



Featured Review

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## Life's Simple 7 Approach to Atrial Fibrillation Prevention

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### Abstract

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. It constitutes a major public health problem, with total related annual expenses estimated at \$6.65 billion. The American Heart Association developed Life's Simple 7 (LS7) to define and monitor ideal cardiovascular health (CVH). In this review, we examine the role of individual components of LS7 to provide further insight regarding potential influence of achieving AHA's strategic goal on AF prevention. While significant advances have been made in the secondary prevention of AF, little progress has been made to prevent the first occurrence of this arrhythmia in at-risk patients. Improvement of overall cardiovascular health as defined by LS7 may substantially reduce AF risk.

### Introduction

Atrial fibrillation (AF) affects 33.5 million people globally. In the United States (US) alone an estimated 3 to 6 million individuals have AF with prevalence projected to double by 2050.<sup>[1-3]</sup> The lifetime risk of developing AF is 1 in 3 among whites and 1 in 5 among African Americans,<sup>[4,5]</sup> and is associated with increased morbidity and mortality with a 5-fold increased risk of stroke and substantially increased risk of systemic thromboembolism.<sup>[6]</sup> It is also associated with increased risk of dementia,<sup>[7]</sup> physical disability,<sup>[8]</sup> heart failure,<sup>[9]</sup> myocardial infarction<sup>[10]</sup> and sudden cardiac death.<sup>[11]</sup> AF thus constitutes a sizeable and growing public health problem, with total health-related annual expenses estimated at \$6.65 billion and projected to rise.<sup>[12],[13]</sup>

The American Heart Association's (AHA) impact goal is to improve the cardiovascular health (CVH) of all Americans by 20% by 2020, while reducing deaths from CVD and stroke by 20%. To help achieve this goal of primary prevention of CVD and ideal cardiovas-

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cular health, the AHA identified seven modifiable factors, also called Life's Simple 7 (LS7). It consists of 3 health factors (cholesterol level, blood pressure, and blood glucose) and 4 behavioral factors (cigarette smoking, physical activity, diet, and body mass index (BMI)). An overall LS7 score ranges 0 to 14 and is calculated as the sum of the LS7 component scores (2 points for ideal, 1 point for intermediate, and 0 for poor).<sup>[14]</sup> This CV health metric has been previously shown to predict CVD and heart failure. Recent data suggests reduced risk of AF with favorable LS7 score.<sup>[15,16]</sup> We review the current literature on the potential role of individual LS7 components in AF prevention.

### Hypertension

Hypertension is a strong independent predictor of AF.<sup>[17-19]</sup> High BP promotes left ventricular diastolic dysfunction, left atrial (LA) dilation, cardiac fibrosis and dilation of pulmonary veins, which in turn shortens refractoriness and increases risk of AF.<sup>[20]</sup> Higher pulse pressure is a better predictor of AF than systolic or diastolic BP alone. Higher systolic blood pressures are associated with higher AF risk, whereas diastolic BP was inversely related with AF incidence.<sup>[21]</sup><sup>[17][22]</sup> This suggests increased pulse pressure associated with vascular aging may be a factor related to increased AF incidence in the elderly.

As part of the ARREST AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of

Ablation) study, strict blood pressure control among other aggressive risk factor modification (RFM) strategies significantly reduced AF recurrence.<sup>[23]</sup> In high-risk patients, primary prevention of AF via renin-angiotensin-aldosterone system (RAAS) inhibition has shown promise. A meta-analysis by Healey et. al suggested that the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) in patients with left ventricular (LV) hypertrophy or LV dysfunction can prevent 20%–30% of new-onset AF.<sup>[24]</sup> Angiotensin II increases sympathetic nervous system activity, oxidant production, atrial inflammation and fibrosis, all of which could increase risk of AF. This is further supported by the effectiveness of ACEI/ARBs in preventing AF over beta blockers and diuretics in patients without structural heart disease.<sup>[25]</sup> Assessment of the effectiveness of RAAS inhibition for preventing recurrent AF has shown mixed results. This may be due to confounding factors such as the timing of treatment onset, and existing irreversible LA structural changes.<sup>[26]</sup> Thus, existing evidence suggest a beneficial effect of BP control, specifically lowering systolic BP, as maybe an important factor in AF prevention.

### Diabetes Mellitus

Optimal, ideal blood glucose is a component of LS7. Diabetes Mellitus (DM) is a well-established risk factor for AF<sup>[27]</sup>. It is estimated that DM explains 2.5 % of the AF burden<sup>[28]</sup>. Mechanisms linking DM to an increased risk of AF remain speculative. It is suggested that cardiac autonomic neuropathy leads to impaired parasympathetic tone and this dysfunctional cardiac autonomic activity then leads to propagation of AF<sup>[29]</sup>.

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, 5250 patients of 15,245 hypertensive patients had DM at baseline. Over 4.2 year follow-up 551 patients developed new-onset AF and 1298 of the initially non-diabetic patients developed DM. Investigators demonstrated that patients with new-onset DM had a significantly higher rate of new-onset AF with a hazard ratio of 1.49 (1.14 to 1.94,  $p = 0.003$ ) compared to patients without DM.<sup>[30]</sup> Dublin et al. showed that the risk of developing AF was higher with longer duration of treated diabetes and worse glycemic control, specifically for every 1% increase in HbA1c, a 14% increased risk for incident AF was observed<sup>[31]</sup>.

There is conflicting data based upon the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in which 10,082 patients with diabetes were randomized into intensive vs. standard glycemic control groups. Targeting a glycated hemoglobin level of <6.0% (intensive group) did not affect the rate of new-onset AF. However, given the study was focused on intensive and standard glycemic control strategies, conclusion regarding the incidence of AF in patients with poor glycemic control cannot be obtained.<sup>[32]</sup> In a meta-analysis by Huxley et al. involving 108,703 cases of AF in 1,686,097 subjects, it was found that patients with DM had an approximate 40% greater risk of AF compared to unaffected patients. After taking confounders into account, the subsequent risk of AF may be closer to 25% rather than 40% as indicated by the overall summary estimate.<sup>[28]</sup> Given the inconsistencies in these results, there is a need for more randomized controlled trials or observational studies to look at management strategy for diabetes that would be

favorable for AF prevention.

### Hypercholesterolemia

Optimal or ideal cholesterol levels are a component of LS7. The literature on the role of blood lipid levels, especially total cholesterol, and AF risk is inconsistent, and the precise role of total cholesterol in the development of AF, if any, remains to be determined.

Potential pathophysiologic mechanisms by which high density lipoprotein cholesterol (HDL-C) can prevent AF could be its direct anti-inflammatory and antioxidant properties<sup>[33]</sup>. In addition it may be though indirect effects by preventing coronary heart disease and heart failure<sup>[34]</sup>. Elevated triglycerides are associated with metabolic syndrome which has been associated with increased AF incidence<sup>[35]</sup>.

In an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study (FSH) cohorts in a fully adjusted model, including BMI, HDL-C was associated with reduced risk of AF (HR 0.89, CI 0.80 to 0.99) and high triglycerides were associated with higher risk of AF (HR 1.16, CI 1.06 to 1.27), whereas level of low density lipoprotein cholesterol (LDL-C) and total cholesterol did not have effect on AF risk (HR 1.04, CI 0.94 to 1.15 and HR 1.05, CI 0.96 to 1.15 respectively)<sup>[36]</sup>. In contrast, the Atherosclerosis Risk in Communities study (ARIC) study reported that high LDL-C and total cholesterol are associated with a lower risk of AF, whereas HDL-C and triglycerides were not related to AF risk.<sup>[37]</sup> Similarly, the Cardiovascular Health Study also found lower risk of AF among subjects with higher total cholesterol<sup>[38]</sup>. Inconsistent results are likely due to impact of comorbid conditions and lack of adjustment of those factors in addition to difference in demographics. The role of lipid lowering with statins in AF prevention is unclear, with observational studies suggesting reduced AF risk and clinical trials failing to do so<sup>[39]</sup>. For now, there is insufficient evidence to support targeting specific lipid-related measures for AF prevention.

### Obesity

Obesity is a major public health problem with increasing prevalence in the US and is an important, potentially modifiable risk factor for AF<sup>[40][41]</sup>. Several studies have shown adiposity measures other than body mass index (BMI) to be associated with increased AF such as waist circumference,<sup>[42]</sup> bioelectrical impedance derived measures of body composition and body fat distribution<sup>[43]</sup>. In a longitudinal cohort study, BMI also independently predicted the progression to permanent AF.<sup>[44]</sup> The pathophysiology linking obesity to AF is multifactorial. Animal models have shown that sustained obesity leads to the development of a global electrophysiological and structural substrate for AF<sup>[45]</sup>. Pericardial fat is highly associated with paroxysmal and persistent AF independent of traditional risk factors including left atrial enlargement<sup>[46]</sup>. It is also associated with worse outcomes after AF ablation. The pericardial adipose tissue is highly metabolically active and has been linked to the increased local release of various pro-inflammatory mediators, such as interleukin-6 and tumor necrosis factor- $\alpha$ , which may promote the activation of ectopic foci in the pulmonary vein ostium contributing to AF<sup>[47]</sup>. A recent study has shown favorable structural remodeling and a reduction in a pericardial adipose tissue after weight loss.<sup>[48]</sup> Increased left atrial (LA) size is also associated with obesity.<sup>[49]</sup> An analysis of

the Framingham cohort showed a stepwise increase in risk for AF with ascending quartiles of LA size. It has been suggested that LA dilatation is associated with structural and functional atrial tissue alterations that facilitate the disturbed impulse propagation of AF.<sup>[50]</sup>

Several trials have evaluated the impact of weight loss on AF and explored the sustainability of weight loss effects, in addition to a potential dose-response relationship. In the LEGACY (Long-Term Effect of Goal-Directed Weight Management on Atrial Fibrillation Cohort) prospective cohort, subjects with >10% weight loss had a 66-fold greater probability of arrhythmia-free survival compared to those who had <10% weight loss. In addition to AF free state, subjects with >3% weight loss had evidence of reverse atrial remodeling, specifically left atrial volume indexed for body surface area decreased significantly.<sup>[51]</sup> In a recently published study of 4021 obese subjects, bariatric surgery was associated with significantly reduced risk of AF (hazard ratio: 0.69; 95% confidence interval: 0.58 to 0.82;  $p < 0.001$ ). Of note, this effect was found with significant obesity at baseline: men with BMI  $\geq 34$  kg/m<sup>2</sup> and women with BMI  $\geq 38$  kg/m<sup>2</sup>.<sup>[52]</sup> However, an analysis of The Action for Health in Diabetes (Look AHEAD) trial did not find an effect of weight loss on AF incidence. Notably, the weight loss achieved in Look AHEAD was less than that reported in the bariatric surgery study, thus it may be that only more extreme weight loss reduces the risk of AF.<sup>[53]</sup>

Although obstructive sleep apnea (OSA) is not component of LS7, obesity is strongly associated with this disorder<sup>[54]</sup>, OSA is an independent risk factor for AF.<sup>[55]</sup> In the large cross-sectional Sleep Heart Health study looking at the prevalence of cardiac arrhythmias in patients with OSA, AF rate was 4.8% compared to 0.9% in subjects without OSA<sup>[56]</sup>.

There is a clear epidemiological association between obesity and AF. There is also substantial evidence that weight control may reduce the increasing incidence of AF, making it an important component for the primary prevention of AF.

### Fitness or Physical Activity

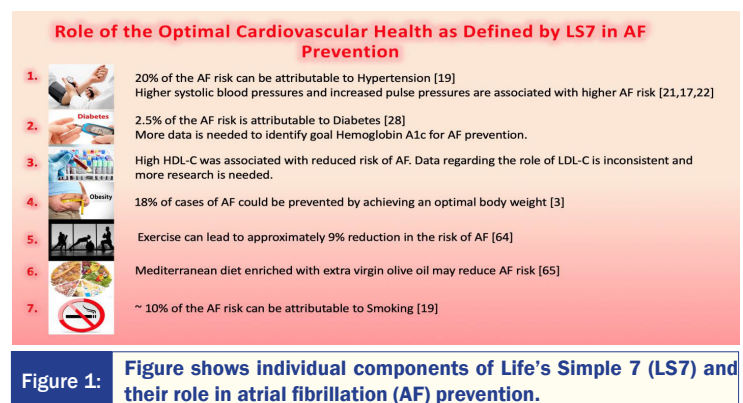
The association between physical activity or fitness and AF is complex. It is important to account for pathophysiologic differences between cardiorespiratory fitness in the general population in comparison to high-intensity physical activity among elite athletes.<sup>[57]</sup> Studies that found increased risk of AF with vigorous physical activity mainly included subjects with moderate to high exercise level such as professional cyclists<sup>[58]</sup> and endurance athletes<sup>[59]</sup> among others. In contrast, the population-based Cardiovascular Health Study of 5446 subjects showed that light to moderate physical activity was associated with significantly lower AF incidence in older adults and high-intensity exercise did not have an effect.<sup>[60]</sup> However, another population-based (n=38,000) study of light to moderate exercise showed no effect on AF.<sup>[61]</sup> Studies looking specifically at fitness level and AF have consistently shown protective effects of fitness. Faselis et al. found high levels of fitness was associated with reduced risk of AF (odds ratio, 0.37  $p < 0.001$ ).<sup>[62]</sup> Similarly, two other studies found reduced risk of AF with increasing level of fitness.<sup>[63]</sup> Pathak et al showed that among 308 obese (BMI >27) subjects in the CARDIO-FIT (Impact of CARDIOrespiratory FITness on

Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation) study, patients who had high cardiorespiratory fitness had less AF. Patients who improved their fitness level by >2 metabolic equivalents (METs) had a 2-fold higher probability of AF-free survival, as well as lower AF. However, Khan and colleagues found a nonlinear relationship between the higher level of cardiopulmonary fitness and AF. Given inconsistency in the available literature, a recent meta-analysis by Zhu et al. looked at the association of physical fitness and AF among 205,094 subjects pooled from 6 studies. Per incremental increase in physical fitness, a 9% reduction in the risk of AF was seen. When physical fitness was assessed, the risk of AF was highest in individuals with the lowest level of physical fitness.<sup>[64]</sup>

Overall, physical activity may have a U-shaped relationship with the risk of AF in athletes and non-athletes, and a non-linear relationship is observed between physical fitness and the risk of AF. However, studies have consistently shown benefit or no harm of light-moderate exercise or fitness at the general population level for AF prevention.

### Dietary Patterns

There is paucity of data on the effect of dietary patterns and development of AF. Most studies are small and include non-homogenous populations. PREDIMED (Prevención con Dieta Mediterránea) trial is the only interventional study evaluating the impact of dietary patterns on AF risk. It enrolled 6705 subjects in Spain, who were randomized into three groups (Mediterranean diet enriched with extra virgin olive oil (EVOO), or mixed nuts or control group). The former intervention reduced AF risk compared with control group; (Hazard Ratio 0.62, 95% confidence interval 0.45–0.85) however, there was no effect in the group with mixed nuts.<sup>[65]</sup> There are no specifics on the quantity of EVOO being consumed, which makes it difficult to reach a feasible conclusion. As well, it is unclear to what degree EVOO was consumed in the control and mixed nuts groups. Data from the Framingham Heart Study found no association between caffeine, fiber, and fish-derived polyunsaturated fatty acids with AF risk.<sup>[66]</sup> Alcohol intake, both “binge” drinking and moderate consumption 67 is a risk factor for AF.<sup>[68]</sup> The Women’s Health Study showed that consumption of even 2 drinks/day was associated with risk of AF.<sup>[69]</sup> The mechanism is thought to be direct toxic effect on the cardiomyocytes, altered atrial conduction, short refractory period and altered autonomic balance with sympathetic predominance.<sup>[70,71]</sup> In ARREST AF trial, reduction in alcohol use contributed to improved AF ablation outcomes.<sup>[23]</sup>



In a case-control study of 800 patients, those with AF were found to have lower adherence to a Mediterranean diet and lower antioxidant intake compared to a control population (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.58–2.81). In addition, patients in the highest quartile of the Mediterranean Score had higher probability of spontaneous conversion of atrial fibrillation to sinus rhythm (OR 1.9; 95% CI 1.58–2.81).<sup>[72]</sup> Thus, current data suggests potential protective effect of EVOO for AF prevention, however future research on the clinical significance of these associations is needed. Effect sizes of dietary exposures are modest leading to potential residual confounding. Lacking direct evidence, Mediterranean dietary pattern with possible EVOO supplementation coupled with an emphasis on physical activity, maintenance of a healthy lifestyle and weight seem reasonable guidance for AF patients, and for those with significant risk of AF.

### Smoking

Smoking has been reported to predict AF among racially different populations.<sup>[73,74]</sup> Data from the atherosclerosis risk in communities (ARIC) study suggests a dose-response relationship, with the highest risk of AF observed in individuals with the greatest cigarette pack-years of smoking.<sup>[73]</sup> Current smoking was more strongly and consistently associated with AF compared with former smoking status.<sup>[75]</sup> The results of smoking cessation interventions in AF have not been well studied. Smoking cessation was one of the risk modification measures of ARREST AF trial which showed the reduction of AF incidence.<sup>[23]</sup> However, despite the absence of studies looking at the effect of smoking cessation alone and AF risk, available evidence supports smoking cessation to be encouraged for prevention of AF and overall cardiovascular health. As other recreational substance use is not included in LS7, we briefly mention their role in AF. In addition to the well-known association of “binge” drinking and AF,<sup>[67]</sup> even moderate intake of alcohol is a risk factor for atrial fibrillation.<sup>[68]</sup> Caffeine consumption on a regular basis was not associated with increased incidence of AF. A meta-analysis of six cohorts and one case-control study with 115,993 subjects showed 13% odds reduction in AF among subjects with regular caffeine intake (OR 0.87; 95% CI 0.80 to 0.94; I<sup>2</sup>=39%).<sup>[76]</sup> Thus, based on existing evidence, recommendations against caffeine intake should not be practiced for the purpose of AF prevention.

While, Desai et al. have shown increased risk of arrhythmias, including AF in hospitalized marijuana users, no prospective trials have been conducted to assess this relationship.<sup>[77]</sup>

### Overall Life's Simple 7 and Atrial Fibrillation

Two recent studies showed role of favorable LS7 in AF prevention. Analysis of Reasons for Geographic and Racial Differences in Stroke (REGARDS) study showed 5% reduction of AF risk with 1 point improvement in LS7 score. Out of individual components only blood pressure and body weight were associated with risk of incident AF. This study had significant limitation in that AF cases were ascertained by self-recall at a single follow up visit, about 10 years after baseline one. More robust results were seen in ARIC study, where 1 point improvement in LS7 score was associated with 17% lower risk of AF. Additionally, improvement of individual components of LS7 by 1 level was associated with 12% lower AF risk. Here, in component

analysis tobacco use and fasting blood glucose level were associated with lower AF risk in addition to blood pressure and body weight in REGARDS

### Conclusions

There is evidence that most of the components of LS7 are risk factors for development of AF and are both preventable and modifiable. Presence of shared risk factors for CAD and AF raises question whether AF is actually a vascular disease. Interestingly, Weijs, et al. found subclinical CAD in high proportion of patients with original diagnosis of lone AF.<sup>[78]</sup> Treatment of HTN, smoking cessation, weight loss, regular physical activity, preventing and controlling diabetes have been shown to have a potential role in AF prevention, while data on lipids and dietary modification is limited. Although some individual components of LS7 may not have strong AF risk, it is possible that these components are related and improvement in one could result in reduction of AF by preventing development of the other component or modifying its effect. Thus, by achieving optimal cardiovascular health profile, as defined by LS7, it is possible to substantially reduce AF risk. Nonetheless, further prospective studies are needed to better understand implications of favorable LS7 profile on AF incidence.

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