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Lifestyle Changes in Atrial Fibrillation Management and Intervention

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Abstract

Atrial fibrillation (AF) is one of the most common arrhythmias in adults, and its continued rise in the United States is complicated by the increased incidence and prevalence of several AF risk factors, such as obesity, physical inactivity, hypertension, obstructive sleep apnea, diabetes mellitus, coronary artery disease, and alcohol, tobacco, or caffeine use. Lifestyle and risk factor modification has been proposed as an additional pillar of AF therapy, added to rhythm control, rate control, and anticoagulation, to reduce AF burden and risk. Although emerging evidence largely supports the integration of lifestyle and risk factor management in clinical practice, randomized clinical trials investigating the long-term sustainability and reproducibility of these benefits remain sparse. The purpose of this review is to discuss potentially reversible risk factors on AF, share evidence for the impact on AF by modification of these risk factors, and then provide an overview of the effects of reversing or managing these risk factors on the success of various AF management strategies, such as antithrombotic, rate control, and rhythm control therapies.

Keywords

Lifestyle; risk factors; atrial fibrillation; ablation; cardioversion; rate control; rhythm control

INTRODUCTION

The prevalence of atrial fibrillation (AF) in the United States (U.S.) is projected to increase to 12.1 million cases in 2030, more than double the prevalence reported in 2010.[1] Countries with high socio-demographic index have the highest burden; however, countries with middle socio-demographic index showed the largest recent increase.[2] As AF incidence and prevalence are projected to continue to increase over the next several decades, AF will undoubtedly remain a large public health challenge.

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Contributing to the increase in AF are its associations with older age and obesity, both risk factors for AF that are rising in the U.S. population. Besides obesity, other risk factors for AF may also be reversible, including physical inactivity, hypertension, obstructive sleep apnea (OSA), diabetes mellitus (DM), coronary artery disease (CAD), and alcohol, tobacco, or caffeine use. Several of these risk factors have been shown to reduce AF incidence as well as AF recurrence and burden.

Lifestyle and risk factor modification (LRFM) has been proposed as an additional pillar of AF therapy, added to rhythm control, rate control, and anticoagulation.[3] This review will provide an overview of LRFM in AF and a comprehensive summary of the impact of reversing or managing these risk factors on the success of various AF management strategies, such as antithrombotic, rate control, and rhythm control therapies.

MECHANISMS UNDERLYING RISK FACTORS AND AF

The link between many of the proposed risk factors and AF is multifactorial. Regarding obesity, several mechanistic studies suggest that the stearic acid present in pericardial and epicardial fat can disrupt and remodel the properties of cardiac ion currents to promote arrhythmogenesis.[4] Inflammatory markers associated with epicardial fat are also correlated with AF burden and severity.[5,6] In addition, obesity is associated with a greater risk for hypertension and diastolic dysfunction, which increases AF susceptibility via stretch-activated left atrial channels.[7,8] The risk of developing obesity and cardiovascular disease can be reduced with physical activity. Hypertension is also seen in association with obesity and is related to alterations in hemodynamics and increased ventricular afterload, causing left ventricular hypertrophy and left atrial enlargement and stiffness. Increased circulatory levels of angiotensin II, induced by hypertension, can also cause atrial fibrosis, hypertrophy, and remodeling, leading to electrophysiological changes that trigger AF development.[9–11] OSA is characterized by recurrent short apneic episodes due to pharyngeal airway collapse. The intermittent hypoxia may also affect the atrial effective refractory period and increase AF susceptibility. These repetitive upper airway occlusions cause large oscillations in intrathoracic pressures, leading to short-term physiological changes, such as increased venous return, increased ventricular afterload, and, subsequently, increased left atrial pressures and enlargement. Over time, OSA can also promote prolonged systemic inflammation, a prothrombotic state, atrial fibrosis, and electrical remodeling.[12,13] Although data on precise mechanistic pathways for DM remain limited, studies suggest that electrical and cardiac remodeling along with hyperglycemia-induced fibrotic change likely contribute to increased AF susceptibility.[14–17]

Mechanisms by which substance use in the form of alcohol, tobacco, and caffeine contributes to the development of AF have been described in the literature. Alcohol likely serves both as a trigger and propagator of AF via atrial remodeling and autonomic effects. Increased oxidative stress and autonomic function during alcohol consumption can directly impact atrial myocytes, resulting in long-term consequences such as left atrial remodeling and dilation.[18,19] Smoking is associated with increased sympathetic tone, inflammation, thrombosis, endothelial dysfunction, atrial fibrosis, and oxidative stress, which are all potential factors in AF development.[20] Cigarette smoke exposure has also been

reported to modify the atrial electrophysiological substrate involved in arrhythmogenesis by increasing the cardiac acetylcholine activated inward rectifier potassium current (I_{KACh}) via phosphatidylinositol 4-phosphate 5-kinase alpha (PIP5K) and ADP ribosylation factor 6 (Arf6) signaling.[21] Precise mechanisms for caffeine's impact on AF need to be elucidated. Moderate doses (<6 cups of coffee daily) of caffeine have been reported to be well-tolerated with little evidence to suggest a proarrhythmic state, whereas unusually large quantities of caffeine (>10g) have been associated with tachydysrhythmias.[22]

EFFECT OF LIFESTYLE OR RISK FACTOR MODIFICATION ON AF

The effect of lifestyle and risk factors on AF and the impact of modification of these risk factors on AF are summarized in Table 1. Most evidence is based on observational or retrospective studies, as few randomized studies have examined the direct effects of intentional modification of lifestyle and risk factors on AF.

Weight Management

Obesity and higher body mass index (BMI) remain strong risk factors for AF that contribute to the incidence of AF, as well as increased AF burden, including the progression from paroxysmal to persistent or permanent AF. A Mendelian randomization study suggests the relationship between obesity and AF may be causal.[23] A 51-study meta-analysis showed that with each 5-unit increase in BMI, there is a corresponding increase in incident AF by 29% and 19% in cohort and case-control studies, respectively, as well as an increase in postoperative AF by 10% and post-ablation AF by 13%.[24]

In a series of studies from a group in Australia, Sanders and colleagues showed a benefit of weight loss on AF burden. A single-center randomized controlled trial (RCT) from this group reported that patients with symptomatic AF who underwent weight management, compared to patients who received only general lifestyle advice, experienced more significant reductions in AF burden, symptom severity scores, cumulative duration, and interventricular septal thickness.[25]

Also from this group, in the LEGACY (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort) study, long-term patient outcomes were assessed over four years by the degree of weight loss: group 1 (>10%), group 2 (3 to 9%), and group 3 (<3%).[26] Group 1 exhibited lower AF burden and greater arrhythmia-free survival rates. The REVERSE-AF (PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation) study, a sub-analysis of the LEGACY study, assessed the degree of weight loss and its impact on the progression of AF.[27] Patients with the greatest degree of weight loss had the lowest rates of progression from paroxysmal to persistent AF and the highest rates of reversal from persistent to paroxysmal or no AF.

Physical Activity

Regular moderate aerobic exercise is effective for reducing AF burden and AF-related symptoms and improving quality of life. In addition to the effect of weight loss on AF outcome in the LEGACY study, the CARDIO-FIT (Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation) study

explored the interaction between cardiorespiratory fitness and weight loss on rhythm control in individuals with a BMI ≥27 kg/m^2 and non-permanent AF.[28] Patients' initial cardiorespiratory fitness were categorized as low (<85%), adequate (86 to 100%), or high (>100%). At the final follow-up, patients were grouped by cardiorespiratory fitness gain [≥2 metabolic equivalents (METs) vs. <2 METs]. Patients in the high cardiorespiratory fitness group experienced the greatest arrhythmia-free survival, and patients in the ≥2 METs improvement group experienced significantly reduced AF burden and symptom severity. Each unit gain in METs was associated with a 9% gain in long-term freedom from AF. Individuals with both >10% weight loss and ≥2 METs gain reported the greatest freedom from AF, suggesting that physical activity and weight loss may have a synergistic relationship.

Physical activity may mitigate some of the AF risk associated with obesity. The Women's Health Initiative (WHI) prospective observational study of postmenopausal women over a period of 11.5 years showed that greater physical activity was correlated with lower incident AF rates and reduced the AF risk conferred by obesity.[29] The HUNT-3 prospective cohort study in Norway of individuals ≥18 years of age showed that higher levels of physical activity could offset some, but not entirely, the AF risk associated with obesity.[30]

Exercise training in patients with AF can have favorable effects beyond AF reduction. A meta-analysis of five RCTs in AF patients found that exercise training was associated with reduced BMI and improved exercise capacity, left ventricular ejection fraction, and quality of life.[31] In one study, AF patients were randomized into either a short-term aerobic and muscle-strengthening exercise program or a two-month control period.[32] Those who received the short-term exercise training reported improved AF-related symptoms and health-related quality of life. A similar study randomized patients with permanent AF into either 12-week aerobic exercise training or a control group.[33] Patients in the exercise training group not only reported greater quality of life, as assessed by the Minnesota Living With Heart Failure (MLHF-Q) questionnaires, but they also demonstrated greater overall exercise capacity and decreased resting pulse rate. Of note, leisure-time activities and walking were associated with decreased AF incidence, which were later supported by findings reported by a prospective study of AF-free women ≥45 years of age without AF and cardiovascular disease at enrollment[34] and a population-based Swedish cohort of AF-free middle-aged and elderly women.[35] These studies suggest that encouraging exercise training in patients with AF may improve not only AF burden but also symptoms and quality of life.

Research on the impact of high-intensity interval training (HIIT) on AF has yielded some conflicting reports. Non-permanent AF patients were randomized to either HIIT or to resume their regular exercise habits. Those in the HIIT group exhibited reduced AF burden and improved AF-related symptoms, peak O_2, left atrial and ventricular function, lipid levels, and quality of life.[36] A separate 12-week RCT showed that high-intensity physical exercise did not reduce AF burden compared to low-intensity physical exercise, though HIIT was more time-efficient.[37] A randomized, prospective, longitudinal study reported greater AF occurrence in patients with concomitant hypertension and chronic kidney disease that engaged in HIIT compared to moderate exercise.[38] Although there was no difference in atrial electrical activity between HIIT and yoga in a randomized study, HIIT was associated

with changes in left atrial mechanical functioning and adverse remodeling of the left atrium and left ventricle.[39]

Although evidence suggests that moderate physical activity benefits AF reduction, extreme levels of exercise may be associated with a higher risk of AF. In a prospective study of adults ≥65 years of age, light-to-moderate-intensity exercise had lower AF incidence compared to no and high-intensity exercise, displaying a U-shaped relationship between exercise intensity and AF incidence.[40] A meta-analysis of six case-control studies reported a greater risk of AF in athletes compared to non-athletes.[41] A cohort study examining long-distance cross-country skiers reported a higher incidence of AF in those with faster finishing times and a high number of completed races, suggesting an exercise-dose-dependent relationship.[42] Similar adverse results have been described in former professional cyclists,[43] sports competitors,[44] and marathon runners.[45] Importantly, this level of extreme exercise capacity is not achieved by the average individual, and the 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity exercise recommended for all adults by the 2018 Physical Activity Guidelines Advisory Committee do not increase the risk of AF.

Multicomponent and mind-body exercises, such as yoga, tai chi, and qigong, have also been proposed as potential domains for exploration. A single-center clinical trial showed that paroxysmal AF patients had improved quality of life and reduced AF burden, AF-related symptoms, heart rate, blood pressure (BP), and anxiety and depression scores after receiving yoga training.[46]

Sleep-disordered Breathing / Obstructive Sleep Apnea Therapy

Sleep-disordered breathing (SDB), including OSA, is often an undiagnosed risk factor among AF patients. A systematic review and meta-analysis showed that SDB is highly prevalent in AF patients, but inconsistent diagnostic tools and thresholds are often used to detect concomitant SDB in AF. Using a SDB diagnosis cutoff of apnea-hypopnea index (AHI) ≥5/h, the pooled SDB prevalence was 78%, with moderate-to-severe SDB making up 40%.[47] An analysis of the ORBIT-AF (Outcomes Registry for Better Informed Treatment of AF) cohort study revealed that patients with OSA treated with continuous positive airway pressure (CPAP) were less likely to progress to more permanent AF compared to those without CPAP treatment.[48] Greater benefits were observed in the younger, obese, and male patients. On the other hand, a RCT of 2,717 patients concluded that the addition of CPAP to usual care for patients with moderate-to-severe OSA and established cardiovascular disease did not significantly improve the prevention of cardiovascular events.[49] Another RCT of 109 patients with paroxysmal AF and moderate-to-severe obstructive and/or central sleep apnea, who tolerated CPAP over a two-week period, failed to show a significant reduction in AF burden.[50] However, the study excluded patients with LVEF <45%, BMI >40 kg/m^2, or severe excessive daytime sleepiness (Epworth Sleepiness Scale score >15), arguably patient groups who may have had the most to gain from the treatment of sleep apnea. A bidirectional Mendelian randomization study found genetically predicted OSA to be causally associated with increased AF risk, suggesting that earlier OSA screening and management may have beneficial anti-arrhythmic effects.[51]

Diabetes Mellitus Management

DM has been associated with risk for incident AF. A large-scale study from the Veterans Health Administration Hospitals identified DM as a strong, independent risk factor for AF occurrence using a multivariate analysis.[52] A large systematic review and meta-analysis of seven prospective cohort studies and four case-control studies showed that DM was associated with a 40% greater risk of AF.[53] This reported association between DM and AF may be reduced after adjusting for confounding risk factors.[54] A recent Swedish cohort study found that individuals with type 2 DM had an overall 35% increased risk of AF after controlling for age and sex.[55]

Poor glycemic control has been independently associated with an increased risk of AF,[56] and certain anti-diabetic agents have been associated with lower AF risk. Serum hemoglobin A1c (HbA1c) levels have been described as a potential predictive biomarker for AF risk.[57] Thiazolidinediones have been correlated with lower AF development in non-insulin-dependent patients.[58] Similarly, metformin was associated with decreased AF risk in a population study of 645,710 type 2 DM patients in Taiwan.[59] Pioglitazone was effective in reducing the progression rate from persistent to permanent AF in a RCT of 146 patients.[60] A recent meta-analysis of 16 RCTs also concluded that sodium-glucose transport protein 2 (SGLT-2) inhibitors were associated with a 24% reduction in AF risk.[61] However, no randomized trials have focused solely on glycemic control as an AF intervention.

Hypertension Management

Hypertension has been implicated as the most important contributor to AF development with the population-attributable fraction for AF being 21.6%, compared to 12.7% for BMI, 7.45% for smoking, and 8.77% for DM.[62] The SPRINT (Systolic Blood Pressure Intervention Trial) RCT of intensive BP control concluded that patients with hypertension and high risk of cardiovascular disease who underwent intensive BP lowering with a target systolic BP <120 mmHg compared to a goal of <140 mmHg had a 26% reduction in AF risk.[63] These results were subsequently corroborated in a recent meta-analysis.[64] Uncontrolled hypertension at the upper high-normal range, systolic BP of 128–138 mmHg or diastolic BP of 80–90 mmHg, is a long-term predictor of incident AF in initially healthy middle-aged men.[65] Although mineralocorticoid receptor antagonist treatment with either eplerenone or spironolactone has been shown in a meta-analysis to be associated with a decreased AF risk and recurrence[66], the use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have yielded mixed results in terms of primary AF prevention.[67,68]

Coronary Artery Disease Treatment

AF and CAD share similar risk factors[69,70], suggesting that management focused on targeting common risk factors may prove beneficial. However, at this point, only beta-blockers have been associated with an antiarrhythmic effect after an acute myocardial infarction.[71] Low-density lipoprotein cholesterol (LDL-C) has been long-established as a causal factor in the development of atherosclerotic cardiovascular disease, which in turn is also an independent risk factor for the development of AF. However, current studies, largely observational, have suggested that elevated levels of LDL-C and total cholesterol

may be inversely associated with incident AF.[72] Although the clinical significance of this "cholesterol paradox" remains unclear, hyperlipidemia should continue to be evaluated and managed as a part of a patient's overall cardiovascular risk.[73]

Alcohol Reduction

Alcohol consumption has been described as having a dose-response relationship with AF development, and consuming even 1 drink/day may significantly increase AF risk.[74,75] The Norwegian HUNT study demonstrated a curvilinear relationship between alcohol consumption and AF risk.[76] <1 drink/day for women and <2 drinks/day for men were not associated with AF risk. There was almost no increase in AF risk up to 7 drinks/week, but >14 drinks/week was correlated with a steep increase in AF risk. Similarly, a pooled cohort study found that consumption of more than one up to 2 drinks/day was associated with a 28% increased risk of AF, and consumption of more than 4 drinks/day was associated with a 47% increased risk of AF.[75]

In patients with AF, AF burden and outcomes may be improved by moderation or abstinence from alcohol use. An observational study stratified patients according to alcohol consumption (abstainer-rare, light (<100 g/week), moderate (100–200 g/week), and heavy (≥200 g/week)) and found that only heavy alcohol consumption increased the risk of adverse events in AF patients, such as ischemic stroke, transient ischemic attack, systemic embolic event, or AF hospitalization.[77] However, alcohol as a trigger of AF in AF patients was confirmed in a recent N-of-1 study by Marcus and colleagues.[78] Furthermore, a multicenter study randomized 140 patients with a history of paroxysmal or persistent AF in sinus rhythm at the time of the study and drank ≥10 drinks/week to either abstain from alcohol or continue usual alcohol consumption.[79] In the abstinence group, alcohol intake was reduced from 16.8±7.7 to 2.1±37 drinks/week, 61% completely abstained, 76% reduced intake to ≤2 drinks/week, and 86% reduced intake by >70% of baseline. In the control group, intake was slightly reduced from 16.4±6.9 to 13.2±6.5 drinks/week. Patients who followed alcohol abstinence showed reduced arrhythmia recurrence as well as lowered AF burden by 58% by six months compared to control subjects. In secondary analyses, greater weight reduction and AF symptom improvement were noted in the abstinence group compared to the control group. Patients who completely abstained had a lower risk of recurrent AF compared to patients who consumed 1–9 drinks/week or ≥10 drinks/week. These data support counseling AF patients on modifying alcohol use to improve AF burden.

Tobacco Smoking Control

A large meta-analysis showed a dose-dependent relationship between smoking and AF risk, with a stronger association in current smokers compared to former smokers.[80] Tobacco smokers had a 33% higher AF risk than individuals who have never smoked.

Smoking cessation after diagnosis of AF may have beneficial consequences on AF and AF outcomes. In another study of 2,372 males with newly diagnosed AF from the Korean National Health Insurance Service database, smokers who quit after AF diagnosis and those who have never smoked had a reduced risk of cardiovascular disease and ischemic and total stroke compared to continual smokers.[81] In a larger study of 97,637 patients from

the Korean National Health Insurance Service database, 6.9% stopped smoking after AF diagnosis, and 14.6% continued to smoke.[82] Quitters had a 30% lower risk of ischemic stroke (55% reduction in fatal stroke) and 16% reduction in all-cause death (34% reduction in death from cerebrovascular events), irrespective of oral anticoagulation status.

Caffeine Consumption

Caffeine may have differential effects on incident AF versus patients with an established history of AF. In a long-term prospective cohort study of men who participated in the Physicians' Health Study, there was a slightly lower risk of AF among those who drank one to three cups of coffee per day; however, there was no significant increase in AF risk for consumption <1 cup/day or >3 cups/day.[83] A univariate analysis of lone AF patients showed that increasing levels of coffee consumption were associated with significantly greater AF risk, with the lowest probability of spontaneous conversion observed in those consuming more than three cups of espresso per day.[84] A meta-analysis of six prospective cohort studies found a very weak association between caffeine exposure and reduced AF risk, specifically an 11% reduction in AF risk for low doses (<500 mg/day) and a 16% reduction for high doses (≥500 mg/day).[85] The study also described a dose-response relationship in which AF incidence decreased by six percent for every 300 mg/day increment increase in habitual caffeine intake. Although there may be a possible protective effect at low[86] and elevated doses as well as habitual caffeine intake, a clear link between caffeine consumption and incident AF risk has not been established. The CRAVE (Coffee and Real-time Atrial and Ventricular Ectopy) trial recently reported at the American Heart Association Scientific Sessions in November 2021 that in healthy patients, caffeine did not increase atrial arrhythmias, though it increased premature ventricular complexes. This was concordant with other observational studies showing no increase in AF in a "primary prevention", no prior AF population. In contrast, 25–28% of patients with AF have reported caffeine as a trigger.[87,88] The I-STOP-AFib (Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation) N-of-1 trial showed no significant change in AF with caffeine; however, self-selection of this trigger in the trial may have affected results.[78]

EFFECT OF LRFM ON AF MANAGEMENT STRATEGIES

Several studies have reported associations of potentially reversible risk factors on the outcomes of AF management therapies (Figure 1). This section will review existing data (Table 2). However, randomized trials studying the impact of LRFM on AF management strategies remain sparse.

Antithrombotic Therapy

Anticoagulation—The impact of obesity on the efficacy of anticoagulation using non-vitamin K antagonist oral anticoagulants (NOACs) has been a concern, as levels are not monitored, in contrast to INR monitoring used for warfarin.[89,90] However, four NOAC versus warfarin trials with BMI stratification data demonstrated preserved efficacy and similar bleeding risk of NOACs versus warfarin in AF patients with obesity.[91] Overall, NOACs can be efficacious and safe for AF patients with a BMI ≤50 kg/m^2. Interestingly, some clinical trials have observed an "obesity paradox" in which higher BMI was

associated with better overall outcomes, such as reduced stroke risk, in patients treated with anticoagulant therapy.[92,93] However, the weight classes of enrolled participants in these trials were not equally distributed, resulting in biased data comparisons. Overall, studies remain limited for patients experiencing severe obesity. A meta-analysis of RCTs suggested no difference in NOAC effects between different BMI classes among AF patients; however, patient data was limited in the class III obesity category, and the overall findings and trends were not significant and/or conclusive.[94]

Although some subanalyses of phase III clinical studies[95], registries, and small-sample prospective trials[96] have reported comparable efficacy and safety of NOACs in patients with or without DM, the original studies were not explicitly designed to examine the effect of DM on clinical outcomes in AF patients treated with NOACs versus warfarin. The impact of DM management on AF anticoagulation outcomes and drug interactions between NOACs and common antidiabetic agents remain areas in need of further study.[97]

The effect of high BP on anticoagulation-associated intracranial hemorrhage or hemorrhagic expansion is variably reported.[98–100] For AF patients, higher BP has been associated with an increased risk of thromboembolic complications. A cross-sectional, longitudinal analysis of data from the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in AF) III and V trials reported increased rates of stroke and systemic embolic events with higher BP levels, especially for individuals with systolic BP levels ≥140 mmHg.[101]

Patients with concomitant CAD and AF may require triple antithrombotic therapy (dual antiplatelet plus oral anticoagulation) around the time of acute coronary syndromes and/or percutaneous coronary intervention (PCI). However, such regimens are associated with a higher risk of bleeding. Current consensus recommendations include: minimization of the use of triple therapy to short durations (e.g., 30 days) due to the increased risk of bleeding; when an antiplatelet is needed along with an anticoagulant, clopidogrel is most often recommended; when aspirin is used, limit dosing to <100 mg/day; use of a proton pump inhibitor when dual antithrombotic agents are used; for PCI in AF patients, a NOAC is preferred over warfarin and use, e.g. oral anticoagulation with a P2Y12 antiplatelet agent for the first six to 12 months (or aspirin for the last six months if stable ischemic disease) with change to anticoagulation monotherapy after one year.[102,103] Recommendations may be subject to change as additional studies in this area are reported.

Left Atrial Appendage Closure—Although AF patients with DM are at higher risk for bleeding and thromboembolism, outcomes after left atrial appendage closure (LAAC) appear comparable to those in non-diabetics.[104,105] However, a recent multicenter study of 277 patients with LAAC and prior gastrointestinal bleeding reported DM as a risk factor for higher mortality after LAAC.[106] Smoking was identified as an independent predictor of device-associated thrombus after LAAC with one device.[107] The impact of modification of lifestyle or risk factors on LAAC outcomes has not been studied.

Rate Control Therapy

Except for better rate control with moderate physical activity, other lifestyle or AF risk factors do not appear to significantly affect pharmacological rate control therapies using AV node blockers or nonpharmacologic approaches with AV node or AV junction ablation.

A prospective pilot study of 10 permanent AF patients observed a significant decrease in ventricular rate with regular moderate physical activity.[108] A retrospective study noted that the presence and severity of OSA had no correlation with inadequate heart rate control, suggesting that successful rate control in AF patients can be achieved regardless of whether the patient has OSA.[109] An association of obesity and/or type 2 DM with cardiac fibrosis that affects the conduction system has been theorized to predispose patients to bradyarrhythmias and heart block following the prescription of AV nodal-blocking drugs.[110] However, we found no data to support a clinically significant hypersensitivity to these drugs in obese or diabetic patients with AF.

Rhythm Control Therapy

In an international, blinded RCT, investigators assigned patients with early AF (diagnosed ≤1 year before enrollment) to either rhythm control (treatment with either antiarrhythmic drugs or AF ablation) or usual care (management of AF-related symptoms).[111] Those receiving early rhythm control therapy had a lower risk of adverse cardiovascular outcomes than the usual care group; however, there were no differences in symptoms and left ventricular function at two years. Although the percentage of primary safety outcome events (composite of death, stroke, or serious adverse events related to rhythm control therapy) did not differ between the two groups, the rate of serious adverse events related to rhythm control therapy was 4.9% compared to 1.4% among those assigned to usual care. In this section, the impact of LRFM on various rhythm control therapies, such as antiarrhythmic drugs, cardioversion, and AF ablation, is discussed.

Antiarrhythmic Drug Therapy—Obesity is an established risk factor for AF, but the precise mechanisms of how it affects antiarrhythmic drug response remain unclear. An observational cohort study found that patients with obesity were less likely to respond to class I antiarrhythmic drugs compared to patients without obesity. However, both groups responded similarly to a potassium channel blocker.[112] Patients with more severe OSA were more likely to be non-responders to antiarrhythmic drug therapy for AF than those with milder disease.[113] Although some retrospective analyses have associated renin-angiotensin system (RAS) inhibitors with the prevention of AF development in patients with a history of chronic heart failure (CHF) or left ventricular hypertrophy (LVH),[114–117] a retrospective analysis of the CTAF (Canadian Trial of Atrial Fibrillation) randomized multicenter study, which enrolled few CHF or LVH patients and excluded patients with severely symptomatic CHF, did not observe additional benefit against AF recurrence with the inclusion of RAS blockers to antiarrhythmic agents.[118] However, there are no randomized studies specifically addressing LRFM effects on antiarrhythmic drug (AAD) therapy outcomes.

Cardioversion—Various observational studies have identified risk factors associated with AF recurrence versus success after cardioversion. Higher direct current cardioversion

(DCCV) failure has been observed in persistent AF patients with obesity. An observational substudy within a RCT studying manual pressure augmentation noted that patients with higher BMIs were more likely to fail shocks.[119] It was hypothesized that the lower success rate may be due to higher transthoracic impedance, longer interelectrode distance, and decreased transthoracic current flow secondary to current dissipation. However, success rates improved among patients with obesity when incorporating the use of paddles with manual pressure augmentation and escalating energy outputs to 360J.

The RACE 3 (Routine vs. Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure) trial randomized patients with early persistent AF and mild-to-moderate heart failure (HF) who received electrical cardioversion to either conventional therapy or targeted therapy of underlying conditions.[120] The targeted therapy group included four therapies: (i) mineralocorticoid receptor antagonists (MRAs), (ii) statins, (iii) angiotensin-converting enzyme inhibitors and/or receptor blockers, and (iv) cardiac rehabilitation including physical activity, dietary restrictions, and counseling. Greater improvement in sinus rhythm maintenance was observed in the targeted therapy group compared to the conventional therapy group. However, conclusions regarding specific interventions are limited since four interventions were started simultaneously in the targeted therapy group.

Higher AF recurrence after cardioversion was noted in patients with untreated OSA compared to patients without a polysomnographic diagnosis of OSA.[121] AF recurrence at 12 months was 82% in the untreated OSA group (n=27), 42% in the treated OSA group (n=12), and 53% in the control group (n=79). Of the patients without any OSA therapy, a greater nocturnal fall in oxygen saturation was associated with higher AF recurrence rates. However, a RCT of adults who underwent successful direct current cardioversion did not find a difference in AF recurrence between the groups that were treated with positive airway pressure versus usual care.[122]

Diabetes mellitus has been a long-established independent risk factor for AF recurrence following successful DCCV, and it has been associated with a 4.6 times higher risk of AF recurrence compared to patients without DM.[123,124] Type 2 DM, higher HbA1c levels, digoxin treatment, statin use, left atrial size, and LV ejection fraction have all been identified as independent risk factors for either immediate DCCV failure or AF relapse.[125] Although pioglitazone has been associated with positive effects following catheter ablation[126], a prospective randomized trial did not find an impact on AF recurrence after electrical cardioversion.[127]

The impact of hypertension management on cardioversion success and AF recurrence varies across observational studies and RCTs. In a post-hoc retrospective analysis, pretreatment with ACEi was observed to improve acute cardioversion but was not associated with reduced AF recurrence or improved sinus rhythm maintenance.[128] A separate retrospective review found that patients who had a lower BP immediately prior to the cardioversion were more likely to achieve sinus rhythm.[129] These results are similar to those reported in a RCT of persistent AF patients, in which those treated with amiodarone plus irbesartan before cardioversion had reduced AF recurrence rates compared to those with amiodarone

alone.[130] Another RCT of persistent AF patients also found that the addition of enalapril to amiodarone decreased arrhythmia recurrence and improved long-term sinus rhythm maintenance.[131] However, a RCT with 171 persistent AF patients did not find that treatment with candesartan for three to six weeks before and six months after cardioversion impacted AF recurrence rates.[132] Similar results were seen in a multicenter RCT that enrolled 1,442 patients with a prior history of at least underlying cardiovascular disease, DM, or left atrial enlargement and had a successful cardioversion for AF in the previous two weeks. Patients assigned to receive valsartan rather than a placebo did not have a reduction in AF recurrence.[133]

In one study of 116 patients with lone AF cardioverted within 48 hours of arrhythmia onset, higher ingestion of coffee (>3 cups/day), but not alcohol nor smoking habits, was associated with a reduced probability of spontaneous conversion.[84] A prospective study later reported smoking to be an independent risk factor for atrial arrhythmia recurrence after cardioversion in women and was associated with increased mortality risk in men.[134]

In summary, randomized controlled studies have shown that targeted therapy of underlying conditions in AF patients and HF effectively improved weight, BMI, lipid profile, and HF and led to greater sinus rhythm maintenance, whereas OSA therapy and DM management did not affect AF recurrence post-cardioversion. Other retrospective or observational reviews have noted an association between obesity and decreased cardioversion success and between higher caffeine use and lower spontaneous AF conversion. Mixed results and conclusions have been reported for hypertension management, coronary artery disease treatment, and smoking cessation.

AF Ablation—The impact of risk factor modification on AF ablation outcomes has been studied mostly via retrospective and prospective observational studies. Very few RCTs regarding this topic have been reported in the literature.

In retrospective studies from Cleveland Clinic, patients with morbid obesity undergoing AF ablation were compared to a control group with BMI <30 kg/m^2 matched by age, sex, ejection fraction, AF type, HF presence and type, and left atrial volume index.[135] Greater arrhythmia recurrence was observed in patients with morbid obesity compared to the control group. Within the morbid obesity group, lower arrhythmia recurrence was seen among those with other risk factor modifications: sleep apnea screening and treatment, BP control, glycemic control, and weight loss ≥5%. A greater number of met risk factor modification goals was correlated with lower arrhythmia recurrence, reduced need for repeat ablation or direct-current cardioversion, and fewer arrhythmia-related hospitalizations. AF recurrence was retrospectively assessed in patients with morbid obesity (BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related complications) who received bariatric surgery either before or after ablation.[136] Patients who had pre-ablation bariatric surgery experienced lower rates of AF recurrence.

In the ARREST (Aggressive Risk Factor Reduction Study for Atrial Fibrillation) prospective, observational cohort study from Australia, patients with a BMI >27 kg/m^2 and at least one cardiac risk factor who underwent AF ablation were offered aggressive

risk factor management consisting of BP control, weight management, lipid management, glycemic control, sleep-disordered breathing management, and smoking and alcohol counseling.[137] Compared to the control group, patients receiving risk factor management showed decreased AF frequency, duration, symptoms, and symptom severity at follow-up. Single-procedure drug-unassisted and multiple-procedure arrhythmia-free survival were significantly better in the risk factor management group. However, these findings may be limited by selection bias and potential confounders.

The SORT-AF (Supervised Obesity Reduction Trial for AF Ablation Patients) study was a prospective RCT of symptomatic AF patients with a BMI between 30 and 40 kg/m^2.[138] All patients underwent AF ablation and were randomized to either weight reduction or usual care. AF ablation was effective at significantly reducing AF burden in patients with obesity; however, interestingly, there was no significant difference in AF burden reduction 3- and 12-months post-ablation between the weight-reduction or usual care groups. Contrary to previous landmark studies, including the LEGACY and CARDIO-FIT studies, that included various AF therapy strategies, the SORT-AF study focused solely on weight loss in the context of AF ablation. In contrast to the ARREST-AF observational study, where AF ablation patients were grouped into risk factor management versus control depending on the patient's personal decision and motivation, SORT-AF randomized all eligible patients into a structured weight reduction program. Despite the rate of non-compliance and differences in motivation in the weight reduction program, the mean weight reduction of four percent of initial body weight was comparable to other studies and provided a more realistic scenario. However, the weight loss may have been too little to significantly impact AF burden, as evidenced by the LEGACY study, which reported the greatest effect in patients who lost >10% of their body weight. BMI reduction and increased exercise capacity were associated with reduced AF recurrence in persistent compared to paroxysmal AF patients, which may be related to the association of obesity with more advanced atrial substrate.

In patients enrolled in the DISCERN AF (Discerning Symptomatic and Asymptomatic Episodes Pre and Post Radiofrequency Ablation of Atrial Fibrillation) study, daily activity level was inversely associated with daily AF burden post-ablation.[139] However, a causal relationship cannot be established since decreased AF burden may permit patients to pursue more daily physical activities.

A nurse-led risk factor modification program to improve weight loss and OSA care among AF patients undergoing catheter ablation was conducted.[140] Nurses provided in-person consultations and monthly telephone calls to patients for up to one year. Enrolled patients demonstrated significant weight loss (4.7% ± 5.3% versus 0.3% ± 4.4%) and improved OSA care compared to patients who declined enrollment in the program; however, outcomes in terms of arrhythmia control (0–6 self-terminating recurrences with ≤1 cardioversion for nonparoxysmal AF) and freedom from arrhythmias (no recurrences on or off antiarrhythmic drugs) were similar at one year. Similar to the SORT-AF study, the failure to show a benefit of weight loss on AF ablation outcomes may be due to an inadequate degree of weight loss (4.7% compared to the 10% weight loss showing effects in the LEGACY study). Also, this program was part of a quality improvement initiative with voluntary participation and was not a research study. Thus, the authors stated that not all enrolled patients were treated to the

original management strategy and/or completed the necessary follow-up, which limited the ability to determine if participation in the program was directly responsible for the findings reported.[140]

OSA has been associated with greater AF recurrence following ablation in AF patients. A meta-analysis of eight studies (one RCT and seven prospective cohort studies) on OSA showed that patients treated with CPAP had a 44% decreased risk of AF, and among those who underwent catheter ablation, AF recurred in 18% of those who used CPAP and 37% in those who did not.[141] Other meta-analyses of observational studies have highlighted similar correlations between OSA, CPAP treatment, and AF recurrence risk after catheter ablation.[142–144] However, these findings are inconsistent with a recent RCT where 83 patients with paroxysmal AF after pulmonary vein isolation (PVI) were assigned to either CPAP treatment or standard care. PVI considerably decreased AF burden in both groups with no between-group difference. Despite a reduction in AHI from 26.7 ± 14 events/hour to 1.7 ± 1.3 events/hour at follow-up in the CPAP group, there was no further reduction in the risk of AF recurrence after ablation with CPAP treatment.[145]

Worse outcomes and greater AF recurrence rates have been observed in patients with DM undergoing ablation. An observational study of seven high-volume European centers found that arrhythmia relapses were more common in diabetic patients 12 months after AF ablation.[146] Additionally, a higher rate of atrial arrhythmia relapse was observed in patients with persistent AF compared to those with paroxysmal AF. A prospective observational cohort study of paroxysmal AF patients with type 2 DM showed that the use of pioglitazone before undergoing catheter ablation increased the probability of achieving sinus rhythm after a single ablation and decreased the necessity for repeat ablation.[126] A retrospective observational cohort study found that worsening and higher 12-month pre-ablation HbA1c levels were associated with greater AF recurrence rates after ablation.[147] Thirty-two point four percent of patients with HbA1c <7% at the time of ablation developed recurrent AF compared to 68.75% of the patients with HbA1c >9%. Treatment of diabetic patients with metformin was also independently associated with a significant decrease in the recurrence of atrial arrhythmias after AF catheter ablation.[148]

Management of hypertension prior to undergoing ablation has been associated with mixed results. Early prospective and retrospective studies did not observe a decreased AF recurrence rate following ablation in patients pretreated with ACEi or ARBs.[149,150] A RCT showed that aggressive BP lowering before AF catheter ablation did not affect arrhythmia recurrence compared to individuals who received standard BP treatment.[151] However, other works have highlighted how the autonomic nervous system may contribute to the development and progression of AF. In one study, 86 patients were randomized to either PVI or PVI with renal artery denervation (RDN) and followed over 12 months. The addition of RDN to PVI was associated with decreased AF recurrence, AF burden, and BP.[152] The ERADICATE-AF (Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation) trial also examined whether adding RDN to PVI could improve freedom from AF, atrial flutter, or atrial tachycardia at 12 months. Three hundred and two patients with paroxysmal AF were randomized into either PVI or PVI with RDN. The mean reduction in baseline systolic BP was three mmHg in the PVI-only group compared to 16

mmHg in the RDN with PVI group. RDN with PVI was associated with a significantly increased likelihood of freedom from AF at 12 months, and patients undergoing RDN developed AF about three months later compared to the PVI-only group. The number of composite fatal and nonfatal major adverse cardiac events was equal in the two groups. The investigators noted the findings of the study are limited by the lack of a formal sham-control RDN.[153] These studies suggest that RDN may be a useful adjunct along with PVI for slowing AF progression, especially in patients with resistant hypertension, or at least may provide some proof of concept that BP control can contribute to AF reduction.

Observational, but no randomized studies, have been published exploring the relationship between alcohol consumption and the success of ablation in AF patients. An observational study of paroxysmal AF patients noted that although the rate of AF recurrence was lower after the initial catheter ablation in those who did not consume alcohol, there was no difference in outcome after the final catheter ablation between those who did and did not consume alcohol.[154] Interestingly, the frequency, rather than the volume, of alcohol consumption was associated with AF recurrence after the initial catheter ablation. A retrospective analysis of both paroxysmal and persistent AF patients did not find moderate or heavy alcohol consumption to be significantly predictive of early or late AF recurrence in patients following PVI.[155] In a single-center, observational study, ethyl glucuronide in hair (hEtG) was used as a marker for long-term alcohol consumption. The study reported that male AF patients with hEtG ≥7pg/mg, indicative of repeated alcohol consumption, experienced higher rates of re-ablation compared to patients with hEtG <7pg/mg.[156]

The association of smoking with AF ablation outcomes has been studied observationally, but little data on the effects of smoking cessation are available. A study recruited 59 patients with drug-refractory AF to examine the impact of cigarette smoking on AF recurrence after PVI. The smoking group consisted of both former and current smokers. Smokers tended to have larger pulmonary vein diameters and left atrial volume and were at higher risk for AF recurrence after PVI than nonsmokers.[157] Another study comparing 201 patients with persistent AF showed no difference in long-term ablation outcomes between smokers and nonsmokers. However, compared to nonsmokers, smokers had a higher incidence of nonpulmonary vein (NPV) triggers, which was associated with increased recurrence and worse outcomes following catheter ablation.[158] No data are available on the effects of caffeine on post-ablation outcomes in AF patients.

In summary, retrospective and prospective observational studies have reported poorer outcomes after AF ablation with greater BMI values, less daily physical activity, OSA without CPAP treatment, DM and higher HbA1c levels, and hypertension. Mixed effects have been observed for alcohol and tobacco, and no congruent evidence currently exists for weight management, OSA treatment, hypertension management, alcohol reduction, or tobacco cessation to decrease AF recurrence or burden after AF ablation. More prospective, randomized studies of various LRFM are needed to establish conclusive recommendations.

CONCLUSIONS

Managing reversible risk factors is a strategy with immense potential to impact the care and treatment success of AF patients, especially relating to AF burden and recurrence. Most reports discussing AF and its management within the context of weight/obesity, physical inactivity, SDB/OSA, DM, hypertension, CAD, and alcohol, tobacco, and caffeine use are observational studies. Thus, more randomized controlled studies are required to delineate the effects of combining LRFM with traditional AF management strategies, such as antithrombotic, rate control, and rhythm control therapies.

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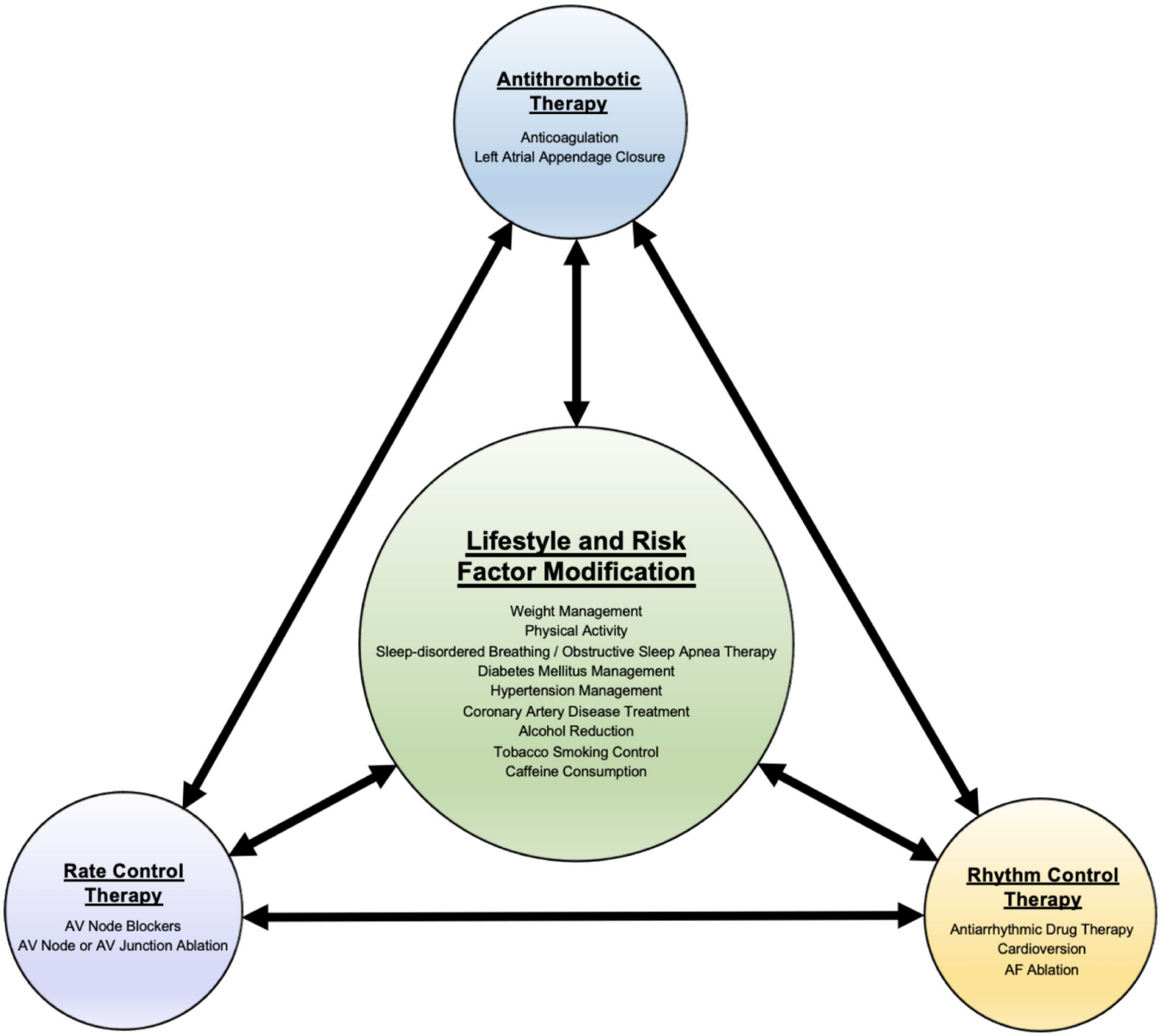

Figure 1: Synergy of LRFM and Traditional AF Management Strategies

AF management should follow an integrated approach, utilizing lifestyle and risk factor modifications in conjunction with antithrombotic, rate control, and/or rhythm control therapies. AF = atrial fibrillation. AV = atrioventricular.

TABLE 1

Associations of modifiable risk factors and lifestyle/risk factor modification on AF incidence, burden, and progression

Risk factors	Effect of risk factor on AF	Effect of LRFM on AF
Weight/obesity	↑	**↓**
Physical inactivity	↑	
Moderate activity		**↓**
High-intensity activity		**↓**/-/**↑**
SDB/OSA	↑	↓/-
DM	↑	**↓**
HTN	↑	**↓**/-
CAD	↑	NA
Alcohol	↑	**↓**
Tabacco	↑	NA
Caffeine	↓/-/↑	-

Note: Bolded symbols indicate at least some evidence is supported directly by randomized controlled trials.

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; LRFM, lifestyle and risk factor modification; NA, no data available; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing.

↑, Increast AF incidence/burden/progression.

-, No effect on AF incidence/burden/progression.

↓, Decreased AF incidence/burden/progression.

TABLE 2

Effect of modifiable risk factors and lifesyle/risk factor modification on AF management strategies

AF management strategy	Weight/ obesity		Phiyslcal inactivity		SDB/OSA		DM		HTN		CAD		Alcohol		Tobacco		Caffeine	
	RF	LHFM	RF	LRFM	RF	LRFM	RF	LRFM	RF	LRFM	RF	LRFM	RF	LRFM	RF	LRFM	RF	LRFM
Antithrombotic therapy																		
Anticoagulation	-/ ⬆	NA	NA	NA	NA	NA	-	NA	↓	NA	NA	NA	NA	NA	NA	NA	NA	NA
LAAC	NA	NA	NA	NA	NA	NA	↓/-	NA	NA	NA	NA	NA	NA	NA	↓	NA	NA	NA
Rate control	NA	NA	NA	↑	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rhythm control																		
AAD therapy	↓/-	NA	NA	NA	↓	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA
cardioversion	↓	↑	NA	↑	↓	-	↓	-	↓	-/⬆	NA	↓/↑	-	NA	↓/-	NA	↓	NA
AF ablation	↓	-/↑	↓	NA	↓	-/↑	↓	↑	↓	-/⬆	NA	↑	↓/-	↑	↓/-	↑	NA	NA

Note: Bolded symbols indicate at least some evidence is supported directly by randomized controlled trials.

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; LAAC, left atrial appendage; closure; LRFM, lifestyle and risk factor modification; NA, no data available; OSA, obstructive sleep apnea; RF, risk factor; SDB, sleep-disordered breathing.

↑, Higher success of AF management strategy.

—, No effect on AF management strategy.

↓. Lower success of AF management strategy.