Risk factors modification for primary and secondary prevention of atrial fibrillation – Part I

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Risk factors modification for primary and secondary prevention of atrial fibrillation – Part I

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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 intervening 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 factors 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 reduce cardiovascular mortality and morbidity. The Part 1 of this review evaluates the association between AF and following risk factors: hypertension, diabetes mellitus, physical activity and cigarette smoking. We systematically discuss on the impact of risk factors modification on primary and secondary prevention of AF.

Key words: atrial fibrillation, lifestyle modification; modifiable risk factors; primary prevention; secondary prevention.
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 (LA) disease, thus underlying the importance of primary prevention of AF (i.e. prevention of new-onset or incident AF).[4]

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 reduce cardiovascular mortality and morbidity.[1,4]

Herein, we discuss the associations of risk factors, such as hypertension, diabetes mellitus (DM), physical activity and cigarette smoking (Part 1), and obesity, obstructive sleep apnea, alcohol use and dyslipidemia (Part 2), and AF occurrence. We summarize the studies reporting therapeutic effects of the risk factor management on primary and secondary AF prevention.

PATHOPHYSIOLOGICAL RELATIONSHIP BETWEEN RISK FACTORS AND ATRIAL Fibrillation

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

Hypertension and risk of AF

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 1.4-2.1 fold increased risk of new-onset AF.[7,8,10] Even pre-hypertension increases the risk of AF.[8] Among middle-aged pre-hypertensive men, the 35-year risk of incident AF was 1.5-fold higher in those with systolic blood pressure (SBP) of 128-138 mm Hg (vs. SBP <128 mm Hg) and 1.79-fold higher in those with diastolic BP (DBP) ≥80 mm Hg (vs. <80 mm Hg).[11]

A significant increase of new-onset AF risk across increasing BP categories has been reported, ranging from a Hazard Ratio (HR) of 1.28 for SBP of 120-129 mmHg to HR 2.74 for SBP readings of ≥160 mmHg.[12] A “J-shaped” association between SBP and risk of incident AF was demonstrated, with the lowest risk for a SBP of 120-130 mmHg and a significant increase in AF incidence for both SBP of <120 mmHg (HR 1.99) and SBP >150 mmHg (HR 2.02-2.27).[13] Diastolic blood pressure (DBP) is significantly associated with increased risk of incident AF only at the level of ≥95 mmHg, suggesting that systolic hypertension is a stronger predictor of new-onset AF than diastolic hypertension.[8,10,12,13]

Pre-procedural hypertension is a risk factor for AF recurrence after electrical cardioversion in older patients[14] as well as after catheter-ablation of AF (HR 2.5-3.2, with normotensive patients used as the reference).[2,15,16]
Hypertension management and AF prevention (see Table 1)

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

**Secondary prevention of AF.** Besides their antihypertensive effects, beta-blockers are superior than placebo for secondary prevention of AF[24] and they facilitate a reliable rate control during recurrent AF episodes.[1] Therefore, beta-blockers are a good choice for hypertensive patients with already documented AF. In AF patients with preserved systolic LV function, ACE-i and ARBs were not shown to prevent recurrent AF and they are not recommended for 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, ACE-i/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 alone strategy.[29] The RACE-III study (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure) showed that BP lowering <120/80 mmHg 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 post-ablation rhythm outcome.[31]

**DIABETES MELLITUS**

**Diabetes and risk of AF**

Patients with DM have a 39% higher risk of incident AF compared with non-diabetics.[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 is higher with longer duration of diabetes and worse glycemic control.[35] Each year of diabetes duration and 1-unit increase in hemoglobin A1c (HbA1c) 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 diabetes history of >5 years or
HbA1c >7.0%, 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 HbA1c 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 post-procedural AF recurrence within next 12 months.[40]

**Treatment of diabetes and AF prevention (see Table 2)**

**Primary prevention.** Studies evaluating the benefits of specific antidiabetic treatment on incident AF reported controversial data.[41,42] The large Taiwan cohort of Type 2 DM patients was followed for 13 years.[41] After adjusting for confounding factors, metformin use was independently associated with 19% decrease of the incident AF risk.[41] Other nationwide cohort study of non-insulin dependent diabetic individuals showed a preventive effects of thiazolidinediones (TZD) on incident AF, which reduced the 5-year AF incidence by 30% compared with TZD non-users (1.2% vs. 1.8%).[42] The recent study that included older DM patients demonstrated a significantly higher incident AF rate among the insulin users (vs. non-users, OR 1.58) as well as a significantly lower rate of new-onset AF among the patients using dipeptidyl peptidase-4 inhibitors (vs. non-users, OR 0.65).[43]
Although poor glycoregulation predicted new-onset AF, the randomized study reported similar 5-year incident AF rates among “high risk” DM patients who underwent the intensive glycol-regulation (targeting HbA1c level of <6.0%) and those who continued with the standard treatment (targeting HbA1c level between 7.0% and 7.9%).[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] The 2-year single PV-isolation procedure success was significantly higher (86.3% vs. 70.7%), while the need for redo-ablation was significantly lower (9.8% vs. 24.2%) among pioglitazidone users than among non-users.[45]

**PHYSICAL ACTIVITY**

**Physical activity and risk of AF**

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] Thus, a regular leisure-time exercise in younger men increases the life-long risk of new-onset AF by almost 20%.[48] whereas a 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 (i.e. walking most of the working hours, often walking upstairs) and very high occupational physical activity (i.e. 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 among AF patients exhibiting a high peak metabolic equivalents - METs (>100% of predicted) than among those showing a low peak METs (<85% of predicted) at baseline testing (66% vs. 12%).[55]

Level of physical activity and prevention of AF (see Table 3)

Primary prevention. A relationship between the life-time 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 non-linear 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/day.[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 1000-1500 METs min/week (i.e. roughly 220 to 330 min of moderate walking per week) may protect against new-onset AF.[60] Interestingly, although an improvement in maximal exercise capacity during life-time was associated with lower risk of all-cause mortality[61] and heart failure, it did not prevent incident AF.[62]

**Secondary prevention.** Regular physical activity emerged as an important part of therapy for recurrent AF.[60] The potential benefits of yoga practicing 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 noninvasive loop-recorder as well as the improvement in quality of life.[63] Another randomized study reported that patients with recurrent AF who completed the 3-month exercise program (consisting of the 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 weekly of low-to-moderate exercise.[55] Increasing the physical exercise level to high intensity (i.e. 80% of
maximal capacity) adds no clinical benefit over low intensity training (50% of maximal exertion) in respect to AF burden and hospitalizations.[65]

CIGARETTE SMOKING

Cigarette smoking and risk of AF

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 a smoking status at baseline was associated with almost 40% increased risk of incident AF during follow-up.[67-69] Moreover, 6.7% and 1.4% of total AF risk in males and females, 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 among heavy smokers (>15 g/day of tobacco) than among light-to-moderate smokers (1-14 g/day).[71] The 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 the 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. non-smokers, 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 non-smokers (43% vs. 14%, HR 3.19). [74]

**Smoking cessation and prevention of AF (see Table 4)**

**Primary prevention.** Data regarding the effects of smoking cessation on 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 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). [68] Nevertheless, former smokers remained at increased risk for AF development as compared with never smokers. [67] Therefore, in respect to primary prevention of AF, it is important never to start smoking.

**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 and former smokers (58% vs. 61% and 47% and 40%, respectively). [73, 74]
CONCLUSION

Long-term history of hypertension, DM, vigorous or low physical activity, and cigarette smoking are associated with the increased life-time risk of new-onset AF as well as the risk of relapse of AF following cardioversion or catheter-ablation. Optimal management of hypertension with ACE-i, ARBs and beta-blockers may prevent new-onset AF and recurrence of AF after cardioversion and ablation. The use of metformin or TZDs could be helpful in primary AF prevention among DM patients, but more intense glycoregulation provides no advantage in prevention of incident AF compared with standard therapy of diabetes. However, well-managed long-term glycemic control before the intervention may reduce recurrent AF post catheter-ablation. Physical activity, consisting of regular moderate exercise may protect against new-onset and recurrent AF. History of former or active cigarrette smoking significantly reduce the efficacy of the rhythm control strategies.
REFERENCES


## Table 1. Clinical studies evaluating the impact of antihypertensive therapy on AF prevention in hypertensive patients.

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<th>Study [ref.]</th>
<th>Study design</th>
<th>Study participants (enrollment criteria)</th>
<th>RFM strategy</th>
<th>Control</th>
<th>Follow-up</th>
<th>Main findings (AF prevention)</th>
</tr>
</thead>
</table>
| Okin et al., 2015 (LIFE) 17 | Multi-center, retrospective, post-hoc, longitudinal | • N=8831  
• Mean (SD) age, 67 (7) years  
• Essential HTN  
• ECG criteria of LVH  
• No previous AF | Atenolol or losartan for hypertension | None | Mean (SD), 4.6 (1.1) years | • In patients with LVH, SBP ≤130 mm Hg (vs. ≥142 mmHg) had a 40% risk reduction of incident AF  
• SBP ≤125 mmHg no longer associated with the incident AF risk reduction |
| Marott et al., 2014 19 | Retrospective, observational, nationwide nested 1:1 matched | • N=277,880  
• Median age across group, 56-59 years  
• Monotherapy for HTN  
• No SHD  
• No history of AF | N=196,092 (1:1 matched): ACE-i vs. other drug-class  
N=81,788 (1:1 matched): ARBs vs. other drug-class | BBs, CCBs, diuretics, ARBs;  
BBs, CCBs, diuretics, ACE-i | Median FU across group, 5.9-6.8 years | • ACE-i or ARBs in patients without SHD are superior to beta-blockers and diuretics but not compared to CCBs in primary prevention of AF |
| Schaer et al., 2010 20 | Retrospective, observational, nationwide nested case-control | • N=23,303  
• Age range, 20-79 years  
• Monotherapy for HTN  
• No other AF risk factors  
• No previous AF | Antihypertensive monotherapy with ACE-i, ARB or BB | CCB monotherapy | ≥1 year | • In patients without SHD, ACE-i, ARB and BB, compared with CCBs, reduces the risk of new-onset AF by 25%, 29% and 22%, respectively |
| Zhang et al., 2010 21 | Meta-analysis of 26 randomized trials | • N=102,365  
• 12 trials without AF history, 11 trials with previous AF, 3 trial with and without AF  
• 9 trials with HTN  
• ± risk factors (CHF, AMI, DM or PVD) | Treatment with ACE-Is or ARBs (N=39,405) | vs. placebo or non-ACE-I/ARB treatment (N=41,119) | Mean FU across studies, 6 months to 6.1 years | • ACE-Is/ARBs had a lower risk of AF than non-ACE-I/ARB therapy  
• ACE-Is and ARBs showed a similar preventive effect on AF occurrence  
• ACE-Is/ARBs are better in secondary (OR 0.45) then in primary AF prevention (OR 0.80)  
• More AF prevention if EF<40% |
| Nasr et al., 2007 22 | Meta-analysis of 7 randomized placebo- | • N=11,952  
• Mean age across group, 57-76 years  
• Systolic HF (EF 20-36%) | Treatment with BB | vs. placebo | Mean 1.35 years | • Addition of BB (vs. placebo) to ACE-I/ARB therapy is associated with 27% relative risk reduction |
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<th>Study [ref.]</th>
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<th>Study participants (enrollment criteria)</th>
<th>RFM strategy</th>
<th>Control</th>
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</tr>
</thead>
</table>
| Swedberg et al., 2012 (EMPHASIS-HF)23 | Subanalysis of multi-center, randomized placebo controlled trial | N=1794  
Age ≥55 years  
NYHA II class HF  
Systolic HF, EF ≤35%  
BB + ACE-i/ARB therapy  
No history of AF | Eplerenone (N=911) vs. placebo (N=883) | Median 21 months | 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% |
| Kühlkamp et al., 200024 | Multi-center, randomized placebo-controlled, double-blind | N=394  
Mean (SD) age, 60 (12)  
Cardioversion of PeAF  
HTN 46-49%, CHF 25% | Metoprolol CR/XL (N=197) vs. 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., 2009 (GISSI-AF)25 | Multi-center, randomized placebo-controlled | N=1442  
Mean (SD) age, 68 (9)  
PAF or terminated PeAF  
HTN 85% | Valsartan (N=722) vs. placebo (N=720) | 1 year | Valsartan was not associated with a reduction in the incidence of recurrent AF compared with placebo (51.4% vs. 52.1%) |
| Goette et al., 2012 (ANTIPAF)26 | Multi-center, randomized placebo-controlled | N=425  
Mean (SD) age, 61 (10)  
PAAF 85%  
HTN 49% | Olmesartan (N=214) vs. placebo (N=211) | 1 year | Olmesartan does not reduce the AF burden and number of hospitalizations nor improve quality of life over placebo |
| Madrid et al., 200227 | Single-center, randomized controlled, prospective | N=154  
Mean (SD) age, 66 (9)  
PeAF (~ 6 months)  
Electrical cardioversion | Irbesartan + amiodarone (N=79) vs. amiodarone (N=75) | Median 254 (IQR: 60-710) days | Addition of irbesartan to amiodarone increase the 6-month AF-freedom post-cardioversion of PeAF (55.9% vs. 79.5%) |
| Ueng et al., 200328 | Single-center, randomized controlled, prospective | N=145  
Mean age across group, 64-66 years  
PeAF >3 months  
Electrical cardioversion | Enalapril + amiodarone vs. amiodarone | Median 270 (61-575) days | Addition of enalapril to amiodarone increase the AF-freedom after cardioversion of PeAF (74.3% vs. 57.3%) |
| Pokushalov et al., 2014<sup>29</sup> | Meta-analysis of 2 randomized prospective trials | • N=80  
• Mean (SD) age, 56 (6) years  
• Ablation of PAF/PeAF  
• HTN resistant to ≥3 antihypertensive drugs | Renal denervation + PVI vs. PVI alone | 1 year | • Renal denervation improves the results of PVI in patients with PeAF (HR 0.39) and severe (≥160/100 mmHg) HTN (0.37) |

| Parkash et al., 2017 (SMAC-AF)<sup>31</sup> | Multi-center, randomized prospective, parallel | • N=143  
• Mean age 60 years  
• Ablation of PAF/PeAF  
• BP >130/80 mmHg | Aggressive BP treatment (target BP <120/80), starting =3 months prior to ablation; N=88 | Standard BP treatment (<140/90 mmHg) N=85 | Median 14 (IQR: 81-27) months | • More aggressive BP treatment did not reduce the AF recurrence rate post-ablation but resulted in higher incidence of hypotension |

AF, atrial fibrillation; RFM, risk factors modification; HTN, hypertension; ECG, electrocardiogram; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; SHD, structure heart disease; ACE-i, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; CHF, congestive heart failure; AIM, acute myocardial infarction; DM, diabetes mellitus; PVD, peripheral vascular disease; HF, heart failure; NYHA, New York Heart Association; EF, ejection fraction; PeAF, persistent atrial fibrillation; PAF, paroxysmal atrial fibrillation; IQR, interquartile range; PVI, pulmonary vein isolation; HR, Hazard Ratio; BP, blood pressure.
Table 2. The studies investigating the effect of antidiabetic treatment on prevention of AF in diabetic patients.

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<th>Main findings (AF prevention)</th>
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<td>Chang et al., 2014</td>
<td>Population-based, retrospective, observational</td>
<td>N=645,710</td>
<td>Metformin users (N=85,198)</td>
<td>Metformin non-users (N=560,512)</td>
<td>13 years</td>
<td>Lower incidence of new-onset AF in metformin users compared with non-users (245 vs. 293 per 100,000 person-years)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>N=645,710</td>
<td>Mean (SD) age, 59 (17) years</td>
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<td>Metformin reduced the relative risk of incident AF by 19%</td>
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<td>Chao et al., 2012</td>
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<td>N=12,065</td>
<td>TZD users (N=4,137)</td>
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<td>Lower rate of incident AF in TZD users than in non-users (1.2% vs. 1.8%)</td>
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<td></td>
<td></td>
<td>N=12,065</td>
<td>Mean (SD) age, 54 (12) years</td>
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<td>TZDs independently protected from de novo AF (HR 0.69) in DM</td>
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<td>Chen et al., 2017</td>
<td>Retrospective, observational, nationwide nested 1:4 matched</td>
<td>N=9,790</td>
<td>Insulin, 8.2% Metformin, 51.6% Acarbose, 12.2% Glinides, 8.2% Sulfonylureas, 55.9% TZDs, 14.3% DPP4 inhibitors, 3.2%</td>
<td>Non-users (as reference)</td>
<td>A span of 7 years</td>
<td>In elderly diabetics, 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 the non-users.</td>
<td></td>
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<tr>
<td>Fatemi et al., 2014</td>
<td>Multi-center, randomized, double-blind, prospective</td>
<td>N=10,082</td>
<td>Intensive glycemic control, targeting HbA1c &lt;6.0% (N=5,040)</td>
<td>Standard glycemic control, HbA1c 7.0-7.9% (N=5,042)</td>
<td>Median 4.7 years</td>
<td>Intensive glycemic control failed to prevent new-onset AF more than a standard DM treatment strategy</td>
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DIABETES MELLITUS and antidiabetic treatment
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<th>Mean (SD), 23 (5) months</th>
<th>A single ablation success was better (86.3% vs. 70.7%) and the rate of redo ablation was lower (9.8% vs. 24.2%) among the pioglitazone users than among non-users</th>
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<td>150</td>
<td>Drug-refractory PAF</td>
<td>Catheter-ablation (PVI)</td>
<td>TZD (pioglitazone) users before ablation (N=51)</td>
<td>TZD (pioglitazone) non-users (N=99)</td>
<td>Mean (SD), 23 (5) months</td>
<td>A single ablation success was better (86.3% vs. 70.7%) and the rate of redo ablation was lower (9.8% vs. 24.2%) among the pioglitazone users than among non-users</td>
</tr>
<tr>
<td>Donnellan et al., 2019</td>
<td>Retrospective</td>
<td>298</td>
<td>Mean (SD) age, 67 (8) years</td>
<td>Catheter-ablation of AF</td>
<td>HbA1c improvement during 12-month period preceding AF ablation: &gt;10% reduction, 0-10% reduction, or worsening</td>
<td>-</td>
<td>Mean (SD), 26 (20) months</td>
<td>The proportion decrease in HbA1c during 12-month period preceding catheter-ablation was independently associated with AF-free survival post-ablation (HR: 0.714)</td>
</tr>
</tbody>
</table>

"high-risk" patients: subjects 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).

T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; TZD, thiazolidinedione; DPP4, dipeptidyl peptidase-4; OR, Odds Ratio; HbA1c, hemoglobin A1c; T1DM, type 1 diabetes mellitus; others, see Table 1.
Table 3. The studies analyzing the dose-response between the physical activity and the risk of AF.

<table>
<thead>
<tr>
<th>PHYSICAL ACTIVITY</th>
<th>Primary prevention of AF</th>
<th>Secondary prevention of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study [ref.]</strong></td>
<td><strong>Study design</strong></td>
<td><strong>Study participants</strong></td>
</tr>
<tr>
<td>Morseth et al., 2016 (Tromsø 3)</td>
<td>Community-based, prospective, longitudinal, observational</td>
<td>N=20,484</td>
</tr>
<tr>
<td>Williams et al., 2013</td>
<td>Population-based, prospective, longitudinal, observational</td>
<td>N=46,807</td>
</tr>
<tr>
<td>Andersen et al, 2013</td>
<td>Population-based, prospective, longitudinal, observational</td>
<td>N=52,755</td>
</tr>
<tr>
<td>Lakkireddy et al., 2013</td>
<td>Single-center, prospective, pre-post cohort study</td>
<td>N=52</td>
</tr>
<tr>
<td>Study Authors, Year</td>
<td>Study Design</td>
<td>Study Population</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
</tbody>
</table>
| Malmo et al., 2016   | Single-center, randomized, prospective, | N=51  
• Mean age across group, 56-62 years  
• 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 months | 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., 2015  | Single-center, observational, prospective, longitudinal | N=308  
• Mean age across group, 58-69 years  
• BMI ≥27 kg/m²  
• PAF and PeAF | A goal-directed program:  
• Tailored diet and CR fitness aiming to reduce weight by ≥10% and BMI to ≤25 kg/m²  
• Risk factors therapy | None  
Mean (SD), 49 (19) months | 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) |

PA, physical activity; MET, metabolic equivalent; AAD, antiarrhythmic drugs; QoL, quality of life; CA, catheter-ablation; BMI, body mass index; CR, cardio-respiratory; others, see Tables 1 and 2.
Table 4. The studies on the relationship between the smoking modification and the risk of AF.

### CIGARETTE SMOKING

#### Primary prevention of AF

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Study design</th>
<th>Study participants (enrollment criteria)</th>
<th>RFM strategy</th>
<th>Control</th>
<th>Follow-up</th>
<th>Main findings (AF prevention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al., 2016</td>
<td>Meta-analysis of 16 prospective studies</td>
<td>N=286,217 • Age range, 39-94 years • No prevalent AF • Available data on smoking history</td>
<td>Smoking cessation (current smokers vs. former smokers)</td>
<td>Never smokers</td>
<td>Range, 2-50 years</td>
<td>• 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</td>
</tr>
<tr>
<td>Wilhelmsen et al., 2001</td>
<td>General male population (random sample), prospective</td>
<td>N=7,495 • Age range, 47-55 years • Available smoking history data</td>
<td>Current smokers (daily tobacco intake: 1-14 g vs. &gt;15 g)</td>
<td>Never + ex.-smokers</td>
<td>Mean, 25.2 years</td>
<td>• Risk of hospitalization for new AF was higher among heavy smokers (tobacco intake of &gt;15 g/day) than among light-to-moderate smokers (1-14 g/day)</td>
</tr>
<tr>
<td>Zuo et al., 2018 (Hordaland Health Study)</td>
<td>Population-based, prospective, observational</td>
<td>N=6,682 • Age range, 46-74 years • Without known AF • Measurement of plasma cotinine level at baseline</td>
<td>Current smokers (categorized by plasma cotinine concentration)</td>
<td>Never smokers and former smokers</td>
<td>Median, 11 years</td>
<td>• The relationship between smoking intensity and plasma cotinine was non-linear, reaching a plateau at 15 cigarettes/day • A 40% increase in risk of new AF in participants with plasma cotinine level ≥85 vs. &lt;85 nmol/l</td>
</tr>
</tbody>
</table>

#### Secondary prevention of AF

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Study design</th>
<th>Study participants (enrollment criteria)</th>
<th>RFM strategy</th>
<th>Control</th>
<th>Follow-up</th>
<th>Main findings (AF prevention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinoshita et al., 2009</td>
<td>Single-center, prospective, observational</td>
<td>N=1,424 • Mean (SD) age, 70 (12) years • Consecutive patients undergoing index cardioversion for AF/AFL</td>
<td>Ex.-smokers (N=536), current smokers (N=113)</td>
<td>Non-smokers (N=664)</td>
<td>1 year</td>
<td>• The 1-year arrhythmia recurrence rate post cardioversion among women was significantly higher in current smokers compared with ex-smokers (76% vs. 61%).</td>
</tr>
</tbody>
</table>
Fukamizu et al., 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N=59</th>
<th>Mean (SD) age, 60 (11) years</th>
<th>Former smokers (N=15), current smokers (N=15)</th>
<th>Never-smokers (N=30)</th>
<th>Mean (SD), 306 (95) days</th>
<th>AF recurrence rate after PVI ablation was significantly higher among former smokers than among never-smokers (47% vs. 14%)</th>
</tr>
</thead>
</table>

AFL, atrial flutter; others, see Tables 1, 2 and 3.
**Figure 1.** Main goals of AF treatment and timelines of different treatment options.

AF, atrial fibrillation; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; CV, cardio-vascular; HF, heart failure; LA, left atrium; AAD, antiarrhythmic drug; TE, thrombo-embolism.
Figure 2. Impact of modifiable risk factors on structural and electrical left atrial remodeling predisposing to development of AF.

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