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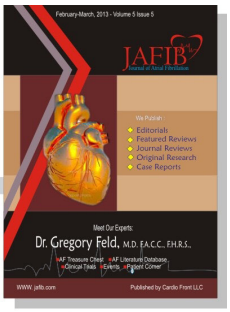

# Primary Prevention of Atrial Fibrillation – The Path Untread

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## Abstract

**The prevalence and incidence of atrial fibrillation (AF) is on the rapid rise. To slow down the AF epidemic, effective primary prevention strategies need to be instituted. Unfortunately, this is an area that has not been well-explored. There is a multitude of risk factors that predispose to the development of AF. Of these, the most common from an epidemiologic perspective are advanced age, hypertension, diabetes, ischemic heart disease, and heart failure. The first-line pharmacologic therapies for these predisposing conditions (e.g. beta blockers, renin-angiotensin system inhibitors, statins, and omega-3 fatty acids) appear to also have potential roles in the primary prevention of AF. Definitive data, however, is lacking as to efficacy of these drugs for this particular purpose. Large-scale, high-quality randomized clinical trials on AF primary preventive strategies are urgently required in order to guide clinical practice. For now, adherence to the guideline-based therapies of each individual risk factor appears to be the most reasonable approach for the primary prevention of AF.**

## Introduction

### Background

Atrial fibrillation (AF) is the most prevalent of the clinically-significant cardiac arrhythmias, with an estimated 2.7 million individuals afflicted in the United States (US). This number is expected to exceed 12 million by 2050 as the population gets older, since the elderly are particularly at risk for developing the disease.[1] AF is closely associated with stroke, a leading cause of death and long-term disability. AF increases the risk of ischemic stroke 5-fold, and is responsible for nearly half of all fatal embolic cerebrovascular events.[2] AF is also linked with increased hospitalization and mortality from ischemic heart disease and heart failure.[3] Given the attendant mortality and morbidity risks, AF is a serious public health burden that would remain as such for the foreseeable future unless treatment patterns change drastically. Recent progress in antiarrhythmic and antithrombotic pharmacotherapeutics, as well as innovations in mechanical approaches to AF treatment, has greatly improved the overall efficacy and safety of modern AF therapy.[4] This has little impact, however, in deterring the emergence of new AF cases, with an incidence currently estimated at 75,000 each year. Clearly, a better effort towards the avoidance of development of new AF cases is required in curbing this epidemic, and more focus toward primary prevention strategies is in order.

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## Risk Factors

In epidemiologic terms, primary prevention refers to the avoidance of development of a particular disease or event through treatment or interventions directed towards the risk factors of said condition. It is, therefore, imperative to understand the main causes of AF in order to prevent its occurrence.

Advanced age is the most important predictor of AF, with a lifetime prevalence of 0.5% in subjects younger than 60 years, to nearly 10% in those above 80 years of age. For each advancing decade of age, the risk of developing AF increases 2-fold. Males are 1.5-times more likely to develop AF than women, independent of age and other comorbidities.Other independent risk factors for AF include hypertension (odds ratio [OR] 1.5), diabetes (OR1.6) left ventricle hypertrophy (OR 1.4), myocardial infarction (OR 1.4), congestive heart failure (OR 5.9), and valvular heart disease (OR 3.4).[5]

Other reported but relatively uncommon cardiac causes of AF include myocarditis, hypertrophic cardiomyopathy, conduction system disease (e.g. Wolff-Parkinson-White syndrome, sick sinus syndrome), congenital heart disease (e.g. atrial septal defect, patent ductus arteriosus), and pericardial disease. Possible non-cardiac etiologies include thyrotoxicosis, pheochromocytoma, obesity, obstructive sleep apnea, severe infections, pulmonary pathology (e.g. pulmonary infections, pulmonary embolism, chronic lung disease), alcohol use ("holiday heart syndrome"), electrolyte disorders, cardiothoracic surgery, hypothermia, and electrocution.

Treatment of the underlying predisposing condition/s is key to preventing AF. While some risk factors are unmodifiable, the recognition of such is nevertheless important in the identification of individual patients and population groups at greatest risk. Patients with multiple risk factors have the highest susceptibility to AF, and are the most appropriate primary target population for primary prevention measures.

## Pathophysiology

While mechanisms for arrhythmogenesis in AF are still not completely understood, it is recognized that certain ectopic foci of atrial tissue in the muscular sleeve of the pulmonary veins can initiate and maintain paroxysms of AF.[6] Repeated firing of these foci lead to a marked shortening of the atrial refractory period and the loss of the normal lengthening of atrial refractoriness at slower heart rates, a phenomenon termed termed "atrial electrical remodeling"[7,8].Also, triggers propagating into the atrial myocardium may induce multiple reentry wavelets, which are small circuits that constantly collide and combine, spawning more wavelets that perpetuate the process.[9]

Conditions that increase atrial size, decrease the conduction velocity or decrease the refractory period permit multiple wavelets and promote AF. This suggests that, in addition to the pathologic electrophysiologic processes, a complex interaction of atrial mechanical, structural and cellular signaling mechanisms significantly contribute to AF pathogenesis. When the atrium dilates and its myocardium is stretched (as seen in AF-associated disorders such as mitral valve dysfunction, congestive heart failure, or hypertension), the action potential is altered and afterdepolarizations occur causing extrasystoles.[10] Furthermore, this mechanical strain induces adverse neurohormonal reactions, including adrenergic stimulation and enhanced synthesis of angiotensin-II that cause cellular calcium dysregulation and contribute to arrhythmogenic electrical dispersion.[11] Stretch-activated myocyte strain has also been shown to disturb the cell-signaling mechanisms by modifying the cytoskeletal connections, membrane ion channels and receptors which regulate atrial excitation-contraction coupling.[12] The function of these ion channels is also susceptible to metabolic changes, such as hypoxia, ischemia, adrenergic stimulation, inflammation or oxidative stress, which increase the propensity to AF.[13]

With chronic atrial hemodynamic load and stretching, fibrosis and scarring occurs to protect the myocytes from stress and strain. Extensive interstitial fibrosis, also seen with advanced age (another risk factor for AF), promotes myocardial macroreentry and fibrillatory conduction.[14] In addition to fibrosis, apoptosis is also believed to contribute substantially to the ultrastructural substrate of AF. Under pathophysiologic conditions, inappropriate programmed

myocyte death occurs which permanently alters the electrophysiologic activity of the myocardium and causes irreversible atrial damage.[15]

There is also ample data point to the role of inflammation in the pathogenensis and maintenance of AF. During the inflammatory process, cytokines such as tumor necrosis factor and interleukins are released and complement is activated, chronic exposure to which is implicated in myocyte necrosis and fibrosis. Atrial structural remodeling ensues, which favors arrhythmogenesis.[16]

## Pharmacotherapeutic Strategies for AF Primary Prevention

A few pharmacologic agents have roused interest for their potential roles in the primary prevention of AF. The antihypertensive and lipid-lowering classes of drugs make up the bulk of these agents, and the evidence for their efficacy mostly comes from retrospective analysis of trial data.

### Beta Blockers

The efficacy of beta-adrenergic blocking agents for rate control in AF and maintenance of sinus rhythm after cardioversion is well-established.[17,18] However, their role in the primary prevention of AF is less defined. Maladaptive adrenergic stimulation is postulated to contribute to the electrophysiologic and structural atrial remodeling mechanisms that initiate and perpetuate AF. Blunting this excessive sympathetic response, in theory, may help prevent the development of this disease.

There is data pointing to a 27% risk reduction in AF incidence with the use of beta blockers in heart failure patients, in addition to their known mortality and morbidity benefits in this population.[19] Majority of the evidence suggesting a primary preventive effect of beta blockers was in the setting of cardiac surgery as prophylaxis against postoperative AF. It is hypothesized the beta blockers attenuate the excessive perioperative adrenergic stimulation that induce atrial arrhythmogenesis during cardiac surgery. In this surgical population, prophylactic beta blocker use was associated with a 15-20% reduction in postoperative AF incidence,[20,21] and is currently the recommended first-line strategy for this purpose, in lieu of stronger antiarrhythmic agents.[22] Outside of the perioperative milieu, however, there is not enough convincing evidence that establishes a primary preventive role of beta blockers against AF. Some suggest that these agents may only have significant anti-atrial fibrillatory effects in those with hypertension.[23] But even in the hypertensive population, beta blockers were shown to be inferior to renin-angiotensin system (RAS) inhibitors in preventing new-onset AF.[24]

### RAS-Inhibitors

Excessive activation of angiotensin-II and other neurohormones induce atrial myocyte fibrosis and electrophysiologic remodeling that create substrates for supraventricular arrhythmogenesis,[25] including AF. RAS agents, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), are able to reverse this maladaptive neurohormonal process, hence they can potentially prevent the occurrence of new AF in individuals at risk.

Retrospective analyses of large randomized trials suggest a possible role of RAS-inhibitors in the primary prevention of AF. In the Trandolapril Cardiac Evaluation (TRACE) study, for instance, treatment with the ACEI trandolapril was associated with a 47% lower incidence of new-onset AF in patients with systolic dysfunction after MI .[26] Also, in a subanalysis of the Studies of Left Ventricle Dysfunction (SOLVD), a 78% risk reduction in AF was seen in patients with heart failure who received the ACEI enalapril compared to placebo.[27]

A similar observation was noted in post-hoc analyses of ARB trials. For example, losartan was associated with a 33% risk reduction in new-onset AF compared with atenolol in hypertensive patients enrolled the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study13. On the other hand, a 37% lower incidence of AF was seen in heart failure patients who were treated with valsartan in Val-HEFT (Valsartan Heart Failure Trial).[28] A more modest 18% reduction in AF occurrence was seen with candesartan in the CHARM trial (Candesartan in Heart Failure: an Assessment of Reduction in Mortality and Morbidity) which enrolled patients with symptomatic heart failure.[29] The Ongoing Telmisartan Alone and in Com-

bination with Ramipril Global Endpoint Trial (ONTARGET) of high-risk hypertensive patients demonstrated a trivial trend towards lower incidence of new-onset AF with combination therapy using telmisartan (an ARB) and ramipril (an ACEI) compared to either treatment alone. These differences, however, were statistically insignificant.[30] Furthermore, analyses of more recent randomized trials, provide contradictory evidence on the anti-AF properties of RAS antagonists. For instance, ramipril therapy had no effect on AF incidence compared to placebo in the Heart Outcomes Prevention Evaluation (HOPE) study involving high-risk cardiovascular patients.[31] Similarly, in the Telmisartan Randomised Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND), no difference AF incidence was seen between treatment with telmisartan or placebo in patients with high-risk cardiovascular diseases.[32]

## Statins

Inflammation, lipid oxidation, and neurohormonal mechanisms have been implicated in the arrhythmogenesis and perpetuation of AF. There is growing evidence role of HMG-CoA reductase inhibitors (statins) in AF prevention, the anti-fibrillatory effects of which are presumed to result from the modulation of these mechanisms.[33] Increasing levels of C-reactive protein (CRP), a marker of inflammation was associated with a 36% increased risk of incident AF in the JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin ). Among over 17,000 arrhythmia-free individuals who participated in the study, treatment with the statin rosuvastatin resulted in a 27% reduction in the risk of AF.[34]

A subanalysis of data from the GISSI-HF trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) found modest reductions in AF occurrence after rosuvastatin treatment in nearly 3,700 patients with chronic heart failure (CHF).[35] In a similar cohort of CHF patients, analysis of data from the ADVANCENT Registry involving more than 25,000 individuals with LV systolic dysfunction showed that lipid-lowering therapy was associated with a 31% reduction in the prevalence of AF, which is larger than that seen in beta blockers and ACE inhibitors.[36]

There have been several small randomized trials which pointed to the efficacy of pre-operative statin therapy, mostly utilizing high-dose atorvastatin, in the prevention of post-operative AF in patient undergoing cardiac surgery.[37,38] A meta-analysis of 8 of these trials involving nearly 800 patients undergoing cardiac surgery showed that pre-operative statin prophylaxis resulted in a 43% reduction in post-operative AF.Earlier therapy appeared to be result in a more profound benefit (3% risk reduction per day), while higher statin doses was not shown to alter the outcomes.[39]

While the preponderance of data support the efficacy of statins in the primary prevention of AF, there have been no large prospective, randomized, multicenter trials conducted to definitively establish such observations. An intensive analysis of existing published and unpublished evidence from 42 trials involving almost 140,000 patients found that, in general, the smaller studies with shorter follow-up period reported significant benefit with statin therapy, while the larger, longer-term trials showed no reduction in risk of AF.[40]

## Omega-3 Fatty Acids

Similar to statins, n-3 polyunsaturated fatty acids (n3-PUFA), such as fish oil, also exert anti-inflammatory properties in addition to its beneficial effects on the lipid profile.[41] Fish oil may reduce C-reactive protein and cytokine levels, which is a possible mechanism for its purported anti-arrhythmic properties. Higher levels of circulating n3-PUFA was found to be associated with lower risk of incident AF in a cohort of over 3300 older individuals who were followed for 14 years in the Cardiovascular Health Study .[42] Prospective observational data from the same study also suggested that dietary consumption of broiled or baked fish, a common source of n3-PUFA, was linearly linked to a lower incidence of AF.[43] This finding, however, was refuted by larger epidemiologic studies that could not show a beneficial effect of fish intake on atrial arrhythmias.[44,45] Small randomized trials of oral[46] and intravenous[47] n-3 PUFA treatment prior to coronary artery bypass graft surgery found significant reductions of occurrence of postoperative AF. More recent randomized tri-

als with somewhat larger sample sizes, however, could not reproduce the same results.[48,49] As such, the clinical utility of n3-PUFA supplementation for the primary prevention of AF in high-risk individuals remains unestablished. ANTIOXIDANT VITAMINS. Oxidative stress that results from excessive reactive oxygen species (ROS) has been linked to atrial electrophysiological remodeling and arrhythmogenesis. Antioxidant vitamins, like vitamins C and E, can reduce ROS and protect the cells from the pathologic processes associated with oxidative stress.[50] There are some reports suggesting that antioxidant vitamin supplementation might have a role in the preventing the subsequent occurrence of AF in patients at risk, specifically in the perioperative setting.[51,52] To date, however, there has been no reliable clinical evidence as to their efficacy in AF primary prevention or treatment.

## Discussion

The recurring theme has been the lack of large, multicenter, prospective, randomized trials evaluating the efficacy and safety of various strategies for the primary prevention of AF. Without such data, definitive recommendations to guide clinical practice could not be made with an acceptable level of certainty. For instance, the 2006 guidelines for AF management by the American College of Cardiology/American Heart Association[53] devoted a section on primary prevention, which acknowledged that this matter has not been widely investigated. Because of insufficient data, no recommendations were made as to the roles of dietary, pharmacologic and device-based interventions in AF primary prevention. This issue has not been addressed further in the latest updates of either American[54] or European[55] guidelines.

While definitive evidence is lacking regarding the role of various antihypertensive and lipid-lowering therapies in AF primary prevention, their efficacy in the treatment of specific risk factors are already well-established. For example, RAS-inhibitors are recommended standard therapies in hypertension and diabetes treatment. Lipid-lowering agents, beta blockers and ACEI are first-line treatments in myocardial infarction and ischemic heart disease. RAS-inhibitors and beta-blockers are standard therapies in heart failure. It appears that perhaps the best strategy in the primary prevention of AF is the optimization and strict adherence to the evidence-based therapies recommended for each individual risk factor , especially in the highest risk individuals with multiple predisposing conditions. From the limited amount of high-quality literature

## Conclusions

The increasing prevalence and incidence of AF needs to be urgently curtailed. To achieve this goal, sufficient large-scale studies, of high quality and adequate power, on the primary prevention of AF are required to guide clinical practice. While the most common risk factors for AF development have been identified, the efficacy of prevailing preventive measures remains unclear. This is the path untread that needs to be resolved sooner rather than later. For now, adherence to the guideline-based therapies of each individual risk factor appears to be the most reasonable primary preventive approach for AF.

## Disclosures

No disclosures relevant to this article were made by the authors.

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