REVIEW ARTICLE

Risk factor modification for the primary and secondary prevention of atrial fibrillation. Part 2

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ABSTRACT
Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased risk of death, stroke, and heart failure. Prevalence and incidence of AF are rising due to better overall medical treatment, longer survival, and increasing incidence of cardiometabolic and lifestyle risk factors. Treatment of AF and AF-related complications significantly increases healthcare costs. In addition, the use of conventional rhythm control strategies (including, antiarrhythmic drugs and catheter ablation) is associated with limited efficacy for sinus rhythm maintenance and serious adverse effects. Aggressive cardiometabolic risk factor management may prevent incident as well as recurrent AF, improve overall health, and reduce mortality. Therefore, modifiable risk factor management became one of the 3 treatment pillars in AF management along with anticoagulation as well as conventional rate and rhythm control strategies.
The second part of this review systematically discusses the association between AF and potentially modifiable risk factors for AF, such as obesity, obstructive sleep apnea, alcohol consumption, and dyslipidemia. We also provide practical guidelines for the risk factor management with respect to primary and secondary prevention of AF.

Introduction Atrial fibrillation (AF) affects 1% to 2% of adult population, and is associated with a 5-fold increase in the risk of stroke, a 3-fold increase in the risk of heart failure, and a 2-fold increase in the risk of death.[1] The incidence of AF has been alarmingly increasing in the last decades due to population aging and cumulation of various cardiometabolic and lifestyle risk factors, such as obesity, hypertension, diabetes mellitus, and alcohol consumption.[1] Consequently, AF is an important cause of rising healthcare costs.

Management of modifiable risk factor is one of the 3 treatment pillars in early AF management, along with optimal anticoagulation and symptom control (ie, rate or rhythm control strategies).[2] Modification of these risk factors may prevent incident AF and improve the efficacy of therapies targeting arrhythmias.[3,4] Moreover, improvement of lifestyle and cardiometabolic risk factors is associated with better overall health and survival.[2]

In the second part of this overview, we analyze the associations between AF and obesity, obstructive sleep apnea (OSA), alcohol consumption, and dyslipidemia. We also discuss benefits of risk factor management with respect to primary and secondary AF prevention.

Obesity **Obesity and the risk of atrial fibrillation** The prevalence of obesity, defined as body mass index (BMI) of 30 kg/m^2 or higher, among adults in the United States is 30% to 35%.[5] Compared with nonobese adults, those who are obese have 50% higher risk of incident AF.[6] The prevalence of other well-established AF risk factors, such as hypertension, diabetes, and OSA, rises substantially with each BMI category.[7] Both overweight (BMI, 25–29 kg/m^2; hazard ratio [HR], 1.54) and obesity (HR, 2.41), were recognized as independent predictors for incident AF.[8] Each 1-unit increase in BMI is associated with a corresponding 4% increase in the risk of new-onset AF.[9]

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It was found that BMI was a predictor of the 5-year progression from paroxysmal to permanent AF.[10] In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, a higher BMI was associated with an increased AF recurrence rate and greater AF burden in the rhythm-control arm.[11] A meta-analysis of 23 studies identified 27% increase in the relative risk of AF recurrence after catheter ablation in overweight or obese patients.[12]

Weight reduction and the prevention of atrial fibrillation **Primary prevention** A structural weight loss program in obese patients could prevent development of AF.[8,13] For every 5 kg in absolute weight loss, the risk of incident AF is reduced by 12%.[8] The SOS (Swedish Obese Subjects) trial included obese men (BMI ≥34 kg/m^2) and women (BMI ≥38 kg/m^2) and compared very long-term outcomes between those who underwent bariatric surgery and others who were treated conventionally.[13] In operated patients, a 25% weight reduction had been registered at 1 year and this weight loss was sustained during the 19-year follow-up, whilst in the control group, a mean weight remained mainly unaffected.[13] Bariatric surgery was associated with a 29% relative risk reduction of new-onset AF compared with conventional treatment.[13] However, the randomized Look AHEAD (Action for Health in Diabetes) trial failed to confirm benefits of a structured weight loss program on primary prevention of AF in overweight / obese patients with type 2 diabetes.[14] The incident AF rate was similar between patients included in an intensive weight reduction program and those who underwent standard treatment (TABLE 1).[14]

Secondary prevention Behavioral weight reduction may prevent recurrent AF.[15-19] In a prospective study, patients with AF and BMI higher than 27 kg/m^2 were randomly assigned to either a physician-guided weight loss program by very-low-calorie intake coupled with low-intensity exercise (the intervention group) or self-directed general lifestyle modification (the control group).[15] Body weight and AF burden on Holter monitoring decreased significantly more in the intervention than the control group.[15] In the LEGACY (Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort) trial, patients with AF with BMI of 27 kg/m^2 or higher who accepted an active weight management program with the goal of 10% weight loss and the target BMI of 25 kg/m^2 or less were followed for 4 years.[16] The weight loss exhibited a "dose-dependent" impact on AF recurrence. Thus, AF-freedom was significantly better in patients who achieved weight loss of 10% or higher.[16] The CENT (Cost-Effectiveness and Clinical Effectiveness of the Risk Factor Management Clinic in Atrial Fibrillation) trial reported that aggressive risk factors modification reduced the use of other specific rhythm control strategies (ie, antiarrhythmic drugs [AADs], cardioversion, and catheter ablation).[17] Furthermore, in overweight and obese patients with cardiovascular risk factors, a structured risk factor modification, as compared with routine postprocedural management, significantly improved long-term AF-free survival after ablation (87% vs 17.8%, respectively) (TABLE 1).[19]

Obstructive sleep apnea

Obstructive sleep apnea and the risk of atrial fibrillation The prevalence of OSA in the general adult population varies from 9% to 38%.[20] It is commonly accompanied by hypertension, obesity, diabetes, and heart failure.[21] Moreover, it is independently associated with incident AF with adjusted odds ratio (OR) between 2.47 and 5.66.[22-24] Severity of OSA correlates with the risk of new-onset AF.[22,25] Thus, the presence of nocturnal hypoxemia, expressed as the apnea-hypopnea index (measured as number of apnea and hypopea events per hour of sleep) of more than 5, and time with oxygen saturation of less than 90% during sleeping was independently associated with new-onset AF.[25]

In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), the prevalence of OSA among more than 10 000 outpatients with AF was 18%.[26] There is a strong association between the severity of OSA and burden of AF, and patients with more frequent AF episodes have a higher prevalence and severity of OSA.[27]

The severity of OSA affects the efficacy of rhythm control strategies. Thus, AADs are less likely to control AF in patients with severe OSA than in those with milder disease (39% vs 70%, respectively).[28] The 12-month arrhythmia recurrence rate after electrical cardioversion of persistent AF was higher in patients with untreated OSA than in those without sleep disordered breathing (82% vs 53%).[29] In addition, OSA patients had a 31% higher risk of AF recurrence after catheter ablation than those without OSA,[30] and severe OSA (ie, apnea-hypopnea index ≥10) was an independent predictor of ablation failure.[31,32]

The treatment of obstructive sleep apnea and the prevention of atrial fibrillation **Primary prevention** Currently, there are only few reports on the effect of continuous positive airway pressure (CPAP) therapy on the primary prevention of AF in patients with OSA. Recently, 2717 patients with moderate-to-severe OSA, free of AF at baseline, were randomized to receive either CPAP plus usual care (consisting of management of cardiovascular risk factors in accordance with national guidelines along with lifestyle changes) or usual care only.[33] Continuous positive airway pressure therapy failed to prevent de novo AF better than usual care

TABLE 1 Studies reporting impact of weight reduction on the prevention of atrial fibrillation in obese patients

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
Berkovitch et al[8]	Single-center, retrospective, observational, longitudinal	n = 18 290 Mean (SD) age, 49 (11) y Adults attending annual screening examinations No previous AF ≥2 BMI measurements	None	None	Mean (SD), 6.4 (3.9) y	1 kg/m^2 BMI reduction corresponds to 7% decrease in the rate of new-onset AF. 5 kg in weight loss corresponds to 12% decline in the incident AF rate.
Jamaly et al,[13] SOS	Multicenter, prospective, matched cohort	n = 4021 Age range, 37–60 y BMI ≥34 kg/m^2 for men, ≥38 kg/m^2 for women No previous AF	Bariatric surgery	Conventional obesity care	Median, 19 y	More pronounced weight loss after surgery New-onset AF rate significantly lower after surgery than in controls (12.4% vs 16.8%) A 29% decrease in the RR of new-onset AF by surgery
Alonso et al,[14] Look AHEAD	Single-center, randomized (1:1), prospective	n = 5067 Mean (SD) age, 59 (7) y Overweight and obese With type 2 DM No previous AF	Intensive lifestyle intervention to achieve ≥7% weight loss: Diet (1200–1800 kcal/d) Moderate physical activity (≥175 min/wk)	Only usual DM care (support and education)	Median, 9.6 y	The lifestyle intervention aiming to modestly reduce weight and improve physical fitness in overweight or obese patients with type 2 DM did not prevent new-onset AF
Secondary prevention of AF						
Abed et al[15]	Single-center, randomized (1:1), prospective	n = 150 Age range, 21–75 y BMI >27 kg/m^2 Waist, >100 cm for men and >90 cm for women PAF, terminated PeAF	A physician-led weight loss program: Very-low-calorie diet (800–1200 kcal/d) Walking or cycling (20–45 min, thrice weekly)	Self-directed general lifestyle measures	Median, 15 mo	Body weight, the mean number and duration of AF episodes, and symptom severity were all significantly more reduced in the intervention than in control group.
Pathak et al,[16] LEGACY	Single-center, observational, prospective, longitudinal	n = 355 Mean age across group, 61–65 y BMI ≥27 kg/m^2 Symptomatic PAF / PeAF	A goal-directed weight loss program (targeted weight reduction by 10% and BMI to ≤25 kg/m^2): Low–glycemic index diet Low-intensity exercise (≥200 min weekly)	None	Mean, 48 mo	Weight loss had a dose--dependent benefit on AF-free survival Weight reduction <10% and weight fluctuation 5% were predictors of AF recurrence
Pathak, et al,[17] CENT	Single-center, observational, prospective, controlled (nonrandomized)	n = 355 Mean (SD) age, 59 (11) y BMI ≥27 kg/m^2 ≥1 risk factor[a] PAF / NPAF	A physician-directed RFM clinic Aggressive RFM[a] (n = 208)	Usual risk factor treatment in local hospitals (n = 147)	Mean follow-up across group, 47–49 mo	Better AF-freedom (79% vs 44%) with more aggressive than usual RFM Aggressive RFM reduces the use of rhythm control strategies[b] and emergency healthcare, and is cost-saving.
Pathak, et al,[19] ARREST-AF	Single-center, observational, prospective, longitudinal	n = 149 Mean age across group, 57–58 y BMI ≥27 kg/m^2 Catheter ablation of drug-resistant PAF or PeAF	A structured RFM program targeting (n = 61): Weight loss ≥10% and BMI ≤25 kg/m^2 Weekly activity ≥200 min Risk factor[a] management	Usual risk factor treatment in local hospitals (n = 88)	Mean, 42 mo	A physician-directed postablation RFM (vs routine postablation management) improves single-procedure (32.9% vs 9.7%) and multiple procedure (87% vs 17.8%) AF-freedom.

a The risk factors (hypertension, glucose intolerance or diabetes, obstructive sleep apnea, hyperlipidemia, alcohol excess >30 g per week, and smoking) were treated according to the current American College of Cardiology / American Heart Association guidelines.
b The rhythm control strategies were antiarrhythmic drugs, cardioversion, and catheter ablation.

Abbreviations: AF, atrial fibrillation; ARREST-AF, Aggressive Risk Factor Reduction Study in Atrial Fibrillation; BMI, body mass index; DM, diabetes mellitus; LEGACY, Long--Term Effect of Goal directed weight management on Atrial Fibrillation Cohort; Look AHEAD, Action for Health in Diabetes; NPAF, nonparoxysmal atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; RFM, risk factor modification; RR, relative risk; SOS, Swedish Obese Subjects

and the incident AF rate was similar between the 2 treatment strategies (1.6% vs 1.1%, respectively).[33] Another study, however, reported that applying CPAP to patients with OSA undergoing catheter ablation of typical atrial flutter may protect against new-onset AF, reducing the postprocedural incident AF rate from 46% to 6% (TABLE 2).[34]

Secondary prevention In patients with AF with severe OSA, CPAP improves the outcome of various rhythm control strategies.[26,29,30,35-39] Thus,

TABLE 2 Studies evaluating the influence of continuous positive airway pressure therapy on the prevention of atrial fibrillation in patients with obstructive sleep apnea

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
McEvoy et al,[33] SAVE	Multicenter, randomized, parallel-group	n = 2717 Age range, 45–75 y Moderate / severe OSA Cardiovascular disease	CPAP + usual care Average 5.2 h of CPAP per night (n = 1359)	Usual care only (n = 1358)	Mean, 3.7 y	CPAP therapy on top of usual care did not prevent new-onset AF in patients with moderate-to-severe OSA and cardiovascular disease.
Bazan et al[34]	Single-center, prospective cohort, observational	n = 56 (OSA, n = 46) Mean (SD) age, 66 (11) y Typical AFL ablation No previous AF (n = 30)	CPAP (n = 17)	No CPAP (n = 13)	12 mo	CPAP significantly reduced the 1-year incidence of new-onset AF after typical AFL ablation (from 46% to 6%) in patients with OSA.
Secondary prevention of AF						
Abe et al[35]	Single-center, prospective, observational, longitudinal	n = 1394 Mean (SD) age, 58 (14) y CPAP in OSA patients with AHI >20	CPAP (n = 316)	After treatment (n = 316)	3.9 wk	CPAP significantly reduced the rates of paroxysmal AF (from 5% to 0.3%) and PAC runs (from 3.8% to 2.2%).
Holmkvist et al,[26] ORBIT-AF	Multicenter, prospective (AF registry)	n = 10 132 with AF (+ OSA, n = 1841) Median age, 69 y	CPAP (n = 602)	No CPAP (n = 411)	2 y	CPAP protected against progression to permanent AF (HR, 0.66) with reduction of the 2-year progression rate from 18% to 16%.
Kanagala et al[29]	Single-center, prospective, observational	n = 39 with OSA Mean age, 65 y DC cardioversion of PeAF	CPAP (n = 12)	No CPAP (n = 27)	12 mo	Lower AF recurrence rate at 12 months after DC cardioversion among CPAP receivers as compared with nonreceivers (42% vs 82%)
Patel et al[38]	Single-center, prospective cohort, observational	n = 3000 (OSA, n = 640) Mean (SD) age, 51 (10) y CA of AF	CPAP (n = 315)	No CPAP (n = 325)	Mean (SD), 32 (12) mo	Not using CPAP in patients with OSA was an independent predictor of AF ablation failure (HR, 8.8). Postablation AF-freedom was significantly better in CPAP users as compared with nonusers (79% vs 68%).
Neilan et al[37]	Single-center, prospective, observational	n = 720 (OSA, n = 142) Mean (SD) age, 56 (11) y CA of AF	CPAP ≥4 h per night (n = 71)	CPAP <4 h per night (n = 71)	Median (IQR), 42 (23–50) mo	The post-CA AF recurrence rate was lower for CPAP ≥4 h than for <4 h per night (35% vs 68%). The AF relapse rates were similar for patients with treated OSA and those without OSA (35% vs 30%).
Fein et al[84]	Single-center, prospective, observational	n = 386 (OSA, n = 62) Mean age across group, 55–58 y CA of AF	CPAP after CA (n = 32)	OSA, No CPAP after CA (n = 30) OSA, no CA (n = 22)	12 mo	Postablation AF-freedom was higher with vs without CPAP (71.9% vs 36.7%). AF recurrence rate in CPAP nonusers after CA was similar to that of OSA patients without CA.
Naruse et al[32]	Single-center, prospective, observational	n = 153 (OSA, n = 116) Mean (SD) age, 60 (9) y RF-CA of AF	CPAP (n = 82)	No CPAP (n = 34)	Mean (SD), 19 (10) mo	AF recurrence rate was lower in patients receiving CPAP than in untreated patients (30% vs 53%). CPAP use was related to the AF relapse rate reduction (HR, 0.41)

Abbreviations: AFL, atrial flutter; AHI, apnea-hypopnea index; CA, catheter ablation; CPAP, continuous positive airway pressure; DC, direct current; HR, hazard ratio; IQR, interquartile range; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; OSA, obstructive sleep apnea; PAC, premature atrial contraction; RF, radiofrequency; SAVE, Sleep Apnea Cardiovascular Endpoints; others, see TABLE 1

CPAP users treated with AADs had a 42% reduced risk of AF relapse compared with CPAP nonusers; younger, male, and obese individuals experienced the most clinical benefits from the treatment.[39] Continuous positive airway pressure therapy reduces the relative risk of progression from paroxysmal or persistent AF to permanent arrhythmia by 44%.[26] Reevaluation of patients with severe OSA after CPAP treatment revealed a significant reduction of the rate of paroxysmal AF (from 5% to 0.3%).[35] The use of CPAP after electrical cardioversion of persistent AF in patients with OSA was associated with significantly lower 12-month postprocedural recurrence rate of AF compared with untreated patients (42% vs 82%, respectively).[29] The risk of AF recurrence in patients with OSA undergoing catheter ablation increased by 57% if they were not concomitantly submitted to CPAP therapy.[30] Importantly, postablation recurrence rates of AF in patients with OSA receiving CPAP matched that of patients with AF without OSA.[30,37] These data emphasize the importance of diagnostic screening and treatment of OSA in patients undergoing AF catheter ablation.[40] Nevertheless, there are no randomized studies on the effects of the treatment of OSA on freedom from AF (TABLE 2).

Alcohol

Alcohol consumption and the risk of atrial fibrillation

Binge drinking is defined as consuming 4 to 5 or more standard drinks over a 2-hour period.[41] A standard drink equals 10 to 14 g of alcohol as is found in one 12-oz beer, 5-oz glass of wine, or 1.5-oz shot of distilled spirits.[41,42] One in six adults are exposed to binge drinking on a monthly basis, and the prevalence of binge drinking is twice higher in men than in women.[42] Acute alcohol intoxication, which is common during weekends and holidays, is associated with an increased risk of transient AF (holiday heart syndrome).[43] In one-third of patients hospitalized for paroxysmal AF, the triggering factor for the arrhythmia event was acute alcohol consumption.[44,45] Patients with a history of binge drinking have a 21% increased risk of future hospitalization for AF.[46]

Half of adults regularly consumes alcohol.[42,47] Arbitrarily, the average weekly alcohol intake was categorized as light (<7 standard drinks per week), moderate (7–21 drinks per week), and heavy (>21 drinks per week).[42] In the Copenhagen City Heart Study, the weekly alcohol consumption of 35 or more drinks was associated with a 45% increase in the relative risk of incident AF among men.[48] It seems that regular drinking of liquor or wine, but not beer, significantly increases the relative risk of new-onset AF.[49]

Alcohol abstinence and the prevention of atrial fibrillation

Primary prevention The studies support a linear dose-response relationship between quantity of chronic alcohol intake and incident AF risk.[49-52] Each 1 standard drink increase in daily alcohol consumption was associated with a 8% increase in the risk of new-onset AF.[49] High alcohol intake increases the risk of incident AF in men and women by 68% and 29%, respectively.[50] Protective effects of moderate alcohol consumption against coronary artery disease could not be extended to AF.[42,49,50] Thus, even moderate alcohol intake, in comparison with abstinence, significantly increases a long-term incident AF risk in men (HR, 1.26), but not in women.[50] It seems that low alcohol intake (ie, up to 6–7 drinks per week) is not significantly related to new-onset AF.[50]

Every decade of abstinence from alcohol among former drinkers was associated with a 20% decline in AF risk.[53] Therefore, early lifestyle changes are very important for primary AF prevention. Nevertheless, not consuming alcohol is probably the most beneficial strategy for primary prevention of AF (TABLE 3).[51]

Secondary prevention Appropriate modification of drinking pattern improves clinical course of recurrent AF.[19,45,54-58] Symptomatic recurrence of paroxysmal AF was documented more commonly in regular drinkers than in those who did not consume alcohol (50% vs 24%) and daily alcohol intake was an independent predictor of AF relapse.[54] In addition, moderate-to-high alcohol consumption is an independent risk factor for progression of paroxysmal toward chronic AF (OR, 3).[55] Several studies demonstrated improvement in AF ablation outcome with alcohol abstinence after the procedure,[56-58] reporting that abstainers compared with former or current drinkers had a significantly lower AF recurrence rate after the first ablation (34.1% vs 41.9%).[56] In obese subjects with more than 1 cardiometabolic risk factor, the postablation lifestyle intervention, including reduction of alcohol intake to less than 30 g/wk, led to a better long-term rhythm outcome after procedure (TABLE 3).[19]

Dyslipidemia

Dyslipidemia and the risk of atrial fibrillation

Available studies showed inconsistent findings on association between dyslipidemia and incident AF.[59] The ARIC (Atherosclerosis Risk in Communities) study suggested a protective effect of hypercholesterolemia against AF, reporting a significant reduction of the 20-year incident AF risk by 12% and 16% among participants with baseline total cholesterol and low-density lipoprotein cholesterol level above 5.18 mmol/l and 2.59 mmol/l, respectively, compared with those who had lower plasma lipid levels.[60] Several studies presented discordant results on the impact of high-density lipoprotein cholesterol level on new-onset AF.[61,62] Finally, hypertriglyceridemia of 2.26 mmol/l or higher was associated

TABLE 3 Studies examining the relationship between the quantity of consumed alcohol and the risk of atrial fibrillation

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
Larsson et al[49]	Meta-analysis of 7 prospective studies	n = 176 179 Age range, 26–83 y No previous AF	Assessment of alcohol consumption with a questionnaire or interview	–	Mean follow-up across group, 4.7 to >50 y	A linear dose-response between alcohol intake and risk of new AF A 6%–10% increase in AF risk per 1 drink/d increase in alcohol intake Among heavy drinkers, risk of AF was higher for liquor and wine than for beer.
Gallagher et al[50]	Meta-analysis of 9 prospective studies	n = 249 496 Mean (SD) age, 60.4 (10.4) y No previous AF	Evaluation of link between level of alcohol intake and risk of incident AF	–	Mean follow-up across group, 4 to 17.6 y	High alcohol intake (≥3 standard drinks/d) was associated with an increased risk of AF in both genders (HR, 1.4). Moderate intake (1–2 standard drinks/d) was associated with increased AF risk in men (HR, 1.26) but not in women (HR, 1.03). Low daily intake (<1 standard drink) was not associated with AF compared to nondrinkers.
Dixit et al,[53] ARIC	Population-based, prospective, observational	n = 15 222 No prevalent AF at baseline	Repeat assessment of alcohol intake modification during follow-up	–	Median 19.7 y	Each decade abstinent from alcohol was associated with a 20% risk reduction for incident AF. Each decade of past alcohol consumption was associated with a 13% increase in the new AF risk.
Secondary prevention of AF						
Planas et al,[54] FAP registry	Multicenter, prospective, observational	n = 115 Mean age across group, 52–54 y Patients with first episode of idiopathic PAF	Assessment of daily alcohol intake	–	Mean (SD), 912 (445) d	Past or current regular alcohol consumption (>40 g/d in men or >20 g/d in women) was an independent risk factor for the relapse of idiopathic AF (RR, 2.34)
Ruigomez et al,[55] UK GPRD	Population-based, prospective, observational	n = 418 (subanalysis) Patients with a first-recorded PAF	Estimation of rate of progression to chronic AF	–	Mean, 2.7 y	Moderate-to-high alcohol consumption (>21 standard drinks per week) was associated with a 3-fold increased risk of progression to chronic AF.
Qiao et al[57]	Single-center, prospective, observational	n = 122 Mean (SD) age, 55.4 (9.4) y Patients undergoing index PVI procedure for symptomatic drug-resistent PAF	Abstainers (n = 70)	Moderate drinkers, 1–2 drinks/d (n = 13) Heavy drinkers (n = 39)	Mean (SD), 20.9 (5.9) mo	Success rate was 81.3%, 69.3%, and 35.1% among abstainers, moderate drinkers, and heavy drinkers, respectively.
Takigawa et al[56]	Single-center, retrospective, observational	n = 1361 Mean (SD) age, 61.2 (10.6) y Patients undergoing CA for symptomatic drug-refractory PAF	Alcohol nonconsumers (n = 738)	Alcohol consumers (patients who drank at least once per week) (n = 623)	Mean (SD), 53 (26) mo	Long-term success rate after the initial CA was better in nonconsumers vs consumers (41.9% vs 34.1%), but the AF relapse rate after the final CA was similar in both groups (17.7% vs 18.7%).

Abbreviations: ARIC, Atherosclerosis Risk in Communities; FAP, Fibrilación Auricular Paroxística; PVI, pulmonary vein isolation; UK GPRD, United Kingdom General Practice Research Database; others, as TABLES 1 and 2

with a 60% higher risk of incident AF compared with low plasma triglycerides (of <1.69 mmol/l).[62]

Dyslipidemia is a risk factor for very late AF recurrence post ablation.[63,64] A long-term study found that hyperlipidemia was independently associated with a 4-fold higher risk of very late arrhythmia recurrence more than 1 year after catheter ablation of AF.[63]

Lipid-lowering treatment and the prevention of atrial fibrillation **Primary prevention** Statins might prevent incident AF[65-68] independently of their lipid-lowering effects.[69] A meta-analysis of randomized trials demonstrated a 40% decrease in the relative risk of new-onset AF after cardiac surgery or acute coronary syndrome with statin use.[65] Observational studies on patients not undergoing invasive cardiac procedures reported a 12% decline in the relative risk of new-onset AF with statin use, but the randomized studies did not support these findings.[68] Statin use for the primary prevention of AF guided by the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age >75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex) has been proposed because patients with a score of 3 or higher yield a 40% AF risk reduction with statins, whereas in those with the score of 0, statins provide no apparent AF prevention.[70] In patients with the left ventricular systolic dysfunction, statin use was associated with a 31% decrease in the prevalence of AF.[69] Atorvastatin (OR, 0.43) was shown to be superior to pravastatin (OR, 1.03) for the primary prevention of AF.[67]

The Danish cohort study deployed an U-shaped relationship between dietary intake of n-3 poly-unsaturated fatty acids (PUFA) and the long-term risk of incident AF, with the lowest AF risk in those consuming moderate daily amount of PUFA (of 0.63 g).[71] Other study reported a linear inverse association between the level of circulating n-3 PUFA and incidence of AF.[72] Two large studies, however, did not support a routine use of PUFA supplementation for the primary prevention of AF (TABLE 4).[73,74]

Secondary prevention The meta-analysis reported that statin use reduces the relative risk of recurrent AF by 25% to 67%,[65-68] and antiarrhythmic effect of statins is more pronounced in recurrent than incident AF.[65,66] The use of statins after electrical cardioversion of persistent AF was associated with a 22% relative risk reduction of AF relapse.[75] Again, atorvastatin was more effective for the secondary prevention of AF than simvastatin / pravastatin.[76,77] In contrast to previous findings, a randomized study

TABLE 4 Studies evaluating effects of lipid-lowering treatment on the prevention of atrial fibrillation (continued on the next page)

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
Fauchier et al[65]	Meta-analysis of 6 randomized trials	n = 3557 Mean age across group, 54–68 y Subanalysis of 3 trials: ACS or CABG setting (no previous AF)	Atorvastatin (20–80 mg/d)	Placebo or control regimen	Range across group, 3–26 wk	A 40% decrease in relative risk of incident AF with the use of atorvastatin in patients with ACS or those undergoing CABG surgery
Bang et al[68]	Meta-analysis of 28 trials	n = 235 945 Mean age across group, 61–69 y Patients not undergoing cardiac interventions Subanalysis of 15 trials (no previous AF)	Atorvastatin or pravastatin	Placebo or control regimen	Range across group, 48 h to 10 y	A significant 12% relative risk reduction of new-onset AF with the statins in observational trials Randomized studies did not support preventive effects of statins on new-onset AF.
Wang et al[67]	Meta-analysis of 20 randomized trials	n = 16 203 Mean age across group, 52–71 y Subanalysis of 14 trials: patients with no prior AF	Atorvastatin, or pravastatin, or rosuvastatin, or simvastatin	Placebo or control regimen	Range across group, 2 d to 6 y	Statins were effective for primary prevention (OR, 0.67) of new-onset or perioperative AF. Atorvastatin was superior to pravastatin (OR, 0.43).
Hanna et al,[69] ADVANCENT	Multicenter, observational registry	n = 25 268 Mean age, 66.4 y LVEF ≤40% Hyperlipidemia, 71%	Lipid-lowering drugs (statins, 92%), n = 16 881	No lipid-lowering drugs, n = 8381	–	Statin use was associated with a lower prevalence of AF (OR, 0.69). Protective effects of statins on AF were independent of plasma lipid level.
Rix et al[71]	Prospective, observational, longitudinal, Danish cohort study	n = 57 053 Age range, 50–64 y No previous AF	Dietary intake of marine n-3 PUFA estimated by semiquantitative food frequency questionnaire	None	Median, 13.6 y	A U-shape association between consumption of PUFA and risk of incident AF The lowest risk of AF at median daily intake of PUFA (0.63 g)

TABLE 4 Studies evaluating effects of lipid-lowering treatment on the prevention of atrial fibrillation (continued from the previous page)

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
Wu et al,[72] Cardiovascular Health Study	Prospective, observational	n = 3326 Age ≥65 y No previous AF No previous heart failure	Plasma level of long--chain n-3 PUFA	None	Mean, 31 169 person--years	A linear inverse association between plasma level of PUFA and risk of incident AF in the elderly Each 1% increment in PUFA corresponded to a 9% lower AF risk.
Brouwer et al,[74] the Rotterdam Study	Prospective, population--based	n = 5184 Age ≥55 y No previous AF	Assessment of dietary fish intake by interview	None	Mean, 6.4 y	Dietary consumption of fish was not associated with the risk of new-onset AF.
Secondary prevention of AF						
Fauchier et al[66]	Meta-analysis of 32 randomized studies	n = 71 005 Mean age across group, 54–68 y Subanalysis of 7 trials: patients with AF undergoing ECV or CA (n = 827)	Atorvastatin 10–80 mg/d, or pravastatin 40 mg/d	Placebo or control regimen	Range across group, 30 d to 12 mo	Use of statins decreases the risk of recurrent AF (OR, 0.57). Benefit of statins is more pronounced in secondary than in primary prevention of AF.
Almroth et al[85]	Single-center, randomized, prospective, double-blind	n = 234 Mean (SD) age, 65 (10) y Patients with PeAF scheduled for ECV	Atorvastatin 80 mg/d	Placebo	30 d	Statins were not superior to placebo for short-term maintaining of sinus rhythm after ECV of PeAF (51% vs 42%).
Dernellis et al[86]	Single-center, randomized, prospective, single-blind	n = 80 Median age, 52 y PAF on 48h-Holter, ECG or exercise test Known plasma CRP level before treatment	Atorvastatin 80 mg/d (n = 40)	Placebo (n = 40)	6 mo	Total PAF resolution more commonly with atorvastatin than with placebo (65% vs 10%), corresponding to plasma CRP level decrease after the treatment
Suleiman et al[78]	Single-center, randomized, prospective, double-blind	n = 125 Mean (SD) age, 57 (10) y Patients undergoing CA of recurrent AF PAF 72%, NPAF 28%	Atorvastatin 80 mg/d (n = 62)	Placebo (n = 63)	3 mo	The 3-month use of statins post-CA of AF was not associated with better atrial arrhythmia outcome compared with placebo (85% vs 88%).
Macchia et al,[79] FORWARD	Multicenter, randomized, prospective, double-blind	n = 586 Mean (SD) age, 66 (11) y Symptomatic PAF +1 risk factor for stroke in patients <65 y	n-3 PUFA, 1g/d (n = 289)	Placebo (n = 297)	12 mo	A similar 1-year AF recurrence rate among participants receiving PUFA and among those receiving placebo (24% vs 18.9%)
Nodari et al[82]	Single-center, randomized, prospective, double-blind	n = 199 Mean age across group, 69–70 y PeAF lasting >1 mo indicated for ECV ≥1 AF relapse after previous cardioversion	n-3 PUFA 2 g/d on top of amiodarone and ACEI / ARBs therapy (n = 100)	Amiodarone and ACEI / ARBs therapy alone (n = 99)	1 y	Probability of maintenance of sinus rhythm at 1 year post-ECV of PeAF was higher with PUFAs than with placebo (HR, 0.62 vs 0.36).
Patel et al[83]	Single-center, retrospective, observational, 1:1 matched cohorts	n = 258 Mean age across group, 58–60 y PAF 70%, NPAF 30% Patients undergoing CA-AF	Treated with n-3 PUFAs after CA (≥655 mg of fish oil capsules) (n = 129)	Untreated with n-3 PUFAs post-CA (n = 129)	Mean (SD), 28 (7) mo	Patients treated with PUFAs after CA compared with placebo had significantly lower rates of early (27% vs 44%) and late AF recurrence (23% vs 32%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADVANCENT, National Registry to Advance Heart Health; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CRP, C-reactive protein; ECG, electrocardiogram; ECV, electrical cardioversion; FORWARD, Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation; LVEF, left ventricular ejection fraction; OR, odds ratio; PUFA, polyunsaturated fatty acids; others, see TABLES 1-3

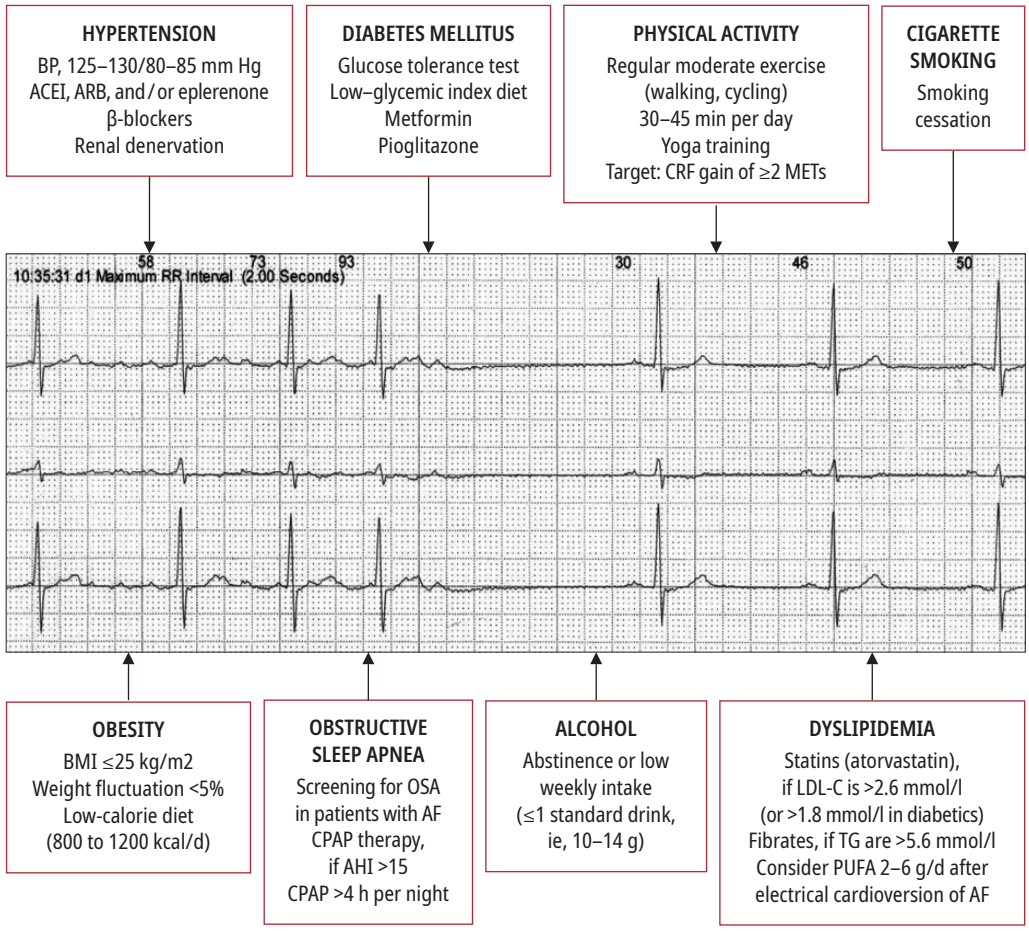

FIGURE 1 A practical guide for risk factors modification to prevent atrial fibrillation.
Abbreviations: BP, blood pressure; CRF, cardiorespiratory fitness; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent (of task); TG, triglycerides; others, see TABLES 2-4

showed that short-term use of statins does not affect the outcome of AF ablation, reporting similar rates of early and late AF recurrence post ablation among patients treated with 80 mg of atorvastatin and among those who received placebo after the procedure.[78]

Supplementation with 1 to 4 g/d of PUFA for 6 to 12 months did not significantly improve the clinical course of paroxysmal AF.[79,80] However, 2 to 6 g/d of PUFA along with AAD therapy was associated with a significant reduction of the arrhythmia recurrence rate following AF cardioversion from 77.5% to 38.5%.[81,82] In addition, PUFAs significantly reduced the early (from 27.1% vs 44.1%) but not the late recurrence rate of AF post ablation (TABLE 4).[83]

Conclusions Structured weight reduction in obese patients prevents incident AF and improves outcome of rhythm control strategies, including AADs, cardioversion, and catheter ablation. The diagnosis of OSA is commonly overlooked among cardiovascular patients. The appropriate use of CPAP therapy in patients with severe OSA reduces the risk of new-onset AF after catheter ablation of typical atrial flutter and significantly increases long-term success of AADs and ablation for recurrent AF in observational studies. Both binge drinking and regular alcohol consumption increase the risk of incident AF. Abstaining from alcohol reduces the risk of new-onset AF and, in patients with recurrent AF, facilitates sinus rhythm maintenance with AADs and catheter ablation. In patients with cardiovascular risk factors, statin use protects against incident and recurrent AF, but benefit of their routine use after AF ablation is still controversial. Practical guidelines for modifiable risk factor management with respect to the primary and secondary prevention of AF is presented in FIGURE 1.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016; 18: 1609-1678.

2 Lau DH, Nattel S, Kalman JM, et al. Modifiable risk factors and atrial fibrillation. Circulation. 2017; 136: 583-596.

3 Panchal G, Mahmood M, Lip GYH. Revisiting the risks of incident atrial fibrillation: a narrative review. Part 2. Kardiol Pol. 2019; 77: 515-524.

4 Mujović N, Marinković M, Mihajlović M, et al. Risk factor modification for the primary and secondary prevention of atrial fibrillation. Part 1. Kardiol Pol. 2020; 78: 181-191.

5 Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010; 303: 235-141.

6 Goudis CA, Korantzopoulos P, Ntalas IV, et al. Obesity and atrial fibrillation: a comprehensive review of the pathophysiological mechanisms and links. J Cardiol. 2015; 66: 361-369.

7 Pantalone KM, Hobbs TM, Chagin KM, et al. Prevalence and recognition of obesity and its associated comorbidities: cross-sectional analysis of electronic health record data from a large US integrated health system. BMJ Open. 2017; 7: e017583.

8 Berkovitch A, Kivity S, Klempfner R, et al. Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. Am Heart J. 2016; 173: 41-48.

9 Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004; 292: 2471-2477.

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

11 Guglin M, Maradia K, Chen R, et al. Relation of obesity to recurrence rate and burden of atrial fibrillation. Am J Cardiol. 2011; 107: 579-582.

12 Lin KJ, Cho SI, Tiwari N, et al. Impact of metabolic syndrome on the risk of atrial fibrillation recurrence after catheter ablation: systematic review and meta--analysis. J Interv Card Electrophysiol. 2014; 39: 211-223.

13 Jamaly S, Carlsson L, Peltonen M, et al. Bariatric surgery and the risk of new--onset atrial fibrillation in Swedish obese subjects. J Am Coll Cardiol. 2016; 68: 2497-2504.

14 Alonso A, Bahnson JL, Gaussoin SA, et al. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. Am Heart J. 2015; 170: 770-777.e5.

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

16 Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal--directed weight management in an atrial fibrillation cohort: a long-term follow--up study (LEGACY). J Am Coll Cardiol. 2015; 65: 2159-2169.

17 Pathak RK, Evans M, Middeldorp ME, et al. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation. The CENT Study. 2017. JACC Clin Electrophysiol. 2017; 3:436-447.

18 Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: the CARDIO-FIT study. J Am Coll Cardiol. 2015; 66: 985-996.

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

20 Senaratna C, Perret JL, Lodge C, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev. 2017; 34: 70-81.

21 Jennum P, Tonnesen P, Ibsen R, et al. All-cause mortality from obstructive sleep apnea in male and female patients with and without continuous positive airway pressure treatment: a registry study with 10 years of follow-up. Nat Sci Sleep. 2015; 7: 43-50.

22 Tanigawa T, Yamagishi K, Sakurai S, et al. Arterial oxygen desaturation during sleep and atrial fibrillation. Heart. 2006; 92: 1854-1855.

23 Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health study. Am J Respir Crit Care Med. 2006; 173: 910-916.

24 Tung P, Levitzky YS, Wang R, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. 2017; 6: e004500.

25 Cadby G, McArdle N, Briffa T, et al. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. Chest. 2015; 148: 945-952.

26 Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation - results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015; 169: 647-654.e2.

27 Stevenson IH, Teichtahl H, Cunnington D, et al. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. Eur Heart J. 2008; 29: 1662-1669.

28 Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. Am J Cardiol. 2012; 110: 369-372.

29 Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003; 107: 2589-2594.

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

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

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

33 McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016; 375: 919-931.

34 Bazan V, Grau N, Valles E, et al. Obstructive sleep apnea in patients with typical atrial flutter: prevalence and impact on arrhythmia control outcome. Chest. 2013; 143: 1277-1283.

35 Abe H, Takahashi M, Yaegashi H, et al. Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients. Heart Vessels. 2010; 25: 63-69.

36 Linz D, Hohl M, Ukena C, et al. Obstructive respiratory events and premature atrial contractions after cardioversion. Eur Respir J. 2015; 45: 1332-1340.

37 Neilan TG, Farhad H, Dodson JA, et al. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. J Am Heart Assoc. 2013; 2: e000421.

38 Patel D, Mohanty P, Di Biase L, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. Circ Arrhythm Electrophysiol. 2010; 3: 445-451.

39 Qureshi WT, Nasir UB, Alqalyoobi S, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. Am J Cardiol. 2015; 116: 1767-1773.

40 Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017; 14: e275-e444.

41 Courtney KE, Polich J. Binge drinking in young adults: data, definitions, and determinants. Psychol Bull. 2009; 135: 142-156.

42 Voskoboinik A, Prabhu S, Ling LH, et al. Alcohol and atrial fibrillation: a sobering review. J Am Coll Cardiol. 2016; 68: 2567-2576.

43 Tonelo D, Providencia R, Goncalves L. Holiday heart syndrome revisited after 34 years. Arq Bras Cardiol. 2013; 101: 183-189.

44 Hansson A, Madsen-Hardig B, Olsson SB. Arrhythmia-provoking factors and symptoms at the onset of paroxysmal atrial fibrillation: a study based on interviews with 100 patients seeking hospital assistance. BMC Cardiovasc Disord. 2004; 4: 13.

45 Krishnamoorthy S, Lip GY, Lane DA. Alcohol and illicit drug use as precipitants of atrial fibrillation in young adults: a case series and literature review. Am J Med. 2009; 122: 851-856.e3.

46 Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J Intern Med. 2001; 250: 382-389.

47 Waskiewicz A, Sygnowska E. Alcohol intake and cardiovascular risk factor profile in men participating in the WOBASZ study. Kardiol Pol. 2013; 71: 359-365.

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

49 Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014; 64: 281-289.

50 Gallagher C, Hendriks JML, Elliott AD, et al. Alcohol and incident atrial fibrillation – a systematic review and meta-analysis. Int J Cardiol. 2017; 246: 46-52.

51 Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol. 2011; 57: 427-436.

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

53 Dixit S, Alonso A, Vittinghoff E, et al. Past alcohol consumption and incident atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study. PLoS One. 2017; 12: e0185228.

54 Planas F, Romero-Menor C, Vazquez-Oliva G, et al. Natural history of and risk factors for idiopathic atrial fibrillation recurrence (FAP Registry). Rev Esp Cardiol. 2006; 59: 1106-1112.

55 Ruigomez A, Johansson S, Wallander MA, et al. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovasc Disord. 2005; 5: 20.

56 Takigawa M, Takahashi A, Kuwahara T, et al. Impact of alcohol consumption on the outcome of catheter ablation in patients with paroxysmal atrial fibrillation. J Am Heart Assoc. 2016; 5: e004149.

57 Qiao Y, Shi R, Hou B, et al. Impact of alcohol consumption on substrate remodeling and ablation outcome of paroxysmal atrial fibrillation. J Am Heart Assoc. 2015; 4: e002349.

58 Barham WY, Sauer WH, Fleeman B, et al. Impact of alcohol consumption on atrial fibrillation outcomes following pulmonary vein isolation. J Atr Fibrillation. 2016; 9: 1505.

59 Allan V, Honarbakhsh S, Casas JP, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. Thromb Haemost. 2017; 117: 837-850.

60 Lopez FL, Agarwal SK, Maclehose RF, et al. Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: the atherosclerosis risk in communities study. Circ Arrhythm Electrophysiol. 2012; 5: 155-162.

61 Watanabe H, Tanabe N, Yagihara N, et al. Association between lipid profile and risk of atrial fibrillation. Circ J. 2011; 75: 2767-2774.

62 Alonso A, Yin X, Roetker NS, et al. Blood lipids and the incidence of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study. J Am Heart Assoc. 2014; 3: e001211.

63 Shah AN, Mittal S, Sichrovsky TC, et al. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. J Cardiovasc Electrophysiol. 2008; 19: 661-667.

64 Baek YS, Yang PS, Kim TH, et al. Delayed recurrence of atrial fibrillation 2years after catheter ablation is associated with metabolic syndrome. Int J Cardiol. 2016; 223: 276-281.

65 Fauchier L, Pierre B, de Labriolle A, et al. Antiarrhythmic effect of statin therapy and atrial fibrillation a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2008; 51: 828-835.

66 Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials. Curr Opin Cardiol. 2013; 28: 7-18.

67 Wang Z, Zhang Y, Gao M, et al. Statin therapy for the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. Pharmacotherapy. 2011; 31: 1051-1062.

68 Bang CN, Greve AM, Abdulla J, et al. The preventive effect of statin therapy on new-onset and recurrent atrial fibrillation in patients not undergoing invasive cardiac interventions: a systematic review and meta-analysis. Int J Cardiol. 2013; 167: 624-630.

69 Hanna IR, Heeke B, Bush H, et al. Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. Heart Rhythm. 2006; 3: 881-886.

70 Hung CY, Lin CH, Wang KY, et al. Dosage of statin, cardiovascular comorbidities, and risk of atrial fibrillation: a nationwide population-based cohort study. Int J Cardiol. 2013; 168: 1131-1136.

71 Rix TA, Joensen AM, Riahi S, et al. A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter – a Danish cohort study. Europace. 2014; 16: 1554-1561.

72 Wu JH, Lemaitre RN, King IB, et al. Association of plasma phospholipid long-chain omega-3 fatty acids with incident atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2012; 125: 1084-1093.

73 Gronroos NN, Chamberlain AM, Folsom AR, et al. Fish, fish-derived n-3 fatty acids, and risk of incident atrial fibrillation in the Atherosclerosis Risk in Communities (ARIC) study. PLoS One. 2012; 7: e36686.

74 Brouwer IA, Heeringa J, Geleijnse JM, et al. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. Am Heart J. 2006; 151: 857-862.

75 Dentali F, Gianni M, Squizzato A, et al. Use of statins and recurrence of atrial fibrillation after catheter ablation or electrical cardioversion. A systematic review and meta-analysis. Thromb Haemost. 2011; 106: 363-370.

76 Komatsu T, Tachibana H, Sato Y, et al. Long-term efficacy of upstream therapy with lipophilic or hydrophilic statins on antiarrhythmic drugs in patients with paroxysmal atrial fibrillation: comparison between atorvastatin and pravastatin. Int Heart J. 2011; 52: 359-365.

77 Naji F, Suran D, Kanic V, et al. Statins and amiodarone improve freedom from recurrence of atrial fibrillation after successful cardioversion. Med Sci Monit. 2009; 15: CR494-CR498.

78 Suleiman M, Koestler C, Lerman A, et al. Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: a double-blind, placebo-controlled, randomized trial. Heart Rhythm. 2012; 9: 172-178.

79 Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013; 61: 463-468.

80 Kowey PR, Reiffel JA, Ellenbogen KA, et al. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. JAMA. 2010; 304: 2363-2372.

81 Kumar S, Sutherland F, Morton JB, et al. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. Heart Rhythm. 2012; 9: 483-491.

82 Nodari S, Triggiani M, Campia U, et al. n-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. Circulation. 2011; 124: 1100-1106.

83 Patel D, Shaheen M, Venkatraman P, et al. Omega-3 polyunsaturated fatty acid supplementation reduced atrial fibrillation recurrence after pulmonary vein antrum isolation. Indian Pacing Electrophysiol J. 2009; 9: 292-298.

84 Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013; 62: 300-305.

85 Almroth H, Höglund N, Boman K, et al. Atorvastatin and persistent atrial fibrillation following cardioversion: a randomized placebo-controlled multicentre study. Eur Heart J. 2009; 30: 827-833.

86 Dernellis J, Panaretou M. Effect of C-reactive protein reduction on paroxysmal atrial fibrillation. Am Heart J. 2005; 150: 1064.