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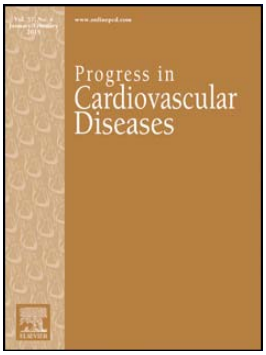

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Lifestyle Modification in the Prevention and Treatment of Atrial Fibrillation

Arthur R. Menezes, MD*, Carl J. Lavie, MD*, Alban De Schutter, MD*, Richard V. Milani, MD*, James O'Keefe, MD^, James J. DiNicolantonio, PharmD^, Daniel P. Morin, MD, MPH*, Freddy M. Abi-Samra, MD*.

* Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute. Ochsner Clinical School- The University of Queensland School of Medicine, New Orleans, Louisiana

^Mid America Heart Institute, Kansas City, Missouri

Corresponding author: Carl J. Lavie, M.D., FACC, FACP, FCCP

Medical Director, Cardiac Rehabilitation and Prevention

Director, Exercise Laboratories

John Ochsner Heart and Vascular Institute Ochsner Clinical School-The University of Queensland School of Medicine1514 Jefferson Highway New Orleans, LA 70121-2483

(504) 842-5874 Phone

(504) 842-5875 Fax

Email: clavie@ochsner.org

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia worldwide and has a significant impact on morbidity and mortality. Additionally, the incidence and prevalence of AF is expected to increase in the United States and worldwide over the next few decades. While the pathophysiology concerning the development of AF is not completely understood, multiple modifiable, as well as non-modifiable risk factors, for AF development have been discovered. The goal of this paper is to provide an overview of the modifiable risk factors that contribute to the development and recurrence of AF, in addition to discussing potential lifestyle changes that may aid in the prevention and treatment of AF.

Abbreviations:

A1c=Hemoglobin A1c

AAD=Anti-arrhythmic drug

ACEI=Angiotensin-converting enzyme inhibitors

AF=Atrial fibrillation

AHI=Apnea/hypopnea index

ARB=Angiotensin receptor blockers

BMI=Body mass index

BP=Blood pressure

CHD=Coronary heart disease

CI=Confidence interval

CPAP=Continuous positive airway pressure

CRF=Cardiorespiratory fitness

CV=Cardiovascular

CVD=Cardiovascular disease

DBP=Diastolic blood pressure

HF=Heart failure

HR=Hazard ratio

HTN=Hypertension

LVEF=Left ventricular ejection fraction

MET=Metabolic equivalent of task

MI=Myocardial infarction

OR=Odds ratio

OSA=Obstructive sleep apnea

PA=Physical activity

RFM=Risk factor management

RR=Relative risk

SBP=Systolic blood pressure

T2DM=Type 2 diabetes mellitus

US=United States

VHD=Valvular heart disease

Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, affecting approximately 1% of the world's population [1] possessing a 25% lifetime risk of AF in the United States [2]. Also, AF has a significant impact on morbidity and mortality, and significantly contributes to the disease burden due to symptoms, hospitalizations, and stroke[3,4].

The prevalence of AF in the United States is expected to increase from 5.2 million in 2010 to 12.1 million cases in 2030, owing largely to the expected increase in the incidence of AF from 1.2 million cases in 2010 to 2.6 million cases in 2030[3]. Furthermore, the estimated increase in the number of elderly individuals in the US over the next few decades most likely also contributes to the projected increase in the prevalence of AF. The age-adjusted prevalence of AF is more common in men than in women [4] and in Caucasians than in African Americans[5]. The prevalence of AF increases with increasing age, and it has been estimated that approximately 70% of individuals with AF are between the ages of 65 and 85 [6]. In addition to the increased prevalence of AF with advancing age, the risk of stroke with AF also increases with increasing age. Evidence demonstrates that there is a steep increase in the risk of stroke in patients with AF ranging from 1.5% at age 50-59 years to 23.5% at age 80-89 [7].

While certain risk factors/conditions, such as increasing age, sleep apnea, type 2 diabetes mellitus (T2DM), obesity, alcohol consumption, hypertension (HTN), heart failure (HF), coronary heart disease (CHD), chronic excessive strenuous endurance exercise, and valvular heart disease (VHD) have been associated with the development of AF, in some patients the underlying etiology is unknown [8,9] **(Table 1)**. Regardless, a significant proportion of the known AF risk factors are modifiable.

The goal of this paper is to provide an overview of established, modifiable risk factors for AF. Based on this, we will also explore potential lifestyle changes that may potentially decrease the risk of AF.

Obesity

Multiple studies have shown an association between obesity and AF [8]. Evidence suggests that large body size during youth, as well as weight gain from age 20 to midlife, are both independently associated with the development of AF [9]. Although the association between obesity and AF is multifactorial, one explanation involves left atrial (LA) size and volume[10], as LA enlargement is a known precursor of AF [11,12]. Furthermore, obesity has been strongly linked to LA size [13,14], as well as electrostructural remodeling, which has been associated with spontaneous and more persistent AF[15]. Additionally, data suggests that obesity is an independent predictor of left ventricular (LV) diastolic dysfunction, in all age groups from children as early as age 9 years to the elderly [16,17,18], which is a known risk factor for the development of AF [19,20].

A study published in 2010 demonstrated pericardial fat as another risk factor for incident AF[21]. The presence of pericardial fat has been associated with the presence of AF, AF chronicity, and symptom burden of AF [22]. Furthermore, pericardial fat was also found to be predictive of long-term AF recurrence after radiofrequency ablation [23]. Despite this, weight reduction has been associated with a reduction in pericardial adipose tissue[24].

A meta-analysis of 16 studies looking at a total of 123,249 individuals demonstrated that obese individuals have a 49% increased risk of developing AF compared to non-obese individuals (relative risk [RR] 1.49, 95% confidence interval [CI] 1.36-1.64) [25]. Importantly, a large, prospective, community-based observational cohort study demonstrated a 4% increase in AF risk per 1-unit increase in body mass index (BMI) in men (95% CI, 1%-7%; P = .02) and in women (95% CI, 1%-7%; P = .009) [26]. Furthermore, obesity has been associated with the risk of AF regardless of the presence or absence of metabolic syndrome[27].

In addition to the association between AF and BMI, evidence suggests that obesity may also be a risk factor for the progression of paroxysmal AF to permanent AF. Progression of AF has been associated with higher morbidity and mortality. Individuals who progressed from having first-detected or paroxysmal AF to persistent or permanent AF have been found to have higher rates of stroke, transient ischemic attack, myocardial infarction (MI), hospital admission, and death when compared to those individuals whose AF had not progressed[28]. A longitudinal cohort study of 3248 patients demonstrated that after adjusting for age and sex, BMI independently

predicted the progression to permanent AF (hazard ratio [HR] 1.04, CI 1.03-1.06; P < 0.0001) [29]. Compared with normal BMI (18.5-24.9 kg/m^2), obesity (30-34.9 kg/m^2) and severe obesity (>or=35 kg/m^2) were associated with increased risk for progression (HR 1.54,95% CI 1.2-2.0; P = 0.0004) and 1.87, 95% CI 1.4-2.5; P < 0.0001, respectively).

Similarly, an observational population-based cohort study demonstrated lower rates of progression of first-detected or paroxysmal AF to persistent or permanent AF in subjects with lower BMI. After adjusting for variables such as age, sex, T2DM, HTN, CHD, cerebral vascular accident, VHD, and HF, compared with normal BMI (18.5–24.9 kg/m^2), BMI levels of 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥ 40.0 kg/m^2 were associated with HRs of permanent AF of 1.26 (95 % CI: 0.92- 1.72); 1.35 (0.96- 1.91); 1.50 (0.97-2.33); and 1.79 (1.13- 2.84) [30].

Fortunately, recent evidence suggests that weight loss with avoidance of weight fluctuations is associated with a dose-dependent, long-term reduction in AF burden [31]. In fact, a reduction of body weight greater than 10% was found to be associated with a 6-fold (95% CI: 3.4-10.3, P<0.001) greater probability of arrhythmia-free survival when compared to those individuals who only lost 3-9% or <3% of body weight. However, of note, weight fluctuation of 5% or more partially offset the benefits with a 2-fold (95% CI: 1.0-4.3; P=0.02) increased risk of AF recurrence. Weight reduction, in addition to management of risk factors such as HTN, T2DM, OSA, alcohol use, and tobacco use has been associated with a greater reduction in AF symptom burden and severity when compared to risk factor management alone[32].

There is also evidence to suggest that physical activity (PA) is associated with a small reduction in the risk of incident AF, even in the presence of excess body weight[33,34]. Cardiorespiratory fitness (CRF) has recently been found to be predictive of arrhythmia-free survival with or without rhythm control strategies[35]. Here, baseline CRF, CRF gains [metabolic equivalent of task (METs) gain ≥2], and weight loss were associated with a greater probability of AF-free survival. In fact, METs gain ≥2 in CRF resulted in a 2-fold greater chance of arrhythmia-free survival.

Finally, among overweight patients, risk factor management (RFM), as per the guidelines set by the American Heart Association and the American College of Cardiology, has been associated with improved long-term success of AF ablation[36]. In this study, individuals with a BMI ≥27 kg/m^2 and ≥1 CHD risk factor were offered RFM in addition to AF ablation. At follow-up, the

RFM group experienced significantly less AF frequency, duration, and symptoms, when compared with the control group ($P < 0.001$). Furthermore, single-procedure drug-unassisted arrhythmia-free survival ($P < 0.001$), as well as multiple procedure arrhythmia free survival ($P = 0.004$) was markedly better in RFM patients compared with control subjects.

Obstructive Sleep Apnea (OSA)

The association between OSA and AF is well established and appears to be independent of HTN, BMI, and cardiac function[37]. There have been multiple studies that have demonstrated this relationship[38,39].

A recent study evaluated 6,841 individuals for OSA at a sleep clinic over a period of 11.9 years[40]. Age, BMI, HTN, T2DM, VHD, CHD or peripheral artery disease, HF, and chronic obstructive pulmonary disease were all univariate predictors of AF (all $P<0.001$). After multivariable analysis, independent predictors of AF included apnea/hypopnea index (AHI) >5/hour, and time with oxygen saturation less than 90%.

Although the exact mechanism behind the relationship between OSA and AF is not fully understood, a few mechanisms have been proposed. A recent study suggested that atrial remodeling associated with OSA may be responsible for the development of AF secondary to reduction in voltage, site-specific and widespread conduction abnormalities, and longer sinus node recovery[41]. OSA-related stretch in the atrium and pulmonary veins are often associated with increases in transmural pressure that may result in atrial and pulmonary vein dilation and subsequently AF [42]. It has also been suggested that negative tracheal pressure during obstructive events is a strong trigger for AF secondary to enhanced vagal activation [43]. Other theories on the relationship between OSA and AF include higher levels of serum amyloid [44], and elevated levels of inflammatory markers such as C-reactive protein [45] and interleukin-6 [46]

Moreover, in addition to the increased risk of AF in patients with OSA, a recent study has shown that AF patients with severe OSA are less likely to respond to anti-arrhythmic drug (AAD) therapy compared to patients with milder forms of OSA [47]. The study evaluated the impact of OSA severity on the treatment of patients with AF using AADs. They included 61 patients with

symptomatic AF who were treated with AADs and underwent overnight polysomnography. They found that individuals with severe OSA were less likely to respond to AADs when compared to those with milder OSA (39% vs 70%, P = 0.02). Furthermore, non-responders had higher AHI indexes than responders (34 ± 25 vs 22 ± 18 events/hour, P = 0.05). There was no difference between these groups with respect to minimum oxygen saturation or percentage of time spent in rapid eye movement sleep.

Additionally, a recent meta-analysis, which included 6 studies of 3,995 patients, suggests that patients with OSA have a greater risk of recurrence of AF even after pulmonary vein isolation [48]. Patients with OSA had a 25% greater risk of AF recurrence after catheter ablation than those without OSA (RR 1.25, 95% CI 1.08 to 1.45, P = 0.003). Furthermore, OSA diagnosed using polysomnography was a much stronger predictor of AF recurrence (RR 1.40, 95% CI 1.16 to 1.68, P = 0.0004) compared to OSA diagnosed using the Berlin questionnaire (RR 1.07, 95% CI 0.91 to 1.27, P = 0.39). In fact, the presence of severe OSA has been shown to be an independent risk factor for AF ablation failure [49].

Fortunately, evidence suggests that OSA patients treated with continuous positive airway pressure (CPAP) have lower rates of AF recurrence and better heart rate control when compared to untreated patients[50]. Patients with OSA on CPAP treatment were also less likely to progress to more permanent forms of AF compared with patients without CPAP [51].

Finally, evidence suggests that patients with untreated OSA have a higher rate of recurrence of AF after ablation when compared to CPAP users[52]. A meta-analysis of 5 studies involving 3,743 individuals with AF demonstrated that patients with OSA had a 31% greater risk of AF recurrence after catheter ablation when compared to those individuals without OSA (RR = 1.31)[53]. This risk increased by 57% among OSA patients without CPAP therapy (RR = 1.57). More importantly, CPAP users had a risk of AF recurrence similar to that of patients without OSA (RR = 1.25, P = 0.37). Furthermore, CPAP utilization in the setting of OSA is associated with a reduction in AF recurrence irrespective of whether they undergo PVI[54].

Hypertension

HTN is the most common cardiovascular (CV) disorder, and is a well-established modifiable risk factor for AF development [55,56,57]. There is evidence to suggest a correlation between systolic blood pressure (BP;SBP) and incident AF [58,59]. Data from the Women's Health Study suggests that among women, SBP, rather than diastolic BP (DBP), was a better predictor of incident AF [60]. Here, multivariable-adjusted HR for SBP categories (<120, 120 to 129, 130 to 139, 140 to 159, and > or =160 mm Hg) were 1.0, 1.14 (95% CI, 0.89 - 1.46), 1.37 (95% CI, 1.07 - 1.76), 1.71 (95% CI, 1.33 - 2.21), and 2.21 (95% CI, 1.45 - 3.36; P for trend <0.0001). By comparison, the adjusted HR for DBP categories (<65, 65 to 74, 75 to 84, 85 to 89, 90 to 94, and > or =95 mm Hg) were 1.0, 1.12 (95% CI, 0.82 - 1.52), 1.13 (95% CI, 0.83 - 1.52), 1.30 (95% CI, 0.89 - 1.88), 1.50 (95% CI, 1.01 - 1.88), and 1.54 (95% CI, 0.75 - 3.14) (P for trend=0.026).

The relationship between BP and AF may also be present among individuals with upper normal BP. A Norwegian study of 2014 healthy males followed for 35 years demonstrated that men with baseline SBP ≥140 mm Hg had a 1.60-fold (95% CI 1.15- 2.21) risk of developing AF, and those with upper normal SBP 128 to 138 mm Hg had a 1.50-fold (95% CI 1.10- 2.03) risk of AF, when compared to those individuals with SBP <128 mm Hg[61]. Furthermore, in this cohort, baseline DBP ≥80 mm Hg increased the risk of incident AF 1.79-fold (95% CI 1.28 - 2.59) compared with DBP <80 mm Hg.

Despite this, there are no clear guidelines recommending a target BP to reduce the risk of AF in patients with HTN. While there is evidence to suggest that elevated SBP increases the risk of developing AF, tightly controlled SBP (<120 mmHg) has also been shown to increase the risk of incident AF. These findings were observed in a case-control study that demonstrated that the odds ratio (OR) and CI for incident AF were 1.99 (1.10 -3.62), 1.19 (0.78 - 1.81), 1.40 (0.93 - 2.09), 2.02 (1.30 - 3.15), 2.27 (1.31 - 3.93), and 1.84 (0.89 - 3.80) among those individuals who had an average achieved SBP (with pharmacologic treatment) of <120, 130-139, 140-149, 150-159, 160-169, and > or =170 mm Hg, respectively[62]. Furthermore, post-hoc analysis from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial demonstrated a U-shaped relationship between BP and all-cause mortality among patients with

AF who were being treated for HTN. Here, the all-cause mortality increased when BP was reduced to < 110/60 mmHg [63].

Furthermore, pooled analysis from the AFFIRM and AF and Congestive HF trial (AF-CHF) trials demonstrated that elevated systolic BP was associated with increased rates of AF recurrence and overall AF burden among individuals with LV ejection fraction (LVEF) ≤40%[64]. Among these individuals, the recurrence rate of AF was higher among those with an SBP >140 mmHg when compared to those individuals with SBP 120-140 mmHg (HR 1.47; 95% CI 1.12-1.93, P = 0.005). In fact, among patients with LVEF ≤40%, the adjusted mean proportion of time spent in AF was 17.2% if SBP was <120 mmHg, 15.4% for SBP 120-140 mmHg, and 24.0% for SBP >140 mmHg (P = 0.025).

Although the underlying pathophysiology is not fully understood, the development of AF among patients is most likely related to atrial remodeling secondary to activity from the renin-angiotensin system[65]. Despite this, the data regarding the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the prevention or treatment of AF is conflicting and, as a result, these classes of medications are not routinely used in the management of AF.

A beneficial effect of ARBs on the development of new-onset AF was demonstrated in two post-hoc analyses of two large hypertension [Losartan Intervention For End Point Reduction in Hypertension trial (LIFE) and Valsartan Antihypertensive Long-term Use Evaluation Trial (VALUE)] trials. In the LIFE study, new-onset AF occurred in 6.6 per 1000 person years among patients randomized to losartan compared with 10.1 per 1000 person years among those randomized to atenolol (RR 0.67, 95% CI 0.55 - 0.83, P < 0.001). Despite similar BP reduction with both drugs, patients receiving losartan tended to stay in sinus rhythm longer (1,809 +/- 225 vs. 1,709 +/- 254 days from baseline, P = 0.057) than those receiving atenolol.

Similarly, data from the VALUE trial demonstrated that the incidence of new-onset AF was 3.67% with valsartan compared to 4.34% with amlodipine (unadjusted HR 0.843, 95% CI 0.713 - 0.997, P = 0.0455) [66]. Additionally, the incidence of persistent AF was 1.35% in the valsartan group compared to 1.97% in the amlodipine group (unadjusted HR 0.683, 95% CI 0.525 to 0.889, P = 0.0046).

A large meta-analysis of 11 studies and 56,308 patients demonstrated that ACEI's and ARB's

decreased relative risk of AF by 28% (95% CI 15% - 40%, P = 0.0002) [67]. However, this reduction in AF was limited to patients with LV systolic dysfunction and LV hypertrophy. No significant reduction in AF was seen in patients with HTN.

Conversely, other studies were unable to demonstrate any beneficial effect of ACEI's and ARB's in the prevention of AF. A small meta-analysis of four ACEI studies consisting of 355 patients, and six ARB studies consisting of 4040 patients demonstrated that while ACEI were statistically significant in preventing AF recurrence, ARB's did not show any effect in the prevention of AF [68]. However, the studies were individually very small and did not have a strong follow-up algorithm to recognize AF episodes.

The GISSI-AF trial was also unable to demonstrate any reduction in the incidence of AF between the valsartan group (51.4% AF recurrences in a 12-month follow-up) and the placebo group (52.1% of AF in a 12-month follow-up, P = non significant)[69].

Diabetes Mellitus

Diabetes mellitus, more commonly T2DM, and AF often coexist with up to 20% of AF patients also having T2DM[70]. There have been multiple trials that have demonstrated the relationship between T2DM and AF. Regardless, this relationship between AF and T2DM is still controversial and various studies have demonstrated conflicting results. A large meta-analysis of seven prospective cohort studies and four case control studies involving 108,703 cases of AF among 1,686,097 individuals demonstrated a 40% increased risk of AF among T2DM patients compared to those individuals without T2DM [71]. Similarly, data from an observational cohort study demonstrated that AF prevalence was greater among those patients with T2DM (3.6 vs. 2.5%, P < 0.0001) [72]. The incidence of AF development among patients with T2DM over 7.2 years was 9.1 per 1,000 person-years (95% CI 8.6-9.7) compared with 6.6 (95% CI 6.2-7.1) among patients without T2DM. After adjusting for multiple risk factors, T2DM remained associated with a 26% increased risk of AF among women (HR 1.26 95% CI 1.08-1.46) but was not a statistically significant factor among men (1.09, 95% CI 0.96-1.24).

Data from the VALUE trial population also demonstrated an association between T2DM and AF[73]. Here, of the 15,245 participants in the trial, 5,250 patients had T2DM at baseline. Over the 4.2 year follow-up period, 1,298 of the initially non-diabetic patients developed T2DM, and 551 patients developed new-onset AF over this time period. The study demonstrated that patients with new-onset T2DM had significantly higher rates of new-onset AF (HR 1.49, 95% CI 1.14 - 1.94, P = 0.0031) compared to patients without T2DM.

A recent population-based case-control study of approximately 3600 participants suggested that persistent, uncontrolled T2DM, based on hemoglobin A1c(A1c), might pose a cumulative risk on the initiation of AF[74]. Among the patients with AF (1,410 patients), 252 (17.9%) had T2DM compared to 311 (14.1%) of the controls (2,203 patients). The adjusted OR for AF was 1.40 (95% CI 1.15 to 1.71) for people with T2DM compared to those without T2DM. It was also observed that the risk of developing AF was 3% higher for each additional year of persistent T2DM (95% CI 1.0 to 6.0). Furthermore, the study demonstrated that compared to patients without T2DM, the OR for AF among those patients with T2DM increased with increasing A1c levels. Patients with an average A1c <or=7 was 1.06 (95% CI 0.74 to1.51); for A1c >7 but <or=8, 1.48 (1.09 to 2.01); for A1c >8 but <or=9, 1.46 (1.02 to 2.08); and for A1c >9, 1.96 (1.22 to 3.14). This suggests that strict long-term glucose control may play a significant role in decreasing incidence of new-onset AF.

Despite the evidence presented, the correlation between T2DM and AF is disputable. Data from the Framingham Heart Study, published in 2009, were unable show any statistically significant association between the AF and T2DM[75]. The presence of AF among patients with T2DM and HTN was evaluated in another study consisting of 1739 individuals (798 men, 941 women)[76]. Patients were categorized as either having HTN (n = 597), both HTN and T2DM (n = 171), or only T2DM (n = 147). The adjusted OR and 95% CI were: 0.7 (0.30-1.5) among the patients with HTN only, 3.3 (1.6-6.7) among those patients with HTN and T2DM, and 2.0 (0.9-4.7) among patients with T2DM only; suggesting no statistically significant association between T2DM and AF.

Based on these data, the presence and duration of T2DM contribute to the development of AF.

Furthermore, as mentioned above, patients with A1c >7.0 appear to be at a higher risk of AF than those with A1c < 7.0. Therefore, strict overall blood glucose control to achieve an A1c <7.0 would seem advisable.

Alcohol Consumption

"Holiday heart syndrome" is one of the oldest descriptions of alcohol-induced arrhythmias[77]. It was first described in generally healthy individuals who presented after holidays or weekends involving heavy alcohol consumption. In these instances, conversion to normal sinus rhythm occurred in approximately 24 hours[78]. Since then, there have been multiple studies that have demonstrated the arrhythmogenic properties of alcohol consumption[79] and a positive relationship between high alcohol consumption and AF[80]. The Copenhagen City Heart Study concluded that among men, consumption of ≥35 alcoholic drinks per week was associated with an increased risk of AF development (HR of 1.45;95% CI 1.02- 2.04) [81]. Furthermore, the study concluded that approximately 5% of all cases of AF are related to alcohol consumption. A meta-analysis published in 2010 demonstrated that compared to nondrinkers, women consuming 24, 60 and 120 grams of alcohol daily (approximately 2,5, and 10 drinks per day, respectively) had a RR of 1.07 (95% CI: 1.04–1.10), 1.42 (95% CI: 1.23–1.64) and 2.02 (95% CI: 1.60–2.97), respectively [82]. Similarly, the corresponding RR were 1.08 (95% CI: 1.04–1.11), 1.44 (95% CI: 1.23–1.69) and 2.09(95% CI: 1.52–2.86) among men.

A large prospective study followed 79,019 Swedish men and women over a 12 year period to assess the association between low to moderate alcohol consumption and AF[83]. Compared to those individuals who consumed <1 drink/week (12 g alcohol/drink), the multivariable RR of AF were 1.01 (95% CI: 0.94 - 1.09) for 1 to 6 drinks/week, 1.07 (95% CI: 0.98 - 1.17) for 7 to 14 drinks/week, 1.14 (95% CI: 1.01 - 1.28) for 15 to 21 drinks/week, and 1.39 (95% CI: 1.22 - 1.58) for >21 drinks/week This association did not differ by sex (P for interaction = 0.74). This suggests that even moderate alcohol consumption is a risk factor for AF.

Conversely, while the Framingham Study demonstrated a significantly increased risk of AF among individuals who consumed >36 grams of alcohol/day (approximately >3 drinks per day), there was no significant association between moderate alcohol consumption and the risk of AF[84].

Similarly, another large study that evaluated the risk of alcohol induced AF specifically in women [85] found that consumption of 2 or fewer 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 significantly increased risk of AF (HR 1.60; 95% CI, 1.13-2.25).

Lowering alcohol intake may be effective in the prevention of AF. While most of the data correlates high alcohol consumption with AF, there is also evidence to suggest that moderate alcohol consumption also may be associated with an increased risk of AF. Limiting alcohol consumption to ≤ 1-2 drinks per day may be beneficial in AF prevention.

Physical Activity

Many studies have demonstrated the beneficial effects of exercise/PA on CV health [86,87]. Despite this, the incidence of AF appears to be increased among elite athletes, and multiple small studies have demonstrated a relationship between AF and vigorous PA, related to either long-term endurance sport participation or occupational PA[88,89,90].

Regardless of the relationship between high intensity PA and AF, recent data suggests a nonlinear relationship between higher levels of CRF and AF[91]. In one study, 1,950 middle-aged males were followed over a 19.5-year period to evaluate the relationship between CRF and incident AF. Here, the rates of incident AF per 1000 person-years of follow-up were 11.5 (95% CI 9.4-14.0) in the first quartile of CRF, to 9.1 (95% CI 7.4-11.2) in the second quartile, 5.7 (95% CI 4.4-7.4) for the third quartile, and 6.3 (95% CI 5.0-8.0) for the fourth quartile suggesting a modest increase in AF incidence in individuals with very high levels of CRF. While the association of high intensity PA and AF is not fully understood, possible mechanisms may involve acute fluxes in catecholamines and autonomic tone, atrial stretch, and RV cardiomyopathy [92,93].

Another recent study evaluated the effects of PA on AF among 36,513 Swedish women over a 12 year period[94]. Among this cohort of women, the risk of AF decreased with increasing levels of leisure-time PA (RR 0.85, 95% CI 0.75 - 0.95 for ≥4 h/week vs <1 h/week) and

walking/bicycling (RR 0.81, 95% CI 0.72 - 0.92, for ≥40 min/day vs almost never), suggesting that moderate PA was associated with a decreased risk of AF.

The association between endurance sports and AF was first described in a longitudinal, prospective study[95] in a series of orienteers (athletes who participate in vigorous exercise) over a 10-year period. Among the orienteers, they observed a RR of 5.5 (95% CI 1.3 -24.4) for AF when compared to healthy age-matched controls. The rate of AF among the orienteers was 5.3% (95% CI 2.8% - 9.0%)) compared to 0.9% (95% CI 0.1%- 3.4%) among the control group. They concluded that long-term vigorous exercise in men was associated with an increased risk of AF.

These findings were collaborated by many subsequent studies. A study of 160 participants (51 subjects with lone AF and 109 controls from the general population) demonstrated that participation in over 1500 lifetime hours of sports was associated with an increased risk of lone AF (OR 2.87; 95% CI: 1.20 - 6.91) when compared to the controls selected from the general population [96]. Another study of 134 former Swiss professional cyclists demonstrated that these athletes with a very high number of years competing in bicycle races had a higher incidence of AF or atrial flutter compared to the control group (P = 0.028) [97]. Fortunately, this risk of AF appears to resolve with moderation of exercise dose and detraining which may be secondary to normalization of the autonomic tone[98].

However, a meta-analysis of 19 studies consisting of 511,503 individuals demonstrated no association between intensive PA and AF (RR 1.00 95% CI 0.82-1.22). In fact, there was no correlation between increased time spent on PA and AF (RR 0.95 95% CI 0.72-1.26). Based on the data from this meta-analysis, in addition to the beneficial effects of PA on CV health and AF as stated above, patients should be encouraged to exercise and remain physically active, but perhaps avoid chronic excessive endurance exercise such as marathons, ultra-marathons, and Ironman-distance triathlons, especially for individuals over age 50.

Caffeine

There is evidence to suggest that caffeine consumption in moderate amounts may actually decrease the occurrence of AF [99,100]. A recent meta-analysis of 6 prospective cohort studies with 228,465 individuals showed a trend towards caffeine consumption being associated with AF risk reduction (RR, 0.90; 95% CI, 0.81-1.01; P = 0.07) [101]. However, subgroup analysis demonstrated an 11% reduction in AF risk with low doses of caffeine consumption (P= 0.032) and a 16% reduction for high doses (P= 0.002). Furthermore, for every 300 mg/d increment in habitual caffeine intake, the incidence of AF decreased by 6% in dose-response meta-analysis.

Another meta-analysis of 7 observational studies with 115,993 subjects showed that in addition to no association between caffeine exposure and risk of AF (OR 0.92, 95% CI 0.82 to 1.04), pooled results showed a 13% reduction in AF risk (OR 0.87; 95% CI 0.80 - 0.94). Furthermore, low-dose caffeine exposure showed OR 0.85 (95% CI 0.78 - 92) without significant differences in other dosage strata.

Despite this evidence showing a negative correlation between AF and caffeine intake, individuals with AF are occasionally advised to avoid drinking tea and coffee[102,103]. Based on the data presented above, caffeine intake should not be discouraged among patients with the sole purpose of AF prevention **(Figure 1)**. In fact, low to moderate amounts of daily caffeine consumption may potentially decrease the risk of AF, though this response is quite variable and thus the advice regarding caffeine intake should be individualized to each patient.

Conclusion

AF is the most common sustained heart rhythm disorder worldwide. Despite our incomplete understanding of this disease process, decades of research have discovered multiple modifiable, as well as non-modifiable risk factors responsible for AF development. Through proper medical

management and lifestyle changes, the impact of these modifiable risk factors, including obesity, OSA, HTN, T2DM, and alcohol consumption, AF risk may be reduced substantially.

Figure Legend

1. Potential risk factor modifications to reduce the incidence and prevalence of atrial fibrillation. AF= atrial fibrillation, HbA1c= hemoglobin A1c, SBP=systolic blood pressure

References

[1] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study. JAMA. 2001;285:2370–2375.

[2] Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110:1042–1046.

[3] Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013;112(8):1142-1147

[4] Friberg J, Scharling H, Gadsboll N, et al. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). Am J Cardiol. 2003; 92: 1419–1423.

[5] Ruo B, Capra AM, Jensvold NG, et al. Racial variation in the prevalence of atrial fibrillation among patients with heart failure: the Epidemiology, Practice, Outcomes, and Costs of Heart Failure (EPOCH) study. J Am Coll Cardiol. 2004; 43: 429–435

[6] Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995; 155(5): 469-473

[7] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-988.

[8] Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med. 2005;118(5):489-495

[9] Rosengren A, Hauptman PJ, Lappas G, et al. Big men and atrial fibrillation: effects of body size and weight gain on risk of atrial fibrillation in men. Eur Heart J. 2009;30(9):1113-1120

[10] Qureshi W, Soliman EZ, Solomon SD, et al. Risk factors for atrial fibrillation in patients with normal versus dilated left atrium (from the Atherosclerosis Risk in Communities Study). Am J Cardiol. 2014;114(9):1368-1372.

[11] Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation: the Framingham Heart Study. Circulation. 1994;89:724

[12] Zhuang J1, Wang Y, Tang K. et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace. 2012;14(5):638-645.

[13] Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. J Am Coll Cardiol. 2003;41:1036

[14] Gerdts E, Oikarinen L, Palmieri V, et al. Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. Hypertension. 2002;39:739-743

[15] Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm. 2013;10(1):90-100.

[16] Dušan P, Tamara I, Goran V, et al. Left ventricular mass and diastolic function in obese children and adolescents. Pediatr Nephrol. 2015;30(4):645-652.

[17] Fenk S, Fischer M, Strack C, et al. Successful weight reduction improves left ventricular diastolic function and physical performance in severe obesity. Int Heart J. 2015;56(2):196-202.

[18] Russo C, Jin Z, Homma S, et al. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. J Am Coll Cardiol. 2011;57(12):1368-1374.

[19] Tsang TS, Gersh BJ, Appleton CP, et al. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. J Am Coll Cardiol. 2002;40(9):1636-1644.

[20] Kumar P, Patel A, Mounsey JP, et al. Effect of left ventricular diastolic dysfunction on outcomes of atrial fibrillation ablation. Am J Cardiol. 2014;114(3):407-411.

[21] M.O. Al Chekakie, C.C. Welles, R. Metoyer, *et al.* Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol, 2010; 56 (10);784–788

[22] G. Thanassoulis, J.M. Massaro, C.J. O'Donnell, *et al.* Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. Circ Arrhythm Electrophysiol, 2010;3:345–350

[23] Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol. 2011;57(17):1745-1751

[24] Abed HS, Nelson AJ, Richardson JD, et al. Impact of weight reduction on pericardial adipose tissue and cardiac structure in patients with atrial fibrillation. Am Heart J. 2015;169(5):655-662

[25] Wanahita N, Messerli FH, Bangalore S, et al. Atrial fibrillation and obesity--results of a meta-analysis. Am Heart J. 2008;155(2):310-315.

[26] Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004;292(20):2471-2477.

[27]Nyström PK, Carlsson AC, Leander K, et al. Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. PLoS One. 2015 15;10(5):e0127111

[28] de Vos CB, Pisters R, Nieuwlaat R, et al. Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. J Am Coll Cardiol. 2010;55:725–731.

[29] Tsang TS, Barnes ME, Miyasaka Y, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J. 2008;29(18):2227-2233.

[30] Thacker EL, McKnight B, Psaty BM, et al. Association of body mass index, diabetes, hypertension, and blood pressure levels with risk of permanent atrial fibrillation. J Gen Intern Med. 2013;28(2):247-253.

[31] Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort: A Long-term Follow-Up StudY (LEGACY Study). J Am Coll Cardiol. 2015. 65(20):2159-2169

[32] Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310(19):2050-2060.

[33] Huxley RR, Misialek JR, Agarwal SK, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. Circ Arrhythm Electrophysiol. 2014;7(4):620-625

[34] Grundvold I, Skretteberg PT, Liestøl K, et al. Importance of physical fitness on predictive effect of body mass index and weight gain on incident atrial fibrillation in healthy middle-age men. Am J Cardiol. 2012;110(3):425-432.

[35] Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation: The CARDIO-FIT Study, Journal of the American College of Cardiology (2015), doi: 10.1016/j.jacc.2015.06.488.

[36] Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64(21):2222-2231.

[37] Asirvatham SJ, Kapa S. Sleep apnea and atrial fibrillation: the autonomic link. J Am Coll Cardiol. 2009;54(22):2084-2086.

[38] Rosario IC. Obstructive sleep apnea: a review and update. Minn Med. 2011;94(11):44-48.

[39] Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49(5):565-571.

[40] Cadby G, McArdle N, Briffa T, et al. Severity of obstructive sleep apnea is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. Chest. 2015 Apr 30. doi: 10.1378/chest.15-0229.

[41] Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm. 2012;9(3):321-327.

[42] Rajagopalan N. Obstructive sleep apnea: not just a sleep disorder. J Postgrad Med. 2011;57(2):168-175.

[43] Linz D, Schotten U, Neuberger HR, et al. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. Heart Rhythm. 2011 Sep;8(9):1436-1443.

[44] Svatikova A, Wolk R, Shamsuzzaman AS, et al. Serum amyloid a in obstructive sleep apnea. Circulation 2003; 108: 1451-1454.

[45] Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; 105: 2462-2464.

[46] Hartmann G, Tschop M, Fischer R, et al. High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. Cytokine 2000; 12: 246-252.

[47] Monahan K, Brewster J, Wang L, et al. Relation of the Severity of Obstructive Sleep Apnea in Response to Anti-Arrhythmic Drugs in Patients With Atrial Fibrillation or Atrial Flutter. Am J Cardiol. 2012; 110(3):369-372

[48] Ng CY, Liu T, Shehata M, et al. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011;108(1):47-51.

[49] Matiello M, Nadal M, Tamborero D, et al. Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients. Europace. 2010;12(8):1084-1089

[50]Dediu GN, Dumitrache-Rujinski S, Lungu R, et al. Positive pressure therapy in patients with cardiac arrhythmias and obstructive sleep apnea. Pneumologia. 2015;64(1):18-22.

[51] Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015;169(5):647-654

[52] Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm. 2013;10(3):331-337.

[53] Li L, Wang ZW, Li J, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. Europace. 2014;16(9):1309-1314.

[54] Shulka A, Aizer A, Holmes D, et al. Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence. A meta-analysis. JACCCEP.2015;1(1):41-51

[55] Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. Mayo Clin Proc. 2013;88(4):394-409

[56] Gbadebo TD, Okafor H, Darbar D. Differential impact of race and risk factors on incidence of atrial fibrillation. Am Heart J. 2011;162(1):31-37.

[57] Manolis AJ, Rosei EA, Coca A, et al. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. J Hypertens. 2012;30(2):239-252.

[58] Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997;96(7):2455-2461.

[59] Minami M, Kobayashi Y, Toyokawa S, et al. Risk factors for new-onset atrial fibrillation during routine medical checkups of Japanese male workers. Int Heart J. 2009;50(4):457-464.

[60] Conen D, Tedrow UB, Koplan BA, et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. Circulation. 2009;119(16):2146-2152.

[61] Grundvold I, Skretteberg PT, Liestøl K, et al. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. Hypertension. 2012;59(2):198-204.

[62] Thomas MC, Dublin S, Kaplan RC, et al. Blood pressure control and risk of incident atrial fibrillation. Am J Hypertens. 2008;21(10):1111-1116.

[63] Badheka AO, Patel NJ, Grover PM, et al. Optimal blood pressure in patients with atrial fibrillation (from the AFFIRM Trial). Am J Cardiol. 2014;114(5):727-736.

[64] Tremblay-Gravel M1, White M1, Roy D1, et al. Blood Pressure and Atrial Fibrillation: A Combined AF-CHF and AFFIRM Analysis. J Cardiovasc Electrophysiol. 2015;26(5):509-514

[65] Go O, Rosendorff C. Hypertension and atrial fibrillation. Curr Cardiol Rep. 2009;11(6):430-435.

[66] Schmieder RE, Kjeldsen SE, Julius S, et al. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens. 2008;26(3):403-411.

[67] Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol. 2005;45(11):1832-1839.

[68] Disertori M, Barlera S, Staszewsky L, et al. Systematic review and meta-analysis: renin-Angiotensin system inhibitors in the prevention of atrial fibrillation recurrences: an unfulfilled hope. Cardiovasc Drugs Ther. 2012;26(1):47-54.

[69] GISSI-AF Investigators, Disertori M, Latini R, Barlera S, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med. 2009;360(16):1606-1617

[70] Pallisgaard JL, Lindhardt TB, Olesen JB, et al. Management and prognosis of atrial fibrillation in the diabetic patient. Expert Rev Cardiovasc Ther. 2015;13(6):643-651

[71] Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case–control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol. 2011;108:56–62

[72] Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care. 2009;32(10):1851-1856

[73] Aksnes TA, Schmieder RE, Kjeldsen SE, et al. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). Am J Cardiol. 2008;101(5):634-638.

[74] Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med. 2010;25(8):853-858.

[75] Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373(9665):739-745.

[76] Ostgren CJ, Merlo J, Råstam L, et al. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes Obes Metab. 2004;6(5):367-374.

[77] Ettinger PO, Wu CF, De La Cruz C, et al. Arrhythmias and the "Holiday Heart": alcohol-associated cardiac rhythm disorders. Am Heart J. 1978;95(5):555–562.

[78]Menz V, Grimm W, Hoffmann J, et al. Alcohol and rhythm disturbance: the holiday heart syndrome. Herz. 1996;21(4):227-231.

[79] Lowenstein SR, Gabow PA, Cramer J, Oliva PB, Ratner K. The role of alcohol in new-onset atrial fibrillation. Arch Intern Med. 1983;143(10):1882–1885.

[80] Sano F, Ohira T, Kitamura A,et al. Heavy alcohol consumption and risk of atrial fibrillation. The Circulatory Risk in Communities Study (CIRCS). Circ J. 2014;78(4):955-961

[81] Mukamal KJ, Tolstrup JS, Friberg J, et al. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation. 2005;112(12):1736-1742.

[82] Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for atrial fibrillation: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2010 ;17(6):706-712.

[83] Conen D, Albert CM. Alcohol consumption and risk of atrial fibrillation: how much is too much? J Am Coll Cardiol. 2014;64(3):290-292

[84] Djoussé L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. Am J Cardiol. 2004;93(6):710-713.

[85]Djoussé L, Levy D, Benjamin EJ, et al. Alcohol consumption and risk of incident atrial fibrillation in women. JAMA. 2008;300(21):2489-2496.

[86] Menezes AR, Lavie CJ, , Milani RV, Arena RA, Church TS. Cardiac rehabilitation and exercise therapy in the elderly: Should we invest in the aged? (2012). J Geriatr Cardiol vol. 9, 68-75.

[87] Lavie CJ, Thomas RJ, Squires RW, et al. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. Mayo Clin Proc 2009; 84: 373–383.

[88] Mont L, Tamborero D, Elosua R, et al. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace. 2008;10(1):15-20.

[89] Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace. 2008;10:618–623.

[90] Link MS, Homoud MK, Wang PJ, Estes NA III. Cardiac arrhythmias in the athlete: the evolving role of electrophysiology. Curr Sports Med Rep 2002;1:75-85.

[91] Khan H, Kella D, Rauramaa R, et al. Cardiorespiratory fitness and atrial fibrillation: A population-based follow-up study. Heart Rhythm. 2015 Mar 14. pii: S1547-5271(15)00281-7. doi: 10.1016/j.hrthm.2015.03.024

[92] O'Keefe JH, Lavie CJ, Guazzi M.Part 1: potential dangers of extreme endurance exercise: how much is too much? Part 2: screening of school-age athletes. Prog Cardiovasc Dis. 2015;57(4):396-405.

[93] Lavie CJ, O'Keefe JH, Sallis RE. Exercise and the heart--the harm of too little and too much. Curr Sports Med Rep. 2015 14(2):104-109.

[94] Drca N, Wolk A, Jensen-Urstad M, et al. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. Heart. 2015 May 27. pii: heartjnl-2014-307145. doi: 10.1136/heartjnl-2014-307145

[95] Karjalainen J, Kujala UM, Kaprio J et al. Lone atrial fibrillation in vigorously exercising middle aged men: case–control study. BMJ. 1998;316:1784–1785.

[96] Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E, et al. Sport practice and the risk of lone atrial fibrillation: a case–control study. Int J Cardiol. 2006;108:332–337.

[97] Baldesberger S, Bauersfeld U, Candinas R, et al. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. Eur Heart J. 2008;29(1):71-78.

[98] O'Keefe JH, Franklin B, Lavie CJ.Exercising for health and longevity vs peak performance: different regimens for different goals. Mayo Clin Proc. 2014;89(9):1171-1175.

[99] Patil, H., Lavie, C.J., and O'Keefe, J.H. Cuppa joe: friend or foe? effects of chronic coffee consumption on cardiovascular and brain health. Mo Med. 2011; 108: 431–438

[100] Zeng, X., Li, Q., Zhang, M., Wang, W., and Tan, X. Green tea may be benefit to the therapy of atrial fibrillation. J Cell Biochem. 2011; 112: 1709–1712

[101] Cheng M, Hu Z, Lu X, et al. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. Can J Cardiol. 2014;30(4):448-454.

[102] Artin, B., Singh, M., Richeh, C., Jawad, E., Arora, R., and Khosla, S. Caffeine-related atrial fibrillation. Am J Ther. 2010; 17: e169–e171

[103] Artin B, Singh M, Richeh C, et al. Caffeine-related atrial fibrillation. Am J Ther. 2010;17(5):e169-171.