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REVIEW

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Modifiable Risk Factors and Atrial Fibrillation: the Quest for a Personalized Approach

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ABSTRACT

Background: *Atrial fibrillation (AF) is the most common tachyarrhythmia, affecting up to 4% of the general population. Susceptibility to AF episodes can be explained by various risk factors (RF) that alter the substrate of the left atrium. Association between several RF and AF development and recurrence has been demonstrated in several studies.*

Areas of uncertainty: *Treatment strategies depend on patients' characteristics and comorbidities. Medical literature and consensus documents recommend an integrated approach, but also identify evidence gaps in treating patients with severe comorbidities.*

Data sources: *Literature search was performed using PubMed electronic database. We used the following terms as key words: atrial fibrillation, risk factors, comorbidities, primary prevention, secondary prevention.*

Results: *Active intervention helps control the burden of AF and increase the chances of a positive outcome on the long term. Aggressive control and individualized treatment of most prevalent modifiable risk factors can reduce the risk of atrial fibrillation. Optimization of treatment strategy should be performed periodically, since RF and comorbidities are dynamic and often evolve.*

Conclusion: *Personalized strategies should be applied to each patient after careful assessment of individual risk. A personalized approach is indicated to both reduce the burden of AF and improve symptoms, quality of life and survival. Close attention to details is required to avoid disease and therapy related complications in the presence of comorbidities.*

Keywords: atrial fibrillation, risk factors, comorbidities, prevention, recurrence.

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INTRODUCTION

Atrial fibrillation (AF) is considered a global pandemic with a prevalence on the rise. The arrhythmia affects about 2-4% of the general population and a person's estimated lifetime risk of developing AF is around 25% (1-5), making AF a major public health problem.

Despite all research efforts in the last decades, prevention of AF remains a challenge for physicians. No new antiarrhythmic drugs have been evaluated in the last years for prevention, and treatment has been focused on anticoagulation and interventional therapy.

Atrial fibrillation is a result of structural and electrical remodeling of the left atrium (LA), that can be explained in almost 50% of cases by underlying risk factors (RF) and comorbidities. Hypertension, obesity, diabetes, respiratory disease, and chronic kidney disease are all well-known, established RF for development of AF. These are all modifiable RF, and their control could bring potential benefits in reducing AF progression. Age, gender, ethnicity as well as genetic factors may modulate their influence on AF development and recurrences (1, 5).

Atrial cardiomyopathy (Figure 1), a cumulative result of different RF, once developed will increase the risk for new onset AF and will provide a substrate for the persistence of AF episodes (6–8). Paroxysmal AF will progress in time to a persistent and finally to a permanent form (9). Therefore, controlling concomitant disorders plays an important role in primary and secondary prevention of this multifactorial arrhythmia (5, 10, 11).

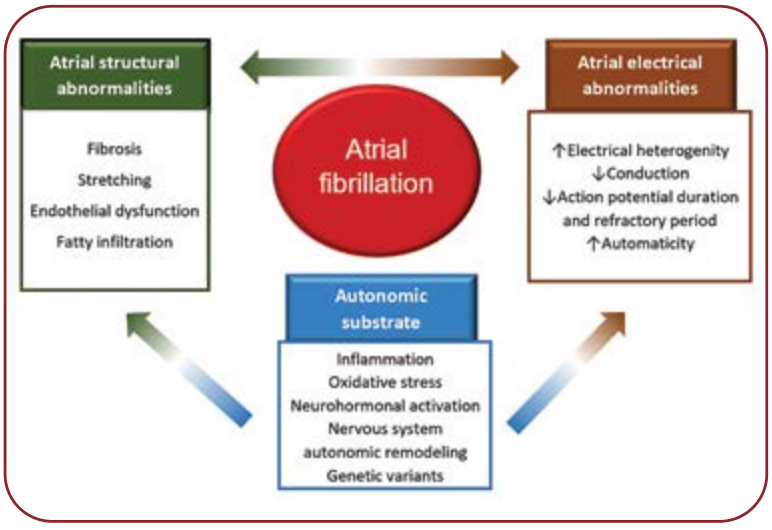

FIGURE 1. Mechanisms related to development and persistence of atrial fibrillation

Treatment includes rate or rhythm control strategies. Current antiarrhythmic drugs (AADs) address electrical changes of myocytes and have a limited longterm efficiency in maintaining sinus rhythm (SR). Also, AADs have side effects and proarrhythmic risk, mainly in patients with comorbidities.

Catheter ablation therapy does not cure AF, but significantly reduces recurrences, especially symptomatic episodes. The success rate after pulmonary vein isolation varies from 50 to 80% on the long term and are affected by the patients characteristics (12-15).

As no cure exists, upstream therapy was studied as complementary prevention treatment to address structural changes of atrial substrate. Renin-angiotensin-aldosterone system (RAAS) inhibition and use of statins relate to a sustained reduction of new cases of AF, especially in patients with comorbidities, however, in secondary prevention, the results are less encouraging (16, 17). Anticoagulation is the only treatment that can protect against stroke and embolic complications. Embolic risk should be reevaluated periodically, since risk factors and comorbidities are dynamic (5). ❑

RISK FACTORS FOR ATRIAL FIBRILLATION

1. Hypertension

Epidemiological studies show that hypertension (HTN) is the most prevalent RF for atrial fibrillation. Results from the Framingham study showed that HTN implies a 50% excess risk for developing AF in men and 40% in women (18). Data from the ARIC (Atherosclerosis Risk in Communities) study confirms that HTN is the most prevalent concomitant RF (diagnosed in 69% of patients with AF), and it explains alone approximately 20% of new cases of AF (19). Hypertension is diagnosed in 60-80% of patients with an established diagnosis of AF (18).

Mechanisms related to increased AF prevalence

a. Blood pressure (BP) values. The risk of AF does not increase linearly with the severity of HTN (20). Systolic BP has a better predicting value of incidental AF development (21), and the pulse pres-

TABLE 1. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) in primary or secondary prevention of atrial fibrillation;
AF = atrial fibrillation

RAAS inhibitors	Studies	Effects on AF
Captopril	CaPP Captopril Prevention Project	No significant effect in primary prevention (37–39)
Lisinopril Enalapril	STOP-2 trial Swedish Trial in Old Patients with Hypertension-2	
Valsartan	VALUE trial The Valsartan Antihypertensive Long-Term Use Evaluation Trial	16% reduction on new-onset AF in hypertensive patients compared with amlodipine (40)
	GISSI-AF Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – atrial fibrillation	No significant reduction in the incidence of recurrent atrial fibrillation in patients with heart failure and a history of paroxysmal or recently converted persistent AF (51% of patients had recurrences in the valsartan group compared to 52% in the placebo group) (45)
Losartan	LIFE Losartan Intervention for Endpoint Reduction in Hypertension	33% reduction of new AF cases compared with atenolol; longer periods of maintained sinus rhythm (28,41)
Candesartan	J-RHYTHM II Candesartan in Japanese Rhythm Management Trial II for Atrial Fibrillation	No effect on reducing the frequency of paroxysmal AF compared to amlodipine (44)
	CHARM Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity	Reduced the incidence of AF in patients with symptomatic CHF (46)
Olmesartan	ANTIPAF Olmesartan in Angiotensin II-antagonist in Paroxysmal Atrial Fibrillation trial	No reduction in the number of AF episodes in patients with documented paroxysmal AF without structural heart disease (47)

sure can also provide incremental value of the prediction (22-24). Data from the MESA study (Multi-Ethnic Study of Atherosclerosis) found that patients with high normal blood pressure values (120-139/80-89 mm Hg) had a 80% higher risk of AF, in spite of all other RF, on a median follow up of 5.3 years (25). Pre-hypertension is a RF for incident AF development in men. Grundvold *et al.* reported that men with upper normal values or baseline HTN had a 1.5-1.6-fold risk of incidental AF when compared with normotensive subjects. Baseline diastolic HTN also increases the risk of AF (26).

b. Duration of HTN is associated with degree of fibrotic remodeling, but studies show that even short periods of high BP can determine electrical alterations, increasing the proarrhythmic risk (27).

c. Hemodynamic factors. Hypertension determines left ventricular hypertrophy, diastolic dysfunction due to elevated left atrial pressures,

LA impairment and dilatation. Treated hypertension reduces the risk of new-onset AF by 25% (28), whereas suboptimal control remains a major risk factor for AF (29).

d. Neurohormonal effects. RAAS is the main mechanism implied in AF (30). Patients with high BP and organ damage particularly have a high blood level of angiotensin II (31). Increased expression of angiotensin converting enzyme was found in atrial tissue samples in patients with permanent AF. This is one of molecular mechanisms responsible for atrial fibrosis (32).

Effects of treatment of HTN on incident AF

a. RAAS inhibitors. Beside lowering BP values, a RAAS inhibitor influences the pathophysiological substrate (33) and could add beneficial effect by reducing left ventricular hypertrophy and the incidence of AF (34-36). Presumed to be an upstream therapy for AF, results from observational and therapeutic studies were at first inconsistent (11). In primary prevention, earlier studies showed no significant reduction of AF occurrence rate on long term follow-up compared with other antihypertensive classes (38, 39). Inhomogeneity of the study populations and lack of methods for monitoring AF occurrence were incriminated for these negative results. More recent trials reported positive outcomes in primary prevention beyond the BP control (41). Information from a US database showed that angiotensin converting enzyme inhibitors (ACEI) reduce the risk of AF by 15% on a period of 4.5 years, when compared with calcium channel antagonists (42), and the percentage reached 25% after analyzing data from a case-control trial in UK (22). Although ACEI and angiotensin receptor blockers (ARBs) have different ways of action, studies failed to show the superiority of one class over the other (43). Data to support their use for AF secondary prevention is also debatable (28, 44). Although starting treatment with an ACEI before cardioversion could increase the success rate in achieving SR, it does not influence the risk of recurrences (48). In the absence of an antiarrhythmic drug (class I or III), a RAAS inhibitor cannot prevent recurrences in patients with a history of either paroxysmal or persistent AF (49, 16, 22) (Table 1).

Drugs that modulate the RAAS did not predict a favorable effect on maintaining SR after catheter ablation in most studies. Rosen found that treatment with ACEI or ARBs not significantly reduce the recurrence rate in the first year. In this study, 60% of patients were hypertensive and 46% used a RAAS inhibitor. Recurrence rate was 31% in the first year and RASS inhibition treatment had no effect. There was no statistical difference, depending on the degree of atrial fibrosis. One hypothesis implied that their antifibrotic effect does not ameliorate fibrosis determined by radiofrequency injury or scaring (50). Inhibition of RAAS did not affect the recurrence rates in a prospective registry of 419 patients who underwent AF ablation for paroxysmal or persistent episodes. The differences between the two group were not significant: 73% of subjects taking RAAS modulators and 70% of those not on ACEI or ARB treatment, maintained SR after a median follow-up of 1.7 years. Multivariate and subgroup analysis showed no positive impact of the treatment (51). Moreover, combination of RAAS inhibitors and statins did not improve the outcome after AF ablation (52).

Aldosterone receptor antagonists could play a role in AF prevention by reducing atrial fibrosis, modulating ion channel functions and lowering AF inducibility (53,54). EMPHASIS-HF showed beneficial effect of eplerenone in reducing new-onset AF compared to placebo in patients with systolic heart failure and mild symptoms (55). However, MRA treatment was not associated with reduced AF progression in the ORBIT-AF trial (56). Similarly, in patients with heart failure and preserved ejection fraction, spironolactone did not reduce the risk of AF (57). In the absence of HF, spironolactone could prevent AF episodes if used in a combination with a beta-blocker (BB), irrespective of the association with an ACEI, as suggested in the SPIR-AF study (58).

b. Beta-blockers are usually preferred in patients with angina, arrhythmias, heart failure or history of myocardial infarction, or in those with a hyperstimulation of the sympathetic nervous system (53). They have limited effect on preventing AF compared with other classes of drugs (41), but could be of use in preventing AF occurrence in patients with systolic heart failure (59).

c. Dihydropyridine calcium channel blockers are used to control HTN and are also indicated in patients with left ventricular hypertrophy (60). Non-dihydropyridines are used only to control atrioventricular response in patients without HF. Regarding the prevention of AF, data is controversial and studies suggest that this class is not as ef-

fective as ACEIs (42, 61), although in the ALLHAT subanalysis no differences were found between amlodipine, lisinopril or chlorthalidone (38).

d. Renal denervation (RDN) as a treatment option for resistant hypertension has shown conflicting evidence. In AF patients, Romanov *et al*, concluded that combined RDN and pulmonary vein isolation (PVI) in patients with resistant HTN have a cumulative effect and are associated with a reduction of AF burden (62). The result seems to be superior in patients with persistent AF. At one year follow-up, 61% of patients who underwent RDN and PVI were AF free, compared with 41% of subjects with PVI only (63). In ERADICATE-AF study, RDN and PVI significantly decreased the risk of AF recurrences among hypertensive patients with paroxysmal AF: 72% of patients in the RDN group were AF free at one year, compared to only 56% of patients from the ablation group (64). Although RDN lowers BP values, it seems that the results are mainly explained by modulation of the autonomic nervous system in patients with concomitant AF ablation.

2. Diabetes mellitus

Diabetes mellitus (DM) is an independent risk factor for AF (18,65).

Mechanism related to AF. Incidence of new onset AF is increased in diabetic patients due to oxidative stress and chronic inflammation that determine fibrosis and dilation of the LA. Autonomic nervous dysfunction is also involved (66, 67). Epicardial adipose tissue (EAT) might also play a role (68-70), since it produces inflammatory mediators and pro-fibrotic molecules that affect the myocardium, promoting AF (71).

Effects of DM treatment. There seems to be a dependent relationship between glycemic control and AF risk (66, 67). Recent studies showed the role of glycemic fluctuations in increasing oxidative stress and promoting AF (72).

Insulin and secretagogues stimulate the nervous system through episodes of hypoglycemia and can induce episodes of AF. On the other hand, drugs that decrease insulin resistance can lower the incidence of AF (73). Treatment with Metformin and Pioglitazone is associated with a decreased risk of developing AF (73-75). Pioglitazone is also correlated to a lower recurrence risk after a first AF ablation (76). Glucagon-like peptide-1 receptor agonists (GLP1) and sodium-glucose co-transporter-2 (SGLT2) showed no impact on AF development in patients with type 2 DM, although these classes of drugs showed a favorable impact on the cardiovascular events (77).

A poor glycemic control represents a RF for AF recurrence after cardioversion and catheter ablation (66). A meta-analysis on 1464 patients from 15 studies, with 15% of patients on insulin regimens, reported that glycated hemoglobin levels directly related to higher AF recurrence rates (78). A better glycemic control prior to ablation therapy could improve the outcome (79), but intensive glycemic control does not ensure protection from AF (80).

Glucose-lowering drug treatment could also reduce EAT. Liraglutide in addition to Metformin showed a substantial reduction in epicardial fat volume at six months (36% reduction compared to metformin alone) (81). Dapagliflozin improves metabolic parameters in diabetic patients, reduces body weight and was also shown to decrease the epicardial adipose tissue (82). Future studies will confirm if GLP-1 analogues or SGLT-2 inhibitors can improve the outcome in patients with AF.

Effects of AF treatment. Antiarrhythmic drugs (AADs) should be used cautiously in diabetic patients. Many of them have silent ischemic coronary disease, diabetic nephropathy or heart failure and have an increased risk for adverse effects or arrhythmias (83). Presence of DM implies a high embolic risk as calculated by the CHA2DS2-VASc score. Patients on DOACs have lower vascular mortality and a lower or similar bleeding risk as patients on vitamin K antagonists (84).

3. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing and is underdiagnosed in the general population: up to 24% of middle-aged men and 9% of women suffer of sleep apnea and 1 in 15 adults has a moderate form (85). Multiple studies correlated OSA with the risk of developing AF (86). AF risk is influenced by the severity of the disease, independent of BMI and BP values (87).

Mechanisms related to AF. Sleep disturbances induce intermittent hypoxemia, increased cardiac afterload, dilation of atria, and increased wall stress. Other effects are activation of the sym-

pathetic nervous system and abrupt surges in blood pressure during sleep (88, 89).

Effects of treatment. Correct continuous positive airway pressure (CPAP) use ameliorates sleep apnea and improves control of AF with reduced risk of recurrence (88). CPAP treatment was associated with a 42% relative risk reduction in AF recurrence, regardless of pharmacological or interventional strategy (90, 91). Untreated OSA patients have a more that two-fold risk of AF recurrence after cardioversion (92) and after catheter ablation of AF (93). Weight control programs and screening for sleep disturbances should be done actively. Treatment of both these comorbidities ameliorates metabolic equilibrium and improves the outcomes.

4. Obesity

Obesity is the second most prevalent RF associated to AF, after hypertension. Obese individuals have a 2.4-fold increased AF risk compared with subjects with normal weight. The BMI value is in direct relationship with the risk of new onset AF and progression from paroxysmal to persistent episodes (94).

Mechanisms related to AF. Obesity can be responsible for cardiac remodeling, as mediator for all other RF. It usually coexists with HTN, DM, and is also linked to OSA, as 88% of patients referred to bariatric surgery have obstructive sleep-breathing disorders (95). It is strongly associated with new onset AF, irrespective of age, gender, DM or high BP (96). Even in „metabolically healthy obese", body weight is an independent risk factor that increases AF risk by almost 20% (97).

Effects of treatment. Weight reduction approaches, alongside cardiovascular RF management, demonstrated decrease of AF burden and maintenance of SR (98-100). A 1 kg/m^2 drop in body weight correlates to a reduction of 7% in AF incidence (98). On the long term, sustained weight loss reduces the risk of AF with 29% (98).

AF ablation has unfavorable results in obese patients (98, 101). Catheter ablation, as rhythm control strategy, seems to be less efficient (100, 102, 103), with higher radiation dose and periprocedural complications. If combined with aggressive weight management, the outcome becomes more favorable, with longer arrhythmia-free survival time, lower rates of recurrences, and less symptomatic episodes (104).

Anticoagulation should be recommended according to patients' embolic risk. DOAC are efficient and safe, but data is lacking in patients with extreme obesity (105). ❑

CONCLUSIONS

Classic modifiable RF are significant contributors to AF development and progression. Recent research has highlighted the beneficial effects of RF management in patients with AF.

Identification and adequate control and treatment of RF are important pillars in the management of AF. Prevention strategies and personalized approaches can reduce AF burden, improve symptoms, quality of life and survival. ❑

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