receive N3-PUFAs, 2 g/d, for at least 5 days before elective coronary artery bypass graft surgery and until the day of hospital discharge demonstrated a 54.4% reduction in postoperative AF and a reduced hospital stay.138

It is well known that persistent AF is associated with a moderately high rate of recurrence after ECV.139 In an open-label randomized study, 178 patients with persistent AF were assigned to either a control group or the N3-PUFAs group, 6 g/d of fish oil, to evaluate the efficacy of N3-PUFAs in preventing post-ECV AF recurrence.140 Participants underwent ECV 1 month after the start of oral therapy. At 90 days, the study demonstrated that 38.5% of patients receiving N3-PUFAs had AF recurrence compared with 77.5% of controls.

On the other hand, in another study, 204 patients with persistent AF were randomly assigned to receive either 3 g/d of N3-PUFAs until ECV and 2 g/d thereafter or placebo.141 The study did not demonstrate a statistically significant difference in AF recurrence. Furthermore, based on a study examining the use of omega-3 acid ethyl esters (LOVAZA) or placebo in 663 patients with symptomatic paroxysmal or persistent AF, the Food and Drug Administration changed the safety labeling for the drug to a mild warning about increased frequency of AF, especially during the first few months of drug use.142 This was due to the fact that the study observed a higher rate of recurrent AF (P=.08) among patients randomized to the LOVAZA group who received 8 g/d for 7 days and 4 g/d thereafter for 23 weeks compared with placebo.143

As mentioned earlier, the role of N3-PUFAs in the setting of AF is still controversial. Although some studies have demonstrated a lower incidence of AF recurrence with N3-PUFA use, others have shown an increased risk. Further studies are needed to assess the role of N3-PUFAs in the prevention of AF.

OTHER CAUSES OF AF

The most frequent cardiac complication of hyperthyroidism is AF, which occurs in approximately 10% to 15% of patients with this condition.144 A low serum thyrotropin level has also been determined to be an independent risk factor for AF.145 Similarly, patients with subclinical hyperthyroidism have nearly 3 to 5 times the likelihood of developing AF.146,147 The pathogenesis of this relationship is multifactorial and likely includes (but is not limited to) increased heart rate, increased sinoatrial node activity, and shortened atrial repolarization.148,149

There is also substantial evidence to suggest that mitral valve disease is significantly related to AF, although the prevalence rates of AF in mitral stenosis and mitral regurgitation are not similar, with mitral stenosis having a more significant relationship with AF than does mitral regurgitation.150,151 This finding may be secondary to the atrial structural remodeling that is associated with mitral valve disease.152 Furthermore, in patients with mitral regurgitation secondary to failed leaflets, the development of AF was independently associated with cardiac mortality and HF (RR, 2.23; P=.025).153 In a 13-year study evaluating 301 patients with rheumatic heart disease (RHD), AF was observed in 50% of the patients.154 This high prevalence of AF in patients with RHD has been demonstrated multiple times in the literature151,155,156 and is more commonly seen in the developing world owing to a higher incidence and prevalence of RHD in these areas.157,158 In addition to mitral valve disease, there is evidence to suggest that aortic stenosis also increases the risk of AF.159

MEDICATIONS TO REDUCE AF

Many drugs have been implicated in the primary and secondary prevention of AF. Although a detailed analysis of all these medications is beyond the scope of this review, which discusses risk factors for AF that are potentially amenable to nonpharmacologic interventions, we felt it was prudent to briefly mention a few.

The role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) in the prevention of AF is currently controversial, with some studies suggesting...
Consume omega-3 fatty acids or a diet rich in these polyunsaturated fatty acids

Consume moderate amounts of caffeine

Avoid strenuous exercise routines

Limit alcohol consumption to 2-3 drinks per day

Close supervision and management of patients with OSA

Maintain normal HDL-C levels

Blood pressure control

TABLE 2. Potential Strategies for the Prevention of Atrial Fibrillation\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (maintaining a BMI of 18-25)</td>
</tr>
<tr>
<td>Tight glucose control (hemoglobin A\textsubscript{1c} \textless \textasciitilde 7.0% of total hemoglobin)</td>
</tr>
<tr>
<td>Blood pressure control</td>
</tr>
<tr>
<td>Maintain normal HDL-C levels</td>
</tr>
<tr>
<td>Close supervision and management of patients with OSA</td>
</tr>
<tr>
<td>Limit alcohol consumption to 2-3 drinks per day</td>
</tr>
<tr>
<td>Avoid strenuous exercise routines</td>
</tr>
<tr>
<td>Consume moderate amounts of caffeine</td>
</tr>
<tr>
<td>Consume omega-3 fatty acids or a diet rich in these polyunsaturated fatty acids</td>
</tr>
</tbody>
</table>

\textsuperscript{a}BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; OSA = obstructive sleep apnea.

\textsuperscript{b}SI conversion factor: To convert hemoglobin A\textsubscript{1c} values to proportion of total hemoglobin, multiply by 0.01.

Finally, there is evidence to suggest that aldosterone antagonists may be beneficial in the primary and secondary prevention of AF. Spironolactone\textsuperscript{170} and eplerenone\textsuperscript{171} have been shown to be beneficial in this setting.

**NONPHARMACOLOGIC AF PREVENTION STRATEGIES**

In this review, we discussed many potential risk factors associated with AF development. A proper understanding and acknowledgment of these risk factors may allow primary care physicians and cardiologists to initiate preventive strategies and, thereby, potentially decrease the risk of AF (Table 2). As mentioned earlier, multiple studies have linked AF to MetS and to the various components of MetS\textsuperscript{24-28} Several studies have linked obesity to the development of AF in men and women\textsuperscript{28-30} Participation in weight loss programs may help decrease the risk of new-onset AF. Furthermore, tighter control of hemoglobin A\textsubscript{1c} levels in patients with T2DM, with a goal of 7\% of total hemoglobin or less (to convert to proportion of total hemoglobin, multiply by 0.01), may prevent development of AF\textsuperscript{46-48} Although there is no clear evidence linking dyslipidemia with AF, studies have shown that lower levels of HDL-C may be linked to AF\textsuperscript{54,55} Although the evidence supporting statin therapy for AF prevention is controversial at best, encouraging patients to increase their HDL-C levels through exercise, a heart-healthy diet, and increased N3-PUFA intake may help reduce the risk of AF in these patients. Niacin at pharmacologic doses (>500 mg/d) will raise the HDL-C level but has been shown to increase the risk of AF\textsuperscript{172} Finally, a strict BP control regimen may prove valuable in the prevention of incident AF\textsuperscript{56-58}

Abundant evidence suggests that patients with OSA have a much higher incidence of AF\textsuperscript{70} and may be refractory to ECV\textsuperscript{80,81} and AAD therapy.\textsuperscript{79} Evidence suggests that patients receiving continuous positive airway pressure therapy respond better to ECV\textsuperscript{82} Patients with suspected or untreated OSA should be encouraged to undergo sleep studies and appropriate therapy to potentially reduce the risk of AF development. Similarly, physicians should encourage patients to limit alcohol consumption to no more than 1 to 2 drinks per day (possibly considerably lower in higher-risk patients) as a preventive measure for AF\textsuperscript{92,93} It is important to consider that although mild to moderate

benefits\textsuperscript{160} and some disputing this.\textsuperscript{161} Post hoc analyses of 2 large HTN trials (the Losartan Intervention For End Point Reduction in Hypertension trial\textsuperscript{162} and the Valsartan AntiHypertensive Long-term Use Evaluation trial\textsuperscript{163}) demonstrated a preventive effect of ARBs on new-onset AF, whereas outcomes from other large trials (the Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation trial\textsuperscript{164} and the Gruppo Italiano per lo Studio della Sopravvenza nell’Infarto Miocardico-Atrial Fibrillation trial\textsuperscript{165}) have shown no benefit in the prevention of recurrent AF. Thus, although the use of ARBs in the prevention of primary AF is controversial, ARBs are likely not beneficial in the prevention of recurrent AF. Furthermore, the trials that did not show any benefit of ARBs in the prevention of recurrent AF were specifically designed to demonstrate this as an end point.\textsuperscript{164,165} On the other hand, most of the post hoc analyses that did show a beneficial effect of ARBs on reducing the rate of AF recurrence were not primarily designed to do so.\textsuperscript{162,163}

β-Blockers (BBs) also have been shown to decrease the incidence of AF in various settings. For example, a large meta-analysis demonstrated that compared with placebo, BBs significantly reduce the incidence of new-onset AF in patients with HF by 27\%.\textsuperscript{166} The BBs, especially carvedilol, also have been shown to significantly reduce the incidence of AF after coronary artery bypass graft surgery, even compared with other BBs, such as metoprolol.\textsuperscript{167,168} There also is evidence to suggest that the use of BBs may reduce the incidence of arrhythmias (including AF) in patients after myocardial infarction.\textsuperscript{169}
exercise may help with weight loss, evidence suggests that extreme levels of intense exercise seem to increase the risk of AF.98-99 The risk of AF seems to begin to increase with durations of vigorous aerobic exercise longer than 40 minutes daily, and so this may be a reasonable upper limit for those at high risk for AF.98-99 Because this outcome seems to result from long-term strenuous exercise, patients who participate in such activities should be warned about potential risks. Finally, contrary to popular belief, drinking moderate amounts of coffee and tea may have protective effects against the development of AF.107,110 However, this should be advised with caution in patients with HTN and CHD.

CONCLUSION
Atrial fibrillation is the most common arrhythmia worldwide, and it has a significant effect on morbidity and mortality. Although our current understanding of the pathogenesis of AF is incomplete, the last few decades have seen dramatic progress in this field. In addition to long-established risk factors for AF, such as MetS, OSA, and alcohol intake, newer etiologies, such as excessive physical activity, elevated vitamin D levels (>100 ng/mL), excessive niacin intake (>500 mg/d), and, possibly, high doses of N3-PUFAs, are being discovered. A better understanding of the etiology of AF better prepares the medical community to implement and endorse preventive measures.

Abbreviations and Acronyms: AAD = antiarrhythmic drug; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BB = β-blocker; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CV = cardiovascular; ECV = electrical cardioversion; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; HTN = hypertension; LA = left atrial; LAF = lone atrial fibrillation; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; N3-PUFA = omega-3 polyunsaturated fatty acid; OR = odds ratio; OSA = obstructive sleep apnea; RHD = rheumatic heart disease; RR = relative risk; T2DM = type 2 diabetes mellitus

Correspondence: Address to Carl J. Lavie, MD, FCCP, John Ochsner Heart and Vascular Institute, Ochsner Clinical School—The University of Queensland School of Medicine, 1514 Jefferson Hwy, New Orleans, LA 70121-2483 (clavie@ochsner.org).

REFERENCES
22. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart


ATRIAL FIBRILLATION IN THE 21ST CENTURY


137. KOEYER PR, REIFFEL JA, ELLENBogen KA, NACCARELLI GV, PRATT CM. Efficacy and safety of prescription omega-3 fatty acids for the


