Obesity, Exercise, Obstructive Sleep Apnea, and Modifiable Atherosclerotic Cardiovascular Disease Risk Factors in Atrial Fibrillation

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ABSTRACT

Classically, the 3 pillars of atrial fibrillation (AF) management have included anticoagulation for prevention of thromboembolism, rhythm control, and rate control. In both prevention and management of AF, a growing body of evidence supports an increased role for comprehensive cardiac risk factor modification (RFM), herein defined as management of traditional modifiable cardiac risk factors, weight loss, and exercise. In this narrative review, we summarize the evidence demonstrating the importance of each facet of RFM in AF prevention and therapy. Additionally, we review emerging data on the importance of weight loss and cardiovascular exercise in prevention and management of AF. (J Am Coll Cardiol 2015;66:2899–906) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) is the most common sustained arrhythmia and represents a rapidly growing epidemic (1). It is projected that the prevalence will rise from 5.2 million in 2010 to 12.1 million in 2030, driven primarily by our aging population (2). AF is associated with increased morbidity, mortality, and rising health care-associated expenses (3,4).

Unsurprisingly, many modifiable risk factors associated with atherosclerotic cardiovascular disease (ASCVD) have also been associated with AF (Central Illustration). Although the most recent AF practice guidelines acknowledge these risk factors, they provide no evidence-based recommendations on diet, exercise, and lifestyle changes in AF primary and secondary prevention (5). In 2013, the Heart Rhythm Society recognized “advancing AF prevention efforts by focusing on risk modification” as a key research focus (6). Of note, there are numerous other risk factors for AF, such as valvular heart disease, thyroid disease, or chronic obstructive pulmonary disease, which are not thought of as classical risk factors for atherosclerotic heart disease. Such conditions also have known causal relationships with AF and also have implications for management strategies. These other AF risk factors warrant investigation in the work-up of new diagnoses of AF.

OBESITY AND WEIGHT LOSS

The rise in prevalence of obesity has been well documented, particularly in the United States, where an estimated one-third of adults are obese (7). During
the past 5 years, a number of studies have established that obesity is closely linked to AF risk. Body mass index (BMI) is part of prediction models for new-onset AF (8). The connection between obesity and AF has been shown to occur independently of the many comorbidities associated with obesity (9,10).

In the ARIC (Atherosclerosis Risk In Communities) study (N = 14,598), 17% of AF risk was attributed to obesity or overweight status (11). In the WHS (Women’s Health Study) (N = 34,309), for every 1 kg/m² increase in BMI, the relative AF risk increased by 5% (10). In the Women’s Health Initiative cohort of 93,676 females, for every 1 kg/m² increase in BMI, AF relative risk increased by 12% (12). Interestingly, higher levels of physical activity attenuated the AF risk conferred by obesity (13). BMI >35 kg/m² was also associated with increased AF risk by a hazard ratio of 3.50 in young, healthy women (14).

In a recent meta-analysis of 51 studies and 626,603 patients, for every 5 kg/m² increase in BMI, there was a 10% to 29% higher relative risk for new-onset or post-operative AF (15). In a subanalysis of 16 studies and 5,864 patients undergoing AF ablation, the risk of AF recurrence increased by 13% for every 5 kg/m² increase in BMI (15). Adiposity measures other than BMI have also been associated with increased AF risk. In a Danish registry of 55,273 participants and 13.5 years of follow-up, increased total body fat mass assessed by bioelectrical impedance was associated with higher incidence of AF (16).

Several mechanisms underlie the association between obesity and AF. In a sheep model fed a high-caloric diet, obesity was associated with left atrial enlargement and fibrosis, atrial inflammatory, and lipid infiltration, as well as changes in atrial electrophysiological properties, ultimately leading to increased rates of spontaneous and induced AF (17). In an ovine model of obesity sustained for 8 months, obesity was associated with infiltration of the left atrial posterior myocardium by epicardial fat and reduced endocardial voltage, representing a potential substrate for AF (18).

In humans, increased BMI has been associated with increased left atrial size (19), which, in turn, is associated with higher AF risk (20). Increased pericardial fat volume has also been described in obese individuals and is related to the presence, severity, and post-ablation recurrence of AF, independent of BMI, suggesting a local pathogenic effect of pericardial fat (21). Obesity has also been associated with increased epicardial fat thickness, which may lead to altered atrial electrophysiology and sympathovagal imbalance of the atria (22–24). Clinically, epicardial fat has been associated with AF (25). Lastly, obesity is a state of chronic, low-grade, systemic inflammation (26). Systemic inflammation has a key role in
in AF management (28). The weight management consisted of versus lifestyle advice, in addition to standard therapy for AF (28). The weight management consisted of a prescribed exercise routine and a low-calorie diet, with improvement in BMI from 32.8 to 27.2 kg/m² at 15 months versus no change for the control group. At 15 months, the weight management group had reduced frequency of AF episodes, reduced duration in AF, and lower symptom severity scores.

The LEGACY-AF (Long-Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort: A 5 Year Follow-Up Study) study investigated the impact of RFM and weight loss in longer-term AF management (30). Patients with a BMI $\geq$27 kg/m² and AF (N = 825) were offered weight management and standard therapy for AF at the discretion of the treating physician. At 5-year follow-up, a dose-response relationship was seen, with greater weight loss resulting in reduced AF burden and symptoms. Weight loss $\geq$10% was associated with $>$6-fold decrease in arrhythmia-free survival. Fluctuations of weight $>$5% within the study time period offset some, but not all, of the benefits of weight loss.

Weight loss has also been demonstrated to reduce AF recurrence after ablation procedures. In the ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation), patients with AF and obesity undergoing catheter ablation were offered the chance to participate in a group in a nonrandomized fashion (29). At a mean follow-up of 42 months after catheter ablation, patients in the RFM group had significant reductions in weight, blood pressure, and lipid profile, and improved glycemic control. There was a significant decrease in AF frequency, duration, symptoms, and arrhythmia-free survival with the RFM group. Additionally, obese patients have been observed to receive at least a 2-fold higher effective radiation dose compared with nonobese patients during an AF ablation (33).

The epidemiological link between obesity and AF is clear, and there is increasing understanding of the pathophysiology linking the 2 conditions. Recent data support the importance of weight loss in AF management. Of note, weight loss did not occur in isolation in the studies discussed earlier, but rather included components of exercise, diet, and modification of other risk factors. The link between weight loss and AF therapy is likely multifactorial, because routine RFM and weight-loss counseling result in improvement in other comorbid conditions that are also independently associated with AF. However, weight loss does result in atrial structural changes, supporting a direct link between weight loss and improved AF outcomes (34). Currently, the body of evidence is enough to strongly recommend weight loss for both prevention and management of AF.

**EXERCISE AND FITNESS**

The benefits of routine exercise in improving ASCVD risk factors have been well established, and guidelines recommend regular brisk exercise for this purpose (35). Observational studies have shown increased risk of AF in young athletes or in those performing endurance training (36,37). A common theme in these studies is involvement in regular long-duration endurance training that is well beyond the scope of what would be practiced by the typical patient with AF and other comorbidities.

In the Cardiovascular Health Study, the incidence of AF was lower in individuals performing light-to-moderate exercise compared with those performing no exercise (38). There was no difference in AF incidence between individuals performing high-intensity exercise versus no exercise. Among those who walked for exercise, walking greater distances or at a faster pace was associated with a greater reduction in incident AF. In the Women’s Health Initiative study, increased physical activity was associated with less incident AF and appeared to mediate some of the relationship between obesity and AF (13). Two meta-analyses examining the relationship of routine nonendurance exercise and AF reported no association between exercise and AF risk (39,40).

In a cohort of 64,561 adults with a mean follow-up of 5.4 years, for each 1 metabolic equivalent (MET) achieved during treadmill stress testing, there was a 7% decreased relative risk for AF development (41). In the recent CARDIO-FIT (Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation) study, 308 obese (BMI $\geq$27 kg/m²) patients with AF were enrolled in a tailored exercise program. Patients that had high cardiorespiratory fitness had greater arrhythmia-free survival with and without rhythm-control strategies. Patients who improved their fitness level by $\geq$2 METs had a 2-fold higher probability of AF-free survival, as well as lower AF burden and symptom severity compared with those that improved their fitness by $<$2 METs (32).
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<th>First Author (Ref. #)</th>
<th>Year</th>
<th>Design</th>
<th>Patient Population</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Follow-up</th>
<th>Results (Intervention vs. Control Group)</th>
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<tbody>
<tr>
<td>Abed et al. (28)</td>
<td>2013</td>
<td>Single-center, partially blinded, RCT (weight-loss counselors were not blinded)</td>
<td>Overweight and obese ambulatory patients with symptomatic AF</td>
<td>150 (I = 75; C = 75)</td>
<td>Weight management</td>
<td>General lifestyle advice</td>
<td>15 months</td>
<td>• Greater weight loss (14.3 vs. 3.6 kg)</td>
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<td>• Reduced AF burden and severity scores (11.8 vs. 2.6 points and 8.4 and 1.7 points, respectively)</td>
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<td>• Less frequent AF episodes</td>
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<td>• Reduced cumulative AF duration (692 min reduction vs. 419 min increase)</td>
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<td>• Greater reductions in weight and blood pressure, as well as improved glycemic control and lipid profile</td>
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<td>• Decreased AF frequency, duration, symptoms, and symptom severity</td>
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<td>• Improved arrhythmia-free survival after a single or multiple procedures (without or without the use of anti-arrhythmic agents)</td>
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<td>• Decreased AF burden and symptom severity in patients that lost ≥10% of their weight compared to those that lost &lt;10%</td>
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<td>• Weight loss ≥10% was associated with a 6-fold greater probability of arrhythmia-free survival</td>
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<td>• Fluctuations of weight &gt;5% offset some, but not all, benefits of weight loss</td>
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<td>Pathak et al. (29)</td>
<td>2014</td>
<td>Single-center, nonrandomized, placebo-controlled trial</td>
<td>Consecutive patients with BMI ≥27 kg/m² and ≥1 RF (HTN, glucose intolerance/DM, HLD, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF, despite the use of antiarrhythmic medication</td>
<td>149 (I = 61; C = 88)</td>
<td>RFM by a physician-led clinic (HTN control, weight management, lipid management, glycemic control, OSA management, smoking and alcohol counseling)</td>
<td>Information on RFM provided</td>
<td>42 months</td>
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<td>Pathak et al. (30)</td>
<td>2015</td>
<td>Single-center, single-arm study</td>
<td>Consecutive patients with symptomatic paroxysmal or persistent AF and BMI ≥27 kg/m²</td>
<td>355</td>
<td>Weight management</td>
<td>No control arm</td>
<td>46-48 months</td>
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<td>Fatemi et al. (31)</td>
<td>2014</td>
<td>Multicentric, RCT</td>
<td>Patients with CVD or aged 55 to 79 yrs and had anatomic evidence of significant ASCVD, albuminuria, LVH, or ≥2 additional RFs (HLD, HTN, current smoking status, or obesity)</td>
<td>10,251 (I = 5,040; C = 5,042)</td>
<td>Intensive glucose control (HbA₁c &lt; 6.0%)</td>
<td>Standard strategy (HbA₁c: 7.0%-7.9%)</td>
<td>4.7 yrs</td>
<td>• There was no difference in AF incidence between the 2 groups</td>
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<td>• Patients with DM and new-onset AF had a hazard ratio of 2.65 for all-cause mortality</td>
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<td>Exercise and cardiorespiratory fitness</td>
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<tr>
<td>Pathak et al. (32)</td>
<td>2015</td>
<td>Single-center, single-arm study</td>
<td>Consecutive patients with symptomatic paroxysmal or persistent AF and BMI ≥27 kg/m²</td>
<td>308</td>
<td>Weight and risk factor management program, structured exercise program</td>
<td>No control arm</td>
<td>49 months</td>
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<td>• Greatest arrhythmia-free survival (with and without rhythm control strategies) was observed in patients with high cardiorespiratory fitness compared with adequate or low cardiorespiratory fitness</td>
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<td>• Decreased AF burden and symptom severity in patients with cardiorespiratory fitness gain ≥2 METs, compared with &lt;2 METs</td>
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<td>• 2-fold greater probability of arrhythmia-free survival in patients with cardiorespiratory fitness gain ≥2 METs, compared with &lt;2 METs</td>
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</table>

AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; C = sample size of the control group; CVD = cardiovascular disease; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; I = sample size of the intervention group; IVS = intraventricular septum thickness; LAA = left atrial area; LVH = left ventricular hypertrophy; METs = metabolic equivalents; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RF = risk factors; RFM = risk factor management.
Although there is a link between endurance exercise and AF, this represents a small fraction of patients and a subgroup of people already at low risk of developing AF. There are no data to suggest that routine light or moderate exercise puts patients at increased risk of AF, and there is evidence that light-to-moderate exercise may decrease incident AF. In addition, increased fitness is associated with reduced AF risk. Given the other cardiovascular benefits of routine exercise, it is logical to recommend regular, moderate exercise as part of routine AF prevention and management.

**Hypertension**

Elevated blood pressure has consistently been one the strongest predictors of the development of AF (42). Even high-normal blood pressure has been linked with increased risk of AF (43). The increased afterload leads to both atrial and ventricular structural remodeling, resulting in diastolic dysfunction and left atrial enlargement and fibrosis (44,45). These changes in turn lead to increased AF (45).

AF risk reduction via blood pressure control has not been consistently shown. Therefore, control of hypertension (HTN) in those without cardiovascular disease is not currently recommended for prevention of AF (5). However, HTN plays an important role in the management of AF in regard to thromboembolic risk. The presence of HTN is a risk factor for stroke in patients with AF in both the CHADS2 and CHADS2-VASc risk stratification instruments (46). Control of HTN with losartan has been associated with a 2-fold reduction of stroke rates (47).

It is well-documented that HTN is associated with increased risk of AF and increased risk of complications of AF, particularly stroke. Although treatment of HTN has not been consistently shown to decrease AF risk, it is an important component of reducing thromboembolic risk and of any AF management strategy.

**Cholesterol**

Studies assessing associations between dyslipidemia and incident AF report variable results. Multiple studies have shown that low levels of high-density lipoprotein cholesterol (<35 mg/dl) are associated with increased risk of new-onset AF (48,49). However, other studies have found no association between high-density lipoprotein cholesterol and incident AF, and increased total cholesterol and low-density lipoprotein cholesterol have been associated with a lower incidence of AF (50,51).

A number of studies have evaluated the roles of statins and fish oil in AF prevention. In a meta-analysis of 6 randomized controlled trials involving 3,557 patients, statin therapy decreased the relative risk of incident or recurrent AF by 61% compared with standard of care (52). In a subgroup analysis, the benefit from statin use was limited to those with a previous history of AF and those undergoing cardiac surgery or treatment for ACS.

Prospective data on the role of fish oil in decreasing the incidence of AF are limited. Two randomized, double-blind, placebo-controlled trials of high-dose omega-3 (4 to 8 g/day) failed to show a reduction in AF recurrence among patients with a history of paroxysmal or persistent AF (53,54). In meta-analyses, fish oil supplementation was not associated with reduction of AF risk (55).

Statins are, however, associated with decreased risk of post-operative AF. A meta-analysis of randomized controlled and observational studies in cardiac surgery including 17,643 patients demonstrated less post-operative AF with pre-operative statin use (56).

In total, the data linking abnormal lipid profiles and incident AF has been mixed, as have been studies of statins and fish oils in prevention of AF. On the basis of the evidence, recommendations for use of lipid-lowering agents for the purpose of preventing or managing AF is limited to its role in cardiac surgery patients.

**Diabetes**

Diabetes is an independent risk factor for AF (57,58). This has been corroborated with long-term prospective population cohort studies. In the Framingham Heart Study, diabetes was associated with 40% higher risk of AF in men and 60% higher risk in women after 38 years of follow-up (59).

Regarding mechanisms underlying the association of diabetes and AF, cardiac autonomic neuropathy has been implicated by leading to sympathetic overactivity and neural remodeling (60,61). Dysfunctional cardiac autonomic activity can trigger AF, especially with changes in vagal tone (62).

There are limited data on diabetes management and AF risk. The Action to Control Cardiovascular Risk in Diabetes study randomized 10,251 patients to intense glycemic control (HbA1c <6.0%) or a standard target (7.0% to 7.9%). There was no difference in new-onset AF between the 2 arms (31). In a prospective study of 263 consecutive patients undergoing first-time catheter ablation for AF, there was no difference in AF recurrence between those patients with and without diabetes; however, there was a significant increase in procedural complications including stroke, cardiac tamponade, and hematomas among those with
diabetes (63). Other studies have shown a greater atrial tachyarrhythmia recurrence rate following catheter ablation for AF in patients with diabetes (64,65).

In summary, there is currently insufficient evidence to suggest that any particular management strategy for diabetes directly affects the risk of developing AF. However, it is reasonable to hypothesize that optimal management of diabetes and prevention of cardiovascular complications may indirectly reduce risk of AF.

**OBSTRUCTIVE SLEEP APNEA**

Obstructive sleep apnea (OSA) is highly prevalent in patients with AF. In a prospective analysis, approximately 50% of AF patients had OSA, as compared with 32% of controls (66). After a multivariate analysis looking at traditional risk factors for OSA, AF had a greater association with OSA than BMI, HTN, or diabetes.

Mechanisms by which OSA contributes to AF risk include intermittent nocturnal hypoxemia/hypercapnia, surges in sympathetic tone and blood pressure during apneic episodes, and increased inflammation (67,68). All of these factors may contribute to left atrial remodeling and chamber dilation, contributing to perpetuation of AF.

Rates of AF recurrence after electrical cardioversion are higher in patients with OSA who are not treated with nocturnal positive-pressure therapy. In a prospective study of patients with OSA referred for electrical cardioversion (N = 39), the 12-month AF recurrence rate was 82% in patients who were not appropriately receiving positive-pressure therapy versus 42% in patients using appropriate OSA treatment (69).

In a prospective study of AF patients with OSA referred for index pulmonary vein isolation (PVI) procedure, arrhythmia-free survival at 1 year was higher in those who were compliant with positive-pressure therapy (71.9%) compared with patients who were not (36.7%) (70). Arrhythmia-free survival after PVI in treated OSA patients was similar to arrhythmia-free survival in patients who did not have OSA. The risk of AF recurrence after PVI in untreated OSA patients was the same as the risk of recurrence in OSA patients with AF who were medically managed without PVI.

There is clear evidence demonstrating OSA to be a significant risk factor for AF. In addition, treatment of OSA is an important component of AF management, particularly when cardioversion or PVI is used. The strength of the evidence warrants consideration of routine clinical screening for OSA prior to use of a rhythm control strategy.

**TOBACCO AND ALCOHOL**

Studies yield conflicting results in regard to the association of tobacco use and incident AF (71–73). Alcohol consumption has been associated with an increased risk of developing AF in a dose-dependent manner (74). Although tobacco and alcohol have been associated with increased risk of AF, the effect of tobacco cessation or reduction in alcohol intake on management of AF is less clear. They are, therefore, components of a comprehensive strategy to lower AF risk, but cannot be recommended specifically for the purpose of improving AF outcomes.

**CONCLUSIONS**

In addition to anticoagulation, rhythm control, and rate control, a fourth pillar of AF management is emerging. There is growing evidence supporting aggressive RFM, especially weight loss, in the context of a comprehensive RFM plan. These benefits are seen in AF prevention, success rates in AF management, and in reducing complications of AF, including stroke. Although fundamental in primary care and cardiology for the management of ASCVD, RFM in AF deserves similar recognition. The current body of evidence supports a comprehensive strategy of weight loss, exercise, and fitness, screening for OSA, and treatment of traditional modifiable ASCVD risk factors. Further research needs to be performed before making specific recommendations and guidelines on appropriate weight loss and fitness targets.

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46. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and


**KEY WORDS** diabetes, hyperlipidemia, hypertension