

# Cardiovigilance in Atrial Fibrillation – Primordial to Quinary Prevention Intervention

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**A**trial fibrillation (AF) is one of the major causes of stroke, heart failure, sudden death and cardiovascular morbidity in the world. Management of AF, its risk factors and complications demands huge cost. The frequent hospitalisations, haemodynamic abnormalities, and thromboembolic events related to AF put a huge emotional and monetary burden on patients, so preventive strategies will be a cost-effective means of reducing this burden. Primordial prevention (i.e., intervention prior to onset of disease risk factors) should be implemented by the government, along with the food industry, to educate the public regarding the importance of a healthy diet and adherence to it. Primary prevention should focus on halting the onset of AF in targeted populations who carry risk factors for development of AF. The strategy at the secondary-prevention level includes optimal control of rate or rhythm either by anti-arrhythmic drugs or catheter ablation. Every effort should be made to reduce the incidence of ischaemic stroke by using optimal oral anticoagulation, devices or surgical closure of left atrial appendage. Tertiary level prevention should focus on the management of complications incurred as a result of AF, such as ischaemic stroke, heart failure or asymptomatic left ventricular dysfunction. Since management of AF demands a huge economic burden and the line between thrombotic complications and bleeding complications is a thin one; over-diagnosis and overtreatment of AF should be avoided. The ultimate aim of quinary prevention is to sensitise the physician to follow evidence-based medicine and to get rid of populated myth. This current review summarises a stepwise preventive strategy for AF from the primordial level to the quinary level.

## Keywords

Atrial fibrillation, cardiovigilance, prevention

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Long-term follow-up of patients with atrial fibrillation (AF) has confirmed a significant increase in cardiovascular events, long-term risk of stroke, heart failure and all-cause mortality (89% in those with AF compared to 27% in those without AF).<sup>1</sup> Not only is AF associated with a five-fold increased risk of stroke, AF-related stroke is also likely to be more severe than non-AF-related stroke.<sup>2-3</sup> AF is associated with a three-fold risk of heart failure<sup>4-6</sup> and a two-fold increased risk of both dementia<sup>7</sup> and mortality.<sup>8</sup> Since AF is associated with multiple modifiable risk factors, prevention strategies should begin right from the primordial level. Stepwise strategies are discussed in this current review (*Table 1*).

## Primordial prevention

In the context of this article, the term 'primordial' is representative of early intervention prior to the onset of risk factors that precede disease. The goal of primordial prevention may be achieved by lifestyle modification. This aims to halt the development of modifiable risk factors (*Table 2*) that can set the stage for development of AF. The STRIP (the Special Turku Coronary Risk Factor Intervention Project for Children) trial investigated the effect of primordial level intervention by providing healthy fats; more fruits, vegetables and whole grains; and less sodium to selected populations from infancy to adolescents, on the prevalence of metabolic syndrome.<sup>9</sup> STRIP Investigators recommended limiting salt intake, substituting unsaturated for saturated fats and promoting healthier foods starting in infancy and toddlerhood in order to help achieve ideal cardiovascular health. These recommendations were based on the fact that healthier outcomes were primarily driven by reduction of high blood pressure in both sexes and high triglyceride in boys. The government, along with the food industry, should help educate the public regarding the importance of a healthy diet and how to adhere to it. The co-operation of the food industry is required to achieve significant reductions in sodium intake.

## Primary prevention

Analysis of the original Framingham Heart Study cohort has concluded that the risk factors for cardiovascular disease also predispose to AF.<sup>10</sup> The authors confirmed the statistically significant association of diabetes (odds ratio [OR] 1.4 for men and 1.6 for women), hypertension (OR 1.5 for men and 1.4 for women) and congestive heart failure (OR 4.5 for men and 5.9 for women), with development of AF in both sexes.<sup>10</sup> Optimal control and modification of these risk factors

**Table 1: Preventive strategy in atrial fibrillation**

Prevention level	Parameter	Intervention
Primordial prevention	Prevention of risk factors for AF	Healthy lifestyle, low-salt diet, increased fruit intake, increased physical activity
Primary prevention	Prevention of onset of AF	Weight reduction, optimal control of hypertension, optimal control of diabetes and endocrine disorder
Secondary prevention	Early diagnosis and prevention of complication secondary to AF	Holter monitoring in case of paroxysmal AF
Tertiary prevention	Rehabilitation: heart failure and post thromboembolic events	Adequate rate control or rhythm control; Optimal OAC
Quaternary prevention	Prevention of overdiagnosis of AF; Prevention of complications secondary to over-treatment	Careful analysis of rhythm; Bleeding risk evaluation before OAC
Quinary prevention	Under- or over-treatment because of myths related to the concerned disease	Promoting evidence-based management

AF = atrial fibrillation; OAC = oral anticoagulant.

**Table 2: Risk factors and intervention at primordial level for atrial fibrillation**

Risk factors	Intervention at primordial level
Modifiable risk factors	Healthy lifestyle
Hypertension	Low-salt diet
Diabetes mellitus	Increase fruit intake
Heart failure	Increase physical activity
Obstructive heart failure	Substitute polyunsaturated fatty acid for saturated fat
Myocardial infarction	
Chronic obstructive pulmonary disease	
Chronic kidney disease	
Smoking	
Alcohol consumption	
Thyroid dysfunction	
Non-modifiable risk factors	
Age	
Genetic	

may substantially reduce the onset of AF. Intervention in these groups of patients may be in the form of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and statins. As AF is one of the major causes of stroke, heart failure, sudden death and cardiovascular morbidity in the world,<sup>11</sup> intervention to prevent the onset of AF in this target population will be a cost-effective means of reducing further burden (Table 3).

### Secondary prevention

AF worsens quality of life and can cause a statistically significant increase in the risk of cardiovascular events (death, heart failure, stroke and sudden cardiac death).<sup>11</sup> To prevent complications associated with AF, secondary prevention strategy is discussed in the following sections.

**Table 3: Example of intervention at primary prevention level in patients with atrial fibrillation**

Target	Intervention	Outcome
Diabetes mellitus	Good glycaemic control; Upfront therapy: ACEI/ARB/Statin	Prevent atrial remodelling; Upfront therapy may help in preventing remodelling of atria
Hypertension	Adequate rate control; Standard treatment for heart failure	Prevent atrial remodelling; Reduce the incidence of AF
Heart failure	Anti-remodelling therapy in form of ACEI/betablockers; Optimal control of filling pressure by diuretics	Betablocker; ACE/ARB
Coronary artery disease	Timely revascularisation and optimal medical treatment to preserve geometry of LV	Betablocker/CCB; Rhythm control strategy

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; LV = left ventricle.

### Lifestyle modification

Lifestyle modification in the form of smoking cessation, good quality sleep, alcohol cessation, incorporation of a Mediterranean diet, physical activity in any form and yoga are beneficial in the management of AF.<sup>12</sup> Lifestyle intervention not only reduces the incidence of AF, but also induces AF remission and more successful ablation outcomes.<sup>12</sup> Even if one may not be able to completely reverse AF with lifestyle modification, intervention at the lifestyle level may likely enhance AF treatment efficacy.<sup>12</sup>

### Optimisation of rate control of and normal sinus rhythm

Restoring and maintaining sinus rhythm should be an integral part of AF management. Antiarrhythmic drugs approximately double the rate of sinus rhythm compared with placebo.<sup>13-7</sup> The effect of modern rhythm control management using catheter ablation, combination therapy, or early catheter ablation on major cardiovascular events is still under investigation.<sup>6,18</sup> Catheter ablation may be considered as a second-line treatment (after failure of, or intolerance to, antiarrhythmic drug therapy) in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent and probably long-standing persistent AF.<sup>19-22</sup> However, catheter ablation should not be used to prevent cardiovascular outcomes, to withdraw anticoagulant, or to reduce hospitalisations.<sup>18</sup> AF catheter ablation has also shown promising results in heart failure with reduced left ventricular ejection fraction in terms of lower mortality rate and reduce hospitalisation for heart failure, especially in patients without prior myocardial infarction.<sup>18</sup> However, since ablating AF can be demanding in these patients, selection of patients should be carefully balanced and the procedures should be performed in experienced centres only.

Fast ventricular rate in AF demands rate control on a priority basis. One must look for and treat the precipitating cause (anaemia, alcohol intake, pulmonary embolism, infection, hyperthyroidism, drug use, acute coronary syndrome, valvular heart disease etc). Rapid rate control during AF may be achieved by intravenous diltiazem/verapamil; both of which have rapid onset of action and are effective at high sympathetic tone.<sup>23,24</sup> Other agents that may be used for rate control in specific conditions are beta blockers, digoxin (heart failure with AF) and amiodarone (AF with severe left ventricular systolic dysfunction).

**Table 4: Intervention as secondary prevention strategy**

Target	Intervention	Outcome
Fast ventricular rate: Rate control strategy	Digoxin; Betablocker; Calcium channel blockers (Diltiazem/Verapamil)	Symptomatic relief; Improved tachycardia induced LV dysfunction
Fast ventricular rate Rhythm control strategy	Structural heart disease; Amiodarone	Symptomatic relief; Improved tachycardia induced LV dysfunction;
	No structural heart disease; Amiodarone/flecainide/ propafenone/ibutilide/ vernakalant	Reduced incidence of stroke
Anticoagulation	VKAs; NOACs (Dabigatran/rivaroxaban/ apixaban/endoxaban)	Reduced incidence of stroke
Invasive approach	Pulmonary vein isolation	Refractory and symptomatic AF
	Watchman device	Less stroke in population at high risk of bleeding with VKAs/NOACs

AF = atrial fibrillation; LV = left ventricle; NOACs = novel oral anticoagulants; VKAs = vitamin K antagonists.

Since clinical events, NYHA class, or hospitalisations rates among patients with lenient heart rate control (target of 110 bpm) are as good as strict heart rate control,<sup>25</sup> either of the strategies may be used while opting for a rate-control strategy over rhythm-control strategy.

### Achievement of adequate anticoagulation

Adequate anticoagulation should be achieved to minimise the risk of thromboembolic events in the setting of AF. The CHA2DS2-VASc score is widely used as a risk stratification tool for the initial decision to start oral anticoagulants in patients with AF. Patients with score of 0 (i.e., without any clinical stroke risk factors) do not need oral-anticoagulant therapy; while patients with CHA2DS2-VASc score of >1 in men, and >2 in women, need to be on oral anticoagulants to prevent ischaemic stroke.<sup>26</sup> Bleeding risk must be assessed before starting oral anticoagulants. Notably, many of the risk factors for stroke and bleeding overlap with each other. Aspirin as monotherapy has no benefit for stroke prevention in patients of AF.<sup>27</sup> Antiplatelet monotherapy therefore is not recommended for stroke prevention in patients with AF, irrespective of their stroke risk. Dual antiplatelet therapy offers significantly less protection against stroke, thromboembolism, myocardial infarction and vascular deaths when compared to vitamin K antagonists (VKAs; annual risk of 5.6% for aspirin and clopidogrel versus 3.9% with VKA therapy) but at the cost of similar bleeding risk (2.0% versus 1.3% with antiplatelet monotherapy;  $p=0.001$ ).<sup>28</sup> HASBLED, ORBIT and ABC are three bleeding risk scores that have been developed for risk assessment of bleeding in patients on VKAs.<sup>29-31</sup> A high bleeding score should not be a reason to defer oral anticoagulants; rather one should identify and treat the underlying risk factors.

### Left atrial appendage closure device

Left atrial appendage closure may be considered for patients with contraindication to long-term oral anticoagulants. Left atrial appendage occlusion has been found non-inferior to VKA treatment for the prevention of stroke in AF patients with moderate stroke

**Table 5: Tertiary level prevention in patient with atrial fibrillation**

Complications	Intervention	Outcome
Thromboembolic complications (repeat stroke/peripheral or pulmonary embolism)	Achieve adequate OAC i. Warfarin/Acitrone ii. NOACs iii. Watchman device	Reduce incidence of recurrent thromboembolic complication
Acute decompensated heart failure	Pharmacological/DC cardioversion; Digoxin; Betablocker; Diuretics; Aldosterone antagonist	Improvement in reversible LV dysfunction; Improvement in cardiovascular outcomes; Improved NYHA Class
Asymptomatic LV dysfunction	Betablocker; ACE/ARB; Diuretics; Aldosterone antagonist	Improvement in reversible LV dysfunction; Improvement in cardiovascular outcomes; Improved NYHA Class

ACE = angiotensin converting enzyme; ARB = Angiotensin receptor blocker; DC = direct current; LV = left ventricle; NOAC = non vitamin K antagonists; NYHA = New York Heart Association; OAC = oral anticoagulant.

risk, with a possibility of lower bleeding rates in the patients. Three studies have focused on left atrial appendage closure in patients with contraindications to oral-anticoagulant therapy and have shown improvement in the incidence of ischaemic stroke from expected 5.6–7.6% (based on CHADS<sub>2</sub> score) to 1.7–3.2%.<sup>32-4</sup> Surgical exclusion of left atrial appendage did not show a clear benefit of left atrial appendage exclusion for stroke prevention in a subgroup undergoing AF surgery.<sup>35</sup> Some of the steps to intervene at secondary level and their outcomes are mentioned in *Table 4*.

### Tertiary prevention

Tertiary prevention addresses the care of patients who have already suffered a stroke/transient ischaemic attack (*Table 5*). These measures are aimed at the prevention of a second or third stroke and reducing the disability through patient rehabilitation. Research shows that patients who suffer recurrent stroke have poorer outcomes than those who suffer a first stroke;<sup>36</sup> hence, anticoagulation is the major goal of therapy in patients with AF. The Stroke Prevention Patient Outcomes Research Team (PORT) study found that 57% of patients with a first stroke survived 24 months after their stroke, compared with 48% of those who had a recurrent stroke.<sup>37</sup> Patients with AF with a mechanical prosthetic valve, moderate to severe mitral stenosis, or those with advanced kidney disease (CrCl <30 mL/min), should be treated exclusively with VKAs.

Multiple randomised controlled trials have demonstrated non-inferiority/superiority of novel oral anticoagulants (NOACs; dabigatran, rivaroxaban, apixaban and edoxaban) in non-valvular AF as compared to VKAs.<sup>38-42</sup> Also, since each anticoagulant carries risks for haemorrhagic complications, it is useful to risk-stratify patients with AF to identify appropriate candidates for anticoagulation.

### Quaternary prevention

Quaternary prevention is an emerging concept that cautions against overdiagnosis and overtreatment of the disease (*Table 6*). A few of

Table 6: Quaternary prevention in atrial fibrillation

Target	Intervention	Outcome
Overdiagnosis of AF	Careful examination of ECG before labelling AF	Proper diagnosis of AF
Over-prescription of OACs	CHA2DS2-VASc score for identification of targeted population	Reduced hospitalisation Less unnecessary OAC Less bleeding
Bleeding complication with OACs	CHA2DS2-VASc of score for identification of targeted population HAS-BLED Score to balance need of OAC Regular monitor of INR Patient education regarding diet interaction in VKAs Dose adjustment after introduction of interacting drug (amiodarone/digoxine)	Less bleeding
Drug toxicity	<i>Digoxin</i> Dose adjustment as per patient profile/renal function Planned drug holiday Dose adjustment after introduction of interacting drug (amiodarone/warfarin) Serum digoxin level <i>Amiodarone</i> Regular monitoring of LFT/thyroid and PFT Regular monitoring of QTc VKAs Risk assessment before initiation of OACs Protocol based INR checking Consideration of drug interaction	Improved quality of life due to fewer side effects

AF = atrial fibrillation; ECG = electrocardiogram; INR = international normalised ratio; LFT = liver function test; OAC = oral anticoagulant; PFT = pulmonary function test; QTc = QT interval; VKA = vitamin K antagonist.

Table 7: Common myths and facts related to atrial fibrillation

Myth/hearsay	Fact	Evidence
Subclinical AF (short-lasting AF) not associated with risk of stroke	Entity associated with significantly higher risk of ischaemic stroke	ASSERT trial <sup>43</sup>
Asymptomatic/incidental AF does not increase the risk of stroke	Risk of stroke is the same as symptomatic AF	Substudy of SPAF trial <sup>44</sup>
OACs are contraindicated in patients with AF with prior stroke	Previous stroke or transient ischaemic attack are the most powerful risk factors for subsequent ischaemic stroke	Block et al., 2009 <sup>28</sup>
Increased risk of bleeding with OACs in elderly population.	Well-managed warfarin is associated with significant reduction in ischaemic stroke with similar bleeding incidence	BAFTA trial <sup>45</sup>
Aspirin as good as OACs for stroke prevention	Aspirin best suitable for "platelet"-rich clot and not "fibrin"-rich clot as found in AF	Pisters et al., 2010 <sup>30</sup>
Dual antiplatelet therapy is as good as OACs in preventing stroke	Double anti-platelet therapy reduced the risk of stroke by 28%, but it increased the risk of major bleeding by 50%	ACTIVE-W <sup>27</sup>

AF = atrial fibrillation; OAC = oral anticoagulant.

the considerations relevant to quaternary prevention are highlighted below as quaternary prevention of AF. Careful evaluation and interpretation of the underlying rhythm is of utmost importance. Treatment must be planned after considering the frequency and type of AF, underlying aetiology and associated risk factors. Over-prescription of oral anticoagulants must be avoided. One must balance between thrombotic risk associated with AF and bleeding risk due to oral anticoagulants.

### Overdiagnosis of atrial fibrillation

Many tachyarrhythmias may mimic AF. Attention should be given to regularity and rate. Atrial premature complexes, junctional ectopic tachycardias, ventricular premature complexes and sinus arrhythmia are the common mimickers of AF. Careful analysis of the rhythm and the presence of well-formed P wave may help one to rule out the possibility of AF.

### Overtreatment of atrial fibrillation

Patients with AF are more likely to suffer stroke compared to those without AF,<sup>2-3</sup> making oral anticoagulants (VKAs or NOACs) mandatory in patients with AF whenever the risk of stroke is high. However, one must balance the benefit of oral anticoagulants with risk of bleeding related to this class of therapy. CHA2DS2-VASc and HASBLED scores are available tools to justify initiation of oral anticoagulation. VKA treatment should further be monitored regularly by international normalised ratio (INR), keeping it in range of 2.0–3.0. The spectrum of overtreatment with various classes of therapy varies from gastrointestinal symptoms (nausea, vomiting or abdominal pain), thyroid dysfunction, abnormal pulmonary function test or bradycardia-induced syncope. Careful follow-up with intermittent treatment holidays may prevent such complications. Intervention at quaternary level related to AF management has been highlighted in *Table 6*.

## Quinary prevention

Quinary prevention deals with popular myths related to the concerned disease (Table 7).<sup>27,28,30,43-5</sup> Quinary prevention is a new concept which has gained traction with the development of information technology and social media. A few examples are:

- asymptomatic/incidental AF does not increase the risk of stroke;
- oral anticoagulants are contraindicated in patients with AF with prior stroke; and
- there is an increased risk of bleeding with oral anticoagulants in elderly populations.

## Summary

AF is a preventable disease and so are its complications. This review provides advice regarding the various methods for the prevention of AF and its related complications. The format described here is easy to understand and apply; it also enhances the appeal of preventive measures and underscores the need to integrate them in routine public health programmes, medical and cardiology practice. □

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