Risk factor modification for the primary and secondary prevention of atrial fibrillation. Part 1

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ABSTRACT
Modifiable risk factors, such as cardiometabolic and lifestyle risk factors, considerably contribute to (bi)atrial remodeling, finally resulting in clinical occurrence of atrial fibrillation (AF). Early identification and prompt intervention on these risk factors may delay further progression of atrial arrhythmia substrate and prevent the occurrence of new-onset AF. Moreover, in patients with previous history of recurrent AF, aggressive risk factor management may improve efficacy of other rhythm control strategies, including antiarrhythmic drugs and catheter ablation in sinus rhythm maintenance. Finally, modification of risk factors improves overall health and reduces cardiovascular mortality and morbidity. The first part of this review evaluates the association between AF and the following risk factors: hypertension, diabetes mellitus, physical activity, and cigarette smoking. We systematically discuss the impact of risk factor modification on primary and secondary prevention of AF.

Introduction Available rhythm control strategies, including antiarrhythmic drugs and catheter-based or surgical ablation, are associated with modest success and significant adverse effects.[1-3] Clinical occurrence of AF commonly reflects the presence of advanced and irreversible stage of left atrial disease, thus the primary prevention of AF (ie, prevention of new-onset or incident AF) is of utmost importance.[4]

A growing body of evidence supports early identification and aggressive management of modifiable cardiometabolic and lifestyle risk factors in order to delay progression of arrhythmia substrate and prevent clinical AF, as illustrated in FIGURE 1.[5,6] Moreover, modification of these risk factors reduces cardiovascular mortality and morbidity.[1,4]

Herein, we discuss the associations of risk factors, such as hypertension, diabetes mellitus (DM), physical activity, cigarette smoking, and AF occurrence. The second part of this review will discuss obesity, obstructive sleep apnea, alcohol use, dyslipidemia and AF. We summarize the studies reporting therapeutic effects of risk factor management on the primary and secondary prevention of AF.

Pathophysiological relationship between risk factors and atrial fibrillation Atrial fibrillation results from interaction of triggers, mostly originating from the pulmonary veins (PVs), left atrial substrate, and autonomic nervous system.[1,2] Pathophysiological link between modifiable risk factors and AF is presented in FIGURE 2.

Hypertension **Hypertension and the risk of atrial fibrillation** Systemic hypertension affects approximately 50% of the general population over 50 years of age and it is the most prevalent risk factor for AF,[7-9] accounting for more incident AF cases than any other known risk factor.[10] Hypertension is associated with a 1.4- to 2.1-fold increased risk of new-onset AF.[7,8,10] Even prehypertension increases the risk of AF.[8] Among middle-aged prehypertensive men, the 35-year risk of incident AF was 1.5-fold higher in those with systolic blood pressure (SBP) of 128 to 138 mm Hg (vs SBP <128 mm Hg) and 1.79-fold higher in those with diastolic blood pressure (DBP) of 80 mm Hg or higher (vs <80 mm Hg).[11]

A significant increase of new-onset AF risk across increasing blood pressure (BP) categories

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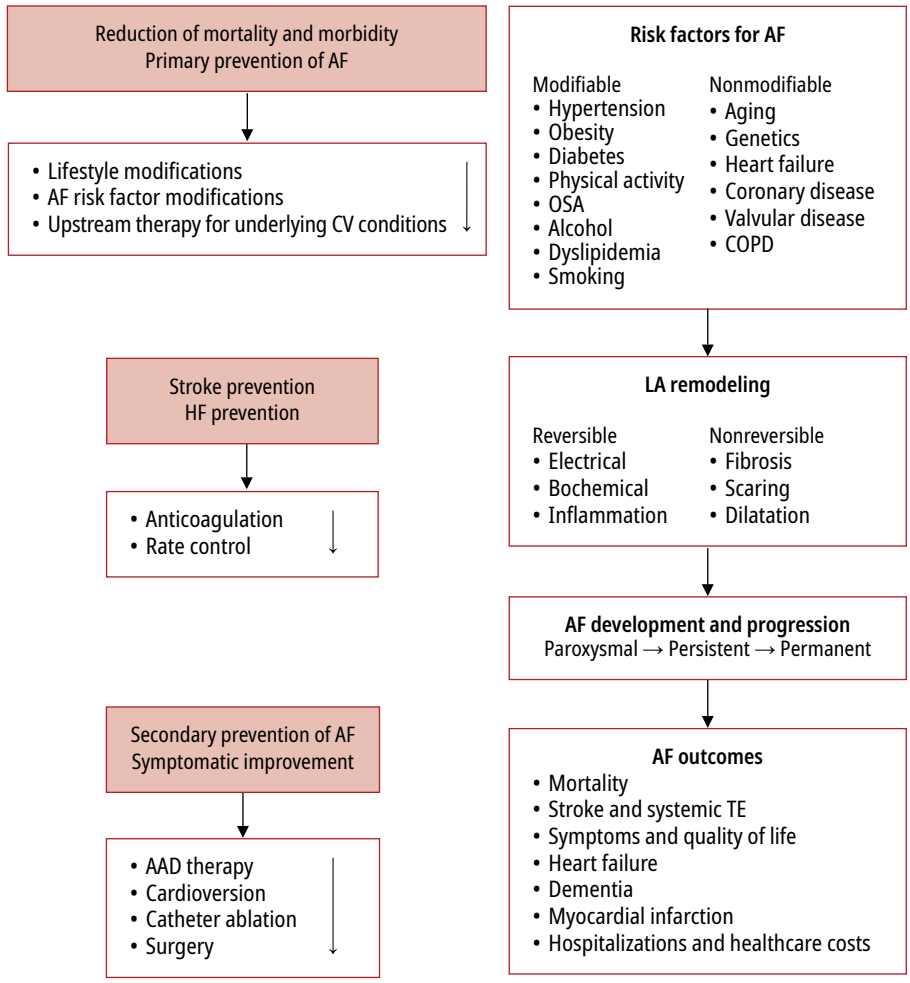

FIGURE 1 Main goals of AF treatment and timelines of different treatment options
Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; LA, left atrium; OSA, obstructive sleep apnea; TE, thromboembolism

has been reported, ranging from a hazard ratio (HR) of 1.28 for SBP of 120 to 129 mm Hg to HR of 2.74 for SBP of 160 mm Hg and higher.[12] A J-shaped association between SBP and risk of incident AF was demonstrated, with the lowest risk for a SBP of 120 to 130 mm Hg and a significant increase in AF incidence for both SBP of less than 120 mm Hg (HR, 1.99) and SBP higher than 150 mm Hg (HR, 2.02–2.27).[13] Diastolic blood pressure is significantly associated with an increased risk of incident AF only at the level of 95 mm Hg and higher, suggesting that systolic hypertension is a stronger predictor of new-onset AF than diastolic hypertension.[8,10,12,13]

Preprocedural hypertension is a risk factor for AF recurrence after electrical cardioversion in older patients[14] as well as after catheter ablation in AF (HR 2.5–3.2, with normotensive patients used as the reference).[2,15,16]

Hypertension management and the prevention of atrial fibrillation **Primary prevention** Lowering SBP to 130 mm Hg or less in hypertensive patients with left ventricular (LV) hypertrophy reduces the risk of incident AF by 40%, while pursuing SBP below 125 mm Hg provides no additional benefit in the prevention of AF.[17] The renin-angiotensin-aldosterone system blockers, such as angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor blockers, in comparison with other antihypertensive drugs, yielded some additional, class-specific benefits with respect to the prevention of AF beyond simple BP control, supporting the profound involvement of the renin-angiotensin-aldosterone system in AF pathogenesis.[18] Monotherapy with ACEIs, ARBs, and β-blockers in hypertensive patients provided a superior prevention of incident AF compared with calcium channel blockers or diuretics.[19,20] The ACEIs and ARBs showed the greatest prevention effect on AF in hypertensive patients with LV systolic dysfunction[21] and addition of β-blockers and a mineralocorticoid receptor blocker eplerenone (on top of ACEI / ARB therapy) significantly decreased the rate of incident AF by 27% and 40%, respectively (TABLE 1).[22,23]

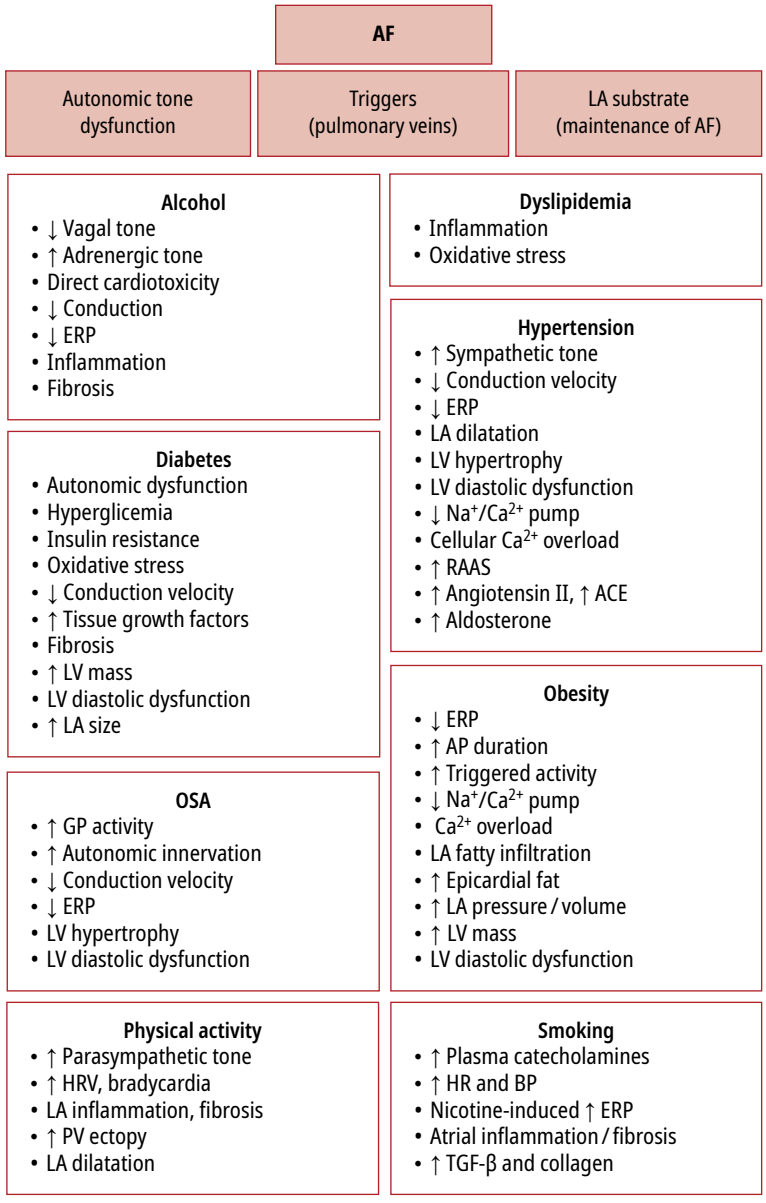

FIGURE 2 Impact of modifiable risk factors on structural and electrical left atrial remodeling predisposing to development of atrial fibrillation

Abbreviations: ACE, angiotensin-converting enzyme; AP, action potential; BP, blood pressure; Ca, calcium; ERP, effective refractory period; GP, ganglionated plexi; HR, heart rate; HRV, heart rate variability; LV, left ventricle; Na, sodium; PV, pulmonary vein; RAAS, renin–angiotensin–aldosterone system; TGF-β, tumor growth factor beta; others, see FIGURE 1

Secondary prevention Besides their antihypertensive effects, β-blockers are superior than placebo for the secondary prevention of AF[24] and they facilitate a reliable rate control during recurrent AF episodes.[1] Therefore, β-blockers are a good choice for hypertensive patients with already documented AF. In patients with AF with preserved systolic LV function, ACEIs and ARBs were not shown to prevent recurrent AF and they are not recommended for the secondary prevention of paroxysmal AF in patients with no structural heart disease.[1] Randomized trials failed to demonstrate superiority of valsartan / olmesartan over placebo in suppression of recurrent AF at 1 year.[25,26] However, ACEI / ARBs could be used in patients undergoing cardioversion of persistent AF,[1] because small randomized trials demonstrated that using enalapril / irbesartan along with amiodarone significantly improved sinus rhythm maintenance post procedure.[27,28] In patients with resistant hypertension, renal artery denervation performed in conjunction with PV isolation provided a better long-term AF suppression than PV-isolation strategy alone.[29] The RACE-III (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure) study showed that BP lowering below 120/80 mm Hg improves sinus rhythm maintenance in patients with persistent AF and heart failure,[30] whereas the SMAC-AF (Substrate Modification With Aggressive Blood Pressure Control) study reported no benefits of aggressive BP control on postablation rhythm outcome (TABLE 1).[31]

Diabetes mellitus

Diabetes mellitus and the risk of atrial fibrillation Patients with DM have a 39% higher risk of incident AF compared with nondiabetics.[32] After adjustment for other comorbidities, DM increased the overall risk of new-onset AF significantly more in women (by 26%) than in men (by 9%).[33] Although younger diabetics had a lower absolute incidence of new-onset AF, their relative risk of AF was significantly higher than in older patients.[34] The risk of new-onset AF increases with duration of DM and worse glycemic control.[35] Each year of DM and 1-unit increase in hemoglobin A_{1c} (HbA_{1c}) were associated with a 3% and 14% increase in the risk of incident AF, respectively. The risk of incident AF was considerably higher among patients with DM history of more than 5 years or HbA_{1c} level higher than 7%, indicating a threshold relationship between hyperglycemia and AF.[35] The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial reported that even in individuals with impaired glucose tolerance (without overt DM), fasting plasma glucose was a predictor of new-onset AF.[36]

Diabetes was an independent risk factor for AF recurrence (odds ratio [OR], 4.6) after electrical cardioversion of persistent AF.[37,38] Although a long-term AF-freedom after catheter ablation was similar in patients with and without DM,[2] a higher basal HbA_{1c} level was associated with the risk of late AF recurrence post ablation among patients with DM.[39] Notably, the quality of glycemic control in the year before catheter ablation of AF was significantly associated with postprocedural AF recurrence within next 12 months.[40]

Treatment of diabetes and the prevention of atrial fibrillation **Primary prevention** Studies evaluating the benefits of specific antidiabetic treatment on incident AF reported controversial data.[41,42]

TABLE 1 Studies evaluating the impact of antihypertensive therapy on the prevention of atrial fibrillation in hypertensive patients (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						
Okin et al,[17] LIFE	Multicenter, retrospective, post hoc, longitudinal	n = 8831 Mean (SD) age, 67 (7) y Essential HTN ECG criteria of LVH No previous AF	Atenolol or losartan for hypertension	None	Mean (SD), 4.6 (1.1) y	In patients with LVH, SBP ≤130 mm Hg (vs ≥142 mm Hg) had a 40% risk reduction of incident AF. SBP ≤125 mm Hg no longer associated with the incident AF risk reduction
Marott et al[19]	Retrospective, observational, nationwide, nested, 1:1 matched	n = 277 880 Median age across group, 56–59 y Monotherapy for HTN No SHD No history of AF	ACEI vs other drug class (n = 196 092) ARBs vs other drug class (n = 81 788)	β-Blockers, CCBs, diuretics, ARBs β-Blockers, CCBs, diuretics, ACEI	Median across group, 5.9–6.8 y	ACEI or ARBs in patients without SHD are superior to β-blockers and diuretics but not compared with CCBs in the primary prevention of AF.
Schaer et al[20]	Retrospective, observational, nationwide nested case--control	n = 23 303 Age range, 20–79 y Monotherapy for HTN No other AF risk factors No previous AF	Antihypertensive monotherapy with ACEI, ARB, or β-blocker	CCB mono--therapy	≥1 y	In patients without SHD, an ACEI, ARB, and β-blocker, compared with CCBs, reduces the risk of new-onset AF by 25%, 29%, and 22%, respectively.
Zhang et al[21]	Meta-analysis of 26 randomized trials	n = 102 365 12 trials without AF history, 11 trials with previous AF, 3 trials with and without AF 9 trials with HTN ±risk factors (CHF, AMI, DM, or PVD)	ACEIs or ARBs (n = 39 405) ACEIs (n = 10 938)	Placebo or non-ACEI / ARB treatment (n = 41 119) ARBs (n = 10 903)	Mean across studies, 6 mo to 6.1 y	ACEIs / ARBs had a lower risk of AF than non-ACEI / ARB therapy. ACEIs and ARBs showed a similar preventive effect on AF occurrence. ACEIs / ARBs are better in secondary (OR, 0.45) than the primary prevention of AF (OR, 0.8). More prevention of AF if EF <40%
Nasr et al[22]	Meta-analysis of 7 randomized placebo--controlled trials	n = 11 952 Mean age across group, 57–76 y Systolic HF (EF 20%–36%) ACEIs / ARBs No history of AF	β-blocker	Placebo	Mean, 1.35 y	Addition of a β-blocker (vs placebo) to ACEI / ARB therapy is associated with a 27% relative risk reduction in patients with systolic (but not diastolic) HF.
Swedberg et al,[23] EMPHASIS--HF	Subanalysis of multicenter, randomized placebo controlled trial	n = 1794 Age ≥55 y NYHA II class HF Systolic HF, EF ≤35% β-blocker + ACEI / ARB therapy No history of AF	Eplerenone (n = 911)	Placebo (n = 883)	Median, 21 mo	Incidence of new-onset AF in systolic HF was reduced by eplerenone (vs placebo) from 4.5% to 2.7% with a relative risk reduction of 42%.
Secondary prevention of AF						
Kühlkamp et al[24]	Multicenter, randomized placebo--controlled, double-blind	n = 394 Mean (SD) age, 60 (12) y Cardioversion of PeAF HTN, 46%–49%; CHF, 25%	Metoprolol CR / XL (n = 197)	Placebo (n = 197)	Approx. 3 months	Metoprolol compared with placebo significantly reduced the risk of recurrence after electrical or pharmacological cardioversion of PeAF.
Disertori et al,[25] GISSI-AF	Multicenter, randomized placebo--controlled	n = 1442 Mean (SD) age, 68 (9) PAF or cardioverted PeAF HTN, 85%	Valsartan (n = 722)	Placebo (n = 720)	1 y	Valsartan was not associated with a reduction in the incidence of recurrent AF compared with placebo (51.4% vs 52.1%).

TABLE 1 Studies evaluating the impact of antihypertensive therapy on the prevention of atrial fibrillation in hypertensive patients (continued from the previous page)

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Secondary prevention of AF						
Goette et al,[26] ANTIPAF	Multicenter, randomized placebo--controlled	n = 425 Mean (SD) age, 61 (10) PAF Without SHD, HTN 49%	Olmesartan (n = 214)	Placebo (n = 211)	1 y	Olmesartan does not reduce the AF burden and number of hospitalizations nor improve quality of life over placebo.
Madrid et al[27]	Single-center, randomized controlled, prospective	n = 154 Mean (SD) age, 66 (9) y PeAF (approx. 6 mo) Electrical cardioversion	Irbesartan + amiodarone (n = 79)	Amiodarone (n = 75)	Median (IQR), 254 (60–710) d	Addition of irbesartan to amiodarone increases the 6-month AF-freedom post cardioversion of PeAF (55.9% vs 79.5%).
Ueng et al[28]	Single-center, randomized controlled, prospective	n = 145 Mean age across group, 64–66 y PeAF >3 mo Electrical cardioversion	Enalapril + amiodarone	Amiodarone	Median (IQR) 270 (61–575) d	Addition of enalapril to amiodarone increases the AF-freedom after cardioversion of PeAF (74.3% vs 57.3%).
Pokushalov et al[29]	Meta-analysis of 2 randomized prospective trials	n = 80 Mean (SD) age, 56 (6) y Ablation of PAF / PeAF HTN resistant to ≥3 antihypertensive drugs	Renal denervation + PVI	PVI alone	1 y	Renal denervation improves the results of PVI in patients with PeAF (HR, 0.39) and severe (≥160/100 mm Hg) HTN (0.37).
Parkash et al,[31] SMAC-AF	Multicenter, randomized prospective, parallel	n = 143 Mean age 60 y Ablation of PAF / PeAF BP >130/80 mm Hg	Aggressive BP treatment (target BP <120/80), starting approx. 3 mo prior to ablation (n = 88)	Standard BP treatment (<140/90 mm Hg) n = 85	Median (IQR), 14 (81–27) mo	More aggressive BP treatment did not reduce the AF recurrence rate post ablation but resulted in higher incidence of hypotension.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ANTIPAF, Angiotensin II-antagonist in Paroxysmal Atrial Fibrillation; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation; HF, heart failure; HTN, hypertension; HR, hazard ratio; IQR, interquartile range; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PVD, peripheral vascular disease; PVI, pulmonary vein isolation; RFM, risk factors modification; SBP, systolic blood pressure; SHD, structural heart disease; SMAC-AF, Substrate Modification with Aggressive Blood Pressure Control

A large Taiwanese cohort of patients with type 2 DM was followed for 13 years.[41] After adjusting for confounding factors, metformin use was independently associated with a 19% decrease of the incident AF risk.[41] Other nationwide cohort study of patients with DM who were not insulin dependent showed a preventive effect of thiazolidinediones (TZDs) on incident AF, which reduced the 5-year AF incidence by 30% compared with TZD nonusers (1.2% vs 1.8%, respectively).[42] The recent study that included older patients with DM demonstrated a significantly higher incident AF rate among the insulin users (vs nonusers, OR, 1.58) as well as a lower rate of new-onset AF among patients using dipeptidyl peptidase-4 inhibitors (vs nonusers, OR, 0.65).[43]

Although poor glycemia control predicted new-onset AF, the randomized study reported similar 5-year incident AF rates among patients with DM and high cardiovascular risk who underwent the intensive glycol regulation (targeting HbA_{1c} level of <6%) and those who continued with the standard treatment (targeting HbA_{1c} level between 7% and 7.9%) (TABLE 2).[44]

Secondary prevention It seems that pioglitazidone, one of the TZDs, may protect patients with type 2 DM and paroxysmal AF from recurrent AF after catheter ablation.[45] In pioglitazidone users, as compared with nonusers, the 2-year single PV-isolation procedure success was significantly higher (86.3% vs 70.7%, respectively), while the need for redo-ablation was significantly lower (9.8% vs 24.2%, respectively) (TABLE 2).[45]

Physical activity

Physical activity and the risk of atrial fibrillation Most trials evaluating the association between physical activity and AF are limited by self-reporting of total exercise level and detection of only documented AF cases.[46-51] It seems that the impact of physical activity on AF risk is influenced by age, sex, and type of exercise.[48,49]

TABLE 2 Studies on the effect of antidiabetic treatment on the prevention of atrial fibrillation in patients with diabetes mellitus

Study	Study design	Study participants (enrollment criteria)	RFM strategy	Control	Follow-up	Main findings (AF prevention)
Primary prevention of AF						
Chang et al,[41] Taiwanese LHDB 1999–2010	Population-based, retrospective, observational	n = 645 710 Mean (SD) age, 59 (17) y Type 2 DM No other antidiabetic therapy except metformin No history of AF	Metformin users (n = 85 198)	Metformin nonusers (n = 560 512)	13 y	Lower incidence of new-onset AF in metformin users compared with nonusers (245 vs 293 per 100 000 person-years); metformin reduced the relative risk of incident AF by 19%
Chao et al[42]	Population-based, retrospective, observational	n = 12 065 Mean (SD) age, 54 (12) y Non–insulin dependent DM	TZD users (n = 4137)	TZD nonusers (n = 7928)	Mean (SD), 63 (25) mo	Lower rate of incident AF in TZD users than in nonusers (1.2% vs 1.8%); TZDs independently protected from de novo AF (HR, 0.69) in DM
Chen et al[43]	Retrospective, observational, nationwide nested 1:4 matched	n = 9790 Age ≥65 y New-diagnosed DM	Insulin, 8.2% Metformin, 51.6% Acarboses, 12.2% Glinides, 8.2% Sulfonylureas, 55.9% TZDs, 14.3% DPP4 inhibitors, 3.2%	Nonusers (as reference)	7 y	In elderly patients with diabetes, the risk of new-onset AF was higher among the insulin users (multivariate OR, 1.58) and was lower among the DPP4 inhibitor users (OR, 0.65) compared with nonusers.
Fatemi et al,[44] ACCORD	Multi-center, randomized, double-blind, prospective	n = 10 082 High-risk[a] DM patients Approx. 35% receiving insulin HbA_{1c} ≥7.5%	Intensive glycemic control, targeting HbA_{1c} <6% (n = 5040)	Standard glycemic control, HbA_{1c} 7%–7.9% (n = 5042)	Median, 4.7 y	Intensive glycemic control failed to prevent new-onset AF more than a standard DM treatment strategy.
Secondary prevention of AF						
Gu et al[45]	Prospective, observational	n = 150 Drug-refractory PAF Catheter ablation (PVI) Type 2 DM	TZD (pioglitazone) users before ablation (n = 51)	TZD (pioglitazone) nonusers (n = 99)	Mean (SD), 23 (5) mo	A single ablation success was better (86.3% vs 70.7%) and the rate of redo ablation was lower (9.8% vs 24.2%) in the pioglitazone users than nonusers.
Donnellan et al[40]	Retrospective, observational	n = 298 Mean (SD) age, 67 (8) y Type 1 DM, 12.1% and type 2 DM, 87.9% Catheter ablation of AF	HbA_{1c} improvement during a 12-month period preceding AF ablation: >10% reduction, 0%–10% reduction, or worsening	–	Mean (SD), 26 (20) mo	The proportion decrease in HbA_{1c} during a 12-month period preceding catheter-ablation was independently associated with AF-free survival post ablation (HR, 0.714).

a High-risk patients: those with cardiovascular disease or aged of 55 to 79 years or those with anatomic evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or 2 additional cardiovascular risk factors (dyslipidemia, hypertension, current smoking status, or obesity)

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; DPP4, dipeptidyl peptidase-4; HbA_{1c}, hemoglobin A1c; LHDB, Longitudinal Cohort of Diabetes Patients Database; OR, odds ratio; TZD, thiazolidinedione; others, see TABLE 1

Thus, a regular leisure-time exercise in younger men increases the lifelong risk of new-onset AF by almost 20%,[48] whereas daily walking or cycling in middle-aged men reduces the risk by 12%.[48] However, a prospective study on middle-aged women reported opposite results, suggesting that protective effects of exercise on AF development were lost after adjusting for their body mass index.[50] The Physicians' Health Study demonstrated that daily jogging (but not cycling, swimming, or racquet sports) increased the long-term risk of incident AF by 53% compared with subjects not regularly participating in vigorous exercise.[51] Interestingly, in the Copenhagen City Heart Study, a high (ie, walking most of the working hours, often walking upstairs) and very high occupational physical activity (ie, heavy physical work) were associated with a 21% and 39% increase in the risk of incident AF, respectively, compared with mostly sedentary work.[52]

Baseline exercise tolerance is inversely associated with long-term risk of incident and recurrent AF.[53,54] Thus, for every 10% increase in functional aerobic capacity at baseline exercise test, the risk of new-onset AF was reduced by 7% during the 14-year follow-up.[53] This holds true also for patients with previous history of AF. A long-term AF-freedom with or without rhythm-control strategies was significantly better in patients with AF exhibiting high-peak metabolic equivalents (METs; >100% of predicted) than in those showing low-peak METs (<85% of predicted) at baseline testing (66% vs 12%, respectively).[55]

Level of physical activity and the prevention of atrial fibrillation **Primary prevention** A relationship between the lifetime exposure to exercise and the risk of new-onset AF is complex.[56-59] Several trials indicate a U-shaped dose-response association between the level of physical activity and AF incidence.[56,57] In the Cardiovascular Health Study regular exercise reduced the risk of incident AF, but the intensity of physical activity showed a nonlinear relationship with AF occurrence, wherein the arrhythmia risk was the lowest (HR, 0.72) with moderate level of exercise and significantly higher with both low and high exercise levels (HR, 0.85 and HR, 0.87, respectively).[57] Other studies found a more linear relationship between exercise level and incident AF, with a decline in long-term risk of new-onset AF across the entire spectrum of various exercise levels, by rate of 4.8% per each 1 MET hr/d.[58] On the contrary, the risk of incident AF increased linearly with intensity of exercise training among competitive athletes.[59] Available evidence suggests that the exercise level in the range of 1000 to 1500 METs min/wk (ie, roughly 220 to 330 minutes of moderate walking per week) may protect against new-onset AF.[60] Interestingly, although an improvement in maximal exercise capacity during lifetime was associated with lower risk of all-cause mortality[61] and heart failure, it did not prevent incident AF (TABLE 3).[62]

Secondary prevention Regular physical activity emerged as an important part of therapy for recurrent AF.[60] The potential benefits of yoga on paroxysmal AF treatment was evaluated in the small randomized study.[63] Practicing yoga for 1 hour twice weekly during 3 months was associated with significant reduction of AF burden assessed by a noninvasive loop-recorder as well as the improvement in quality of life.[63] Another randomized study reported that patients with recurrent AF who completed a 3-month exercise program (consisting of 35-minute physician-controlled walking/running sessions performed 3 times per week) significantly reduced the average time in AF detected by implantable loop recorder from 8.1% to 4.8%, while those who continued their usual physical activities actually increased the time in AF from 10.4% to 14.6%.[64] In addition, the CARDIO-FIT (Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation) study demonstrated a dose-response relationship between improvement in cardiorespiratory fitness and AF burden in obese patients participating in a structured exercise program, consisting of at least 200 min/wk of low-to-moderate exercise.[55] Increasing the level of physical exercise to high intensity (ie, 80% of maximal capacity) adds no clinical benefit over low intensity training (50% of maximal exertion) with respect to AF burden and hospitalizations (TABLE 3).[65]

Cigarette smoking

Cigarette smoking and the risk of atrial fibrillation Approximately 25% of adult men and 20% of women are currently declared as cigarette smokers.[66] Although epidemiological studies provided inconsistent findings, in several large population-based cohorts, smoking status at baseline was associated with an increased risk of incident AF during follow-up by almost 40%.[67-69] Moreover, 6.7% and 1.4% of total AF risk in men and women, respectively, can be attributed to tobacco use.[67] Even an early exposure to second-hand smoke during childhood increase the risk of AF later in life by 40%.[70]

Duration and intensity of smoking affect the risk of new-onset AF. Thus, AF incidence was directly related to years of previous smoking exposure.[69] The incident AF risk was significantly higher in heavy smokers (>15 g/d of tobacco) than among light-to-moderate smokers (1–14 g/d).[71] A recent study suggested a more complex dose-response relationship because plasma level of nicotine metabolite, cotinine, which is strongly associated with AF occurrence, rises steeply with consumption of first 10 cigarettes per day, but then reaches a plateau.[72]

Among patients with recurrent AF, smokers have a higher risk of arrhythmia relapse after cardioversion and catheter ablation compared with never smokers. In a large prospective study, the risk of AF recurrence at 1 year following cardioversion was independently associated with the baseline smoking status in elderly women (vs nonsmokers, HR, 1.71), but not in men.[73] Furthermore, the 1-year AF recurrence rate after PV-isolation was significantly higher in smokers than in nonsmokers (43% vs 14%; HR, 3.19).[74]

Smoking cessation and the prevention of atrial fibrillation **Primary prevention** Data regarding the effects of smoking cessation on the prevention of incident AF are conflicting. The Rotterdam Study suggests that persons who quit smoking remain at the increased risk of new-onset AF similar to

TABLE 3 Studies on dose-response between physical activity 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						
Morseth et al,[56] Tromsø 3	Community-based, prospective, longitudinal, observational	n = 20 484 Mean age across group, 36–39 y No previous AF Leisure time PA data 7 y prior to inclusion	Low PA: sedentary lifestyle Moderate PA: ≥4 h/wk of PA (cycling, walking) High PA: ≥4 h/wk of recreational sports Vigorous PA: competitive sports	–	Mean, 20 y	U-shaped dose--response between PA level and new AF risk Those with moderate PA had a 19% lower risk of incident AF compared with those with low and high PA.
Williams et al[58]	Population-based, prospective, longitudinal, observational	n = 46 807 Mean age across group, 44–59 y Recreational runners and walkers No previous AF	Baseline questionnaire on running and walking history Light PA: <3 METs Moderate PA: 3–6 METs Vigorous PA: >6 METs	–	Mean, 6.2 y	A linear decline in the relative risk of incident cardiac arrhythmias by reported level of PA: each 1 MET hr/d increment was associated with the 4.8% risk reduction.
Andersen et al[59]	Population-based, prospective, longitudinal, observational	n = 52 755 Mean (SD) age, 39 (12) y Former participants in the 90 km cross--country skiing race No AF at baseline	Evaluation of the association between the number of completed races during sports career and the risk of subsequent cardiac arrhythmias	–	Median, 9.7 y	Former athletes showed a linear rise in the future risk of new AF by the number of finished races: the risk was 22%, 27%, and 29% in participants who completed 2, 3–4, and ≥5 races, respectively.
Secondary prevention of AF						
Lakkireddy et al[63]	Single-center, prospective, pre--post cohort study	n = 52 Mean (SD) age, 61 (11) y Symptomatic PAF No AADs change during the study	Control phase (3 mo) followed by yoga phase (next 3 mo) Twice-weekly 60-min yoga training AF detection by cardiac external event monitors	None	3 mo	Yoga reduced symptomatic AF attacks (mean [SD], 3.8 [3] vs 2.1 [2.6]) and improved the QoL. In 22% of patients, no AF episode was recorded during the yoga intervention phase.
Malmo et al[64]	Single-center, randomized, prospective	n = 51 Mean age across group, 56–62 y Symptomatic PAF / PeAF (referred for CA of AF) Implanted loop recorder	The 12-week aerobic interval training, consisting of four 4-min intervals at 85%–95% of peak heart rate 3-times per week (n = 26)	Controls, patients continuing usual exercise habits (n = 25)	4 mo	12-week structured aerobic interval training reduced the mean time in AF (from 8.1% to 4.8%) and improved symptoms of AF and QoL.
Pathak, et al,[55] CARDIO-FIT	Single-center, observational, prospective, longitudinal	n = 308 Mean age across group, 58–69 y BMI ≥27 kg/m^2 PAF and PeAF	A goal-directed program: Tailored diet and CR fitness aiming to reduce weight by ≥10% and BMI to ≤25 kg/m^2 Risk factors therapy	None	Mean (SD), 49 (19) mo	AF-freedom and symptomatic AF burden were better with CR fitness gain ≥2 METs (vs <2 METs) CR fitness enhances the benefits of weight loss on AF outcome (1 MET gain was associated with a 9% decline in AF recurrence rate)

Abbreviations: AAD, antiarrhythmic drugs; BMI, body mass index; CA, catheter ablation; CARDIO-FIT, Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation; CR, cardiorespiratory; MET, metabolic equivalent; PA, physical activity; QoL, quality of life; others, see TABLES 1 and 2

TABLE 4 Studies on the relationship between smoking modification 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						
Zhu et al[67]	Meta-analysis of 16 prospective studies	n = 286 217 Age range, 39–94 y No prevalent AF Available data on smoking history	Smoking cessation (current smokers vs former smokers	Never smokers	Range, 2–50 y	The incident AF risk in current and former smokers was 39% and 16%, respectively, compared with never smokers. The AF risk due to smoking was higher in men than in women.
Wilhelmsen et al[71]	General male population (random sample), prospective	n = 7495 Age range, 47–55 y Available smoking history data	Current smokers (daily tobacco intake: 1–14 g vs >15 g)	Never + ex-smokers	Mean, 25.2 y	Risk of hospitalization for new AF was higher among heavy smokers (tobacco intake of >15 g/d) than among light-to-moderate smokers (1–14 g/d).
Zuo et al,[72] Hordaland Health Study	Population-based, prospective, observational	n = 6682 Age range, 46–74 y Without known AF Measurement of plasma cotinine level at baseline	Current smokers (categorized by plasma cotinine concentration)	Never smokers and former smokers	Median, 11 y	The relationship between smoking intensity and plasma cotinine was nonlinear, reaching a plateau at 15 cigarettes/d. A 40% increase in risk of new AF in participants with plasma cotinine level ≥85 vs <85 nmol/l.
Secondary prevention of AF						
Kinoshita et al[79]	Single-center, prospective, observational	n = 1424 Mean (SD) age, 70 (12) y Consecutive patients undergoing index cardioversion for AF / AFL	Ex-smokers (n = 536), current smokers (n = 113)	Nonsmokers (n = 664)	1 y	The 1-year arrhythmia recurrence rate post cardioversion among women was significantly higher in current smokers compared with ex-smokers (76% vs 61%).
Fukamizu et al[74]	Single-center, prospective, observational	n = 59 Mean (SD) age, 60 (11) y Consecutive patients undergoing index PVI ablation procedure for drug-resistant AF	Former smokers (n = 15), current smokers (n = 15)	Never-smokers (n = 30)	Mean (SD), 306 (95) d	The AF recurrence rate after PVI ablation was significantly higher among former smokers than among never-smokers (47% vs 14%).

Abbreviations: AFL, atrial flutter; others, see TABLES 1-3

current smokers (relative risk, 1.49 and 1.51, respectively, with never smokers used as the reference).[69] However, the ARIC (Atherosclerosis Risk in Communities) study presented more encouraging conclusions, reporting a significantly lower HR for incident AF in former compared with current smokers (1.32 vs 2.05, respectively).[68] Nevertheless, former smokers remained at increased risk for AF development as compared with never smokers.[67] Therefore, with respect to the primary prevention of AF, it is important never to start smoking (TABLE 4).

Secondary prevention It seems that smoking cessation does not seemingly improve outcome of rhythm control strategies in patients with recurrent AF. The 1-year AF recurrence rate following cardioversion of persistent AF and catheter ablation of recurrent AF was similar among current (58% vs 61%, respectively) and former smokers (47% and 40%, respectively) (TABLE 4).[73,74]

Conclusions Long-term history of hypertension, DM, vigorous or low physical activity, and cigarette smoking are associated with an increased lifetime risk of new-onset AF as well as the risk of relapse of AF following cardioversion or catheter ablation. Optimal management of hypertension with ACEIs, ARBs, and β-blockers may prevent new-onset AF and recurrence of AF

after cardioversion and ablation. The use of metformin or TZDs could be helpful in the primary prevention of AF among patients with DM, but more intense glycemia control provides no advantage in the prevention of incident AF compared with standard therapy of diabetes. However, well-managed long-term glycemic control before the intervention may reduce recurrent AF after catheter ablation. Physical activity, consisting of regular moderate exercise may protect against new-onset and recurrent AF. History of former or active cigarette smoking significantly reduces the efficacy of the rhythm control strategies.

ARTICLE INFORMATION

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